New applications of UVA-1 cold light therapy

Polderman, M.C.A.

Chapter 3

A double-blind, placebo-controlled trial of UVA-1 in the treatment of dyshidrotic eczema

M.C.A. Polderman, J.C.M. Govaert, S. le Cessie and S. Pavel

Clin Exp Dermatol 2003;28:584-587

Abstract

We carried out a randomized, double-blind, placebo-controlled study to examine the therapeutic effect of UVA-1 irradiation on dyshidrotic hand eczema. Twenty-eight patients were randomised to receive UVA-1 irradiation (40 J/cm^2) or placebo, five times a week for 3 weeks. Evaluated by the DASI and the VAS, UVA-1 was significantly more effective after 2 and 3 weeks. Also, desquamation and area of affected skin improved significantly more after UVA-1. We did not find any difference regarding the response of patients with increased IgE blood levels (>100 IE/ml) compared with those having normal IgE concentrations. No side effects were observed. This study indicates that UVA-1 can cause a significant improvement of both objective and subjective signs of dyshidrotic eczema.

Introduction

Dyshidrotic eczema is a chronic symptomatic palmoplantar dermatitis. Frequently, patients do not respond properly to topical treatment and occasionally systemic corticosteroids are needed. Photo(chemo)therapy can be effective in dyshidrotic eczema, and in particular, PUVA has been reported to have some beneficial effect.[1-3] However, the use of psoralens is associated with increased carcinogenic risk. The absence of psoralen in UVA-1 therapy represents a significant advantage over PUVA. The first trial of UVA-1 in the treatment of chronic vesicular dyshidrotic eczema of the hands was reported in an uncontrolled study of 12 patients.[4] As patients with dyshidrotic eczema may experience spontaneous remissions, efficacy of UVA-1 needed to be tested in a controlled manner. Here we describe the results of a double-blind, placebo-controlled study in which we examined the effectiveness of UVA-1 phototherapy.

Patients and methods

Patients

In the period of November 1999 until March 2001, 28 patients with dyshidrotic eczema of the hands were included in a randomized double-blind, placebo-controlled study after approval of the research project by the ethics committee of the hospital. Patients younger than 18 years and patients who used systemic immunosuppressive or immnunomodulating medication in the 2 months prior to participation were excluded. Other exclusion criteria were pregnancy and a history of UV-sensitivity or skin malignancy. Patients signed informed consent forms before participating in the study. They were randomly assigned to either UVA-1 (n=15) or placebo

treatment (n=13) by an independent investigator using a lottery system. A blinded investigator was responsible for the evaluation of the parameters.

The average duration of the patients' complaints was 8 years and 4 months (range, 4 months–34 years). All had used potent topical steroids prior to the study, with little or no apparent benefit. There was no washout period for topical steroids. Seven patients had been successfully treated with PUVA in the past, but this had been delivered at least 6 months prior to UVA-1 therapy.

Irradiation equipment

A Photomed CL 3000 cold-light unit (Photomed World Industries, Hamburg, Germany, irradiance 60 mW/cm^2) was used as hand irradiation equipment emitting photons with wavelengths of 340-500 nm. Owing to a filter system that eliminates all infrared irradiation and a ventilation system providing a cool breeze, Photomed UVA-1 therapy is also called UVA-1 cold-light therapy. Placebo treatment comprised of TL tubes, emitting visible light, covered with a blue plastic plate to mimic the blue UVA-1 light. During both treatments patients wore protective eyewear and their forearms were protected against scattered radiation.

Treatment schedule and evaluation

Patients were treated with 40 J/cm^2 UVA-1 or with placebo using the same irradiation time (11 min), 5 times a week for 3 weeks. The primary endpoint was the DASI (dyshidrotic area and severity index, maximum score 60). It consisted of the sum of the severity scores of vesicles (V), erythema (E), desquamation (D) and itch (I) (0 = none, 1 = mild, 2 = moderate, 3 = severe), multiplied by the surface of the affected area of the hand (A) (1= <20%,

to 5 = 81-100%).[5] Secondary endpoints were a VAS (visual analogue score) for itch (maximum 10) and the separate items of the DASI. All parameters were determined before treatment, at the end of each week, and 3 and 6 weeks after treatment. Photographs were taken before and after 3 weeks of irradiation. Furthermore, we compared the effect of UVA-1 in non-atopic patients with that in atopic patients, the latter defined as those with increased IgE levels. During the entire treatment period patients used no topical steroids or antihistamines. No emollient was applied in the 3 h before irradiation.

Statistical methods

A paired *t*-test was used to assess changes in the DASI, its subscores and the VAS for itch during and after treatment. A nonpaired *t*-test was used to evaluate differences between the effect of UVA-1 and placebo treatment. Analysis was performed according to the intention-to-treat principle. Statistical significance was defined as p = 0,05.

Results

UVA-1 treatment resulted in a statistically significant mean decrease of the DASI of 6.5 points (SD 5.7) at the end of the second week and of 8.7 points (SD 6.7) at the end of the third week. Placebo showed a mean increase of DASI of 1.1 points (SD 7.3) and 0.4 points (SD 8.9) respectively. Difference between both regimens reached statistical significance at the end of the second and third week (p = 0.006 and p = 0.005, respectively) (Fig.3.1.). After therapy, there was also a significantly greater mean reduction of DASI subscores of desquamation (p = 0.005), itch (p = 0.005), and the affected skin area (p = 0.039) in the UVA-1 treated group when compared to the placebo treated patients. Although the mean DASI subscore of vesicles demonstrated

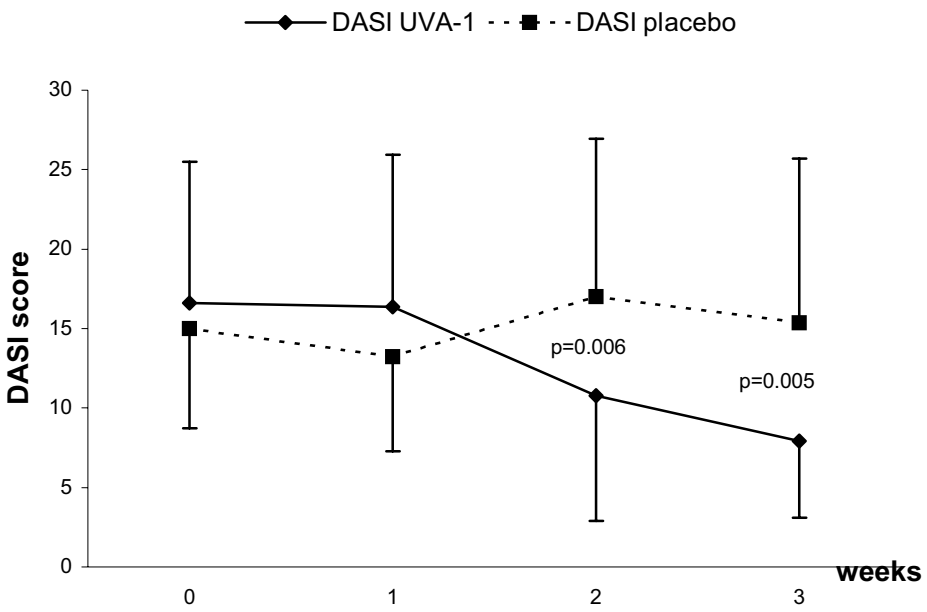

Figure 3.1. Changes in mean DASI score with standard deviations (SD) in patients with dyshidrotic hand eczema as a result of phototherapy with UVA-1 radiation and placebo light.

Table 3.1. Improvement of DASI, DASI subscores and VAS during 3 weeks of UVA-1 and placebo treatment.

	UVA-1 (n = 15)			Placebo (n = 13)		
Parameter	Mean (SD)	95% CI	*P*	Mean (SD)	95% CI	*P*
DASI	8.67 (6.72)	4,95-12,39	0,000*	-0,38 (SD 8,87)	–5,75-4,98	0,878
Desquamation	0.53 (0.74)	0,12-0,94	0,015*	-0,46 (SD 0,97)	–1,05-0,12	0,111
Itch	0.8 (0.68)	0,43-1,17	0,000*	-0,23 (SD 1,09)	–0,89-0,43	0,461
Affected area	0.6 (0.63)	0,25-0,95	0,003‡	0,08 (SD 0,64)	–0,31-0,46	0,673
Vesicles	0.73 (0.88)	0,24-1,22	0,006	0,69 (SD 1,32)	–0,1-1,49	0,082
Erythema	0.4 (0.91)	–1,0-0,9	0,111	0,08 (SD 0,86)	–0,44-0,6	0,753
VAS	2.31 (2.01)	1.16-3.42	0.001*	-1,37 (SD 4,05)	–3,82-1,08	0,26

*P = 0.005; ‡P = 0.039 when UVA-1 is compared to placebo. CI, Confidence interval.

a statistically significant reduction during UVA-1 ($p = 0.006$), there was no difference between UVA-1 and placebo. At the same time, there was a clear reduction ($p = 0.005$) in the mean VAS for itch in the UVA-1 group when compared to placebo (Table 3.1).

Nine patients had increased serum IgE (>100 IU/ml) levels. The four of them belonging to the UVA-1 group did not respond better or worse to UVA-1 than the patients with IgE serum concentrations within the normal range ($p = 0.4$). Four patients in the UVA-1 group who were previously successfully treated with PUVA did not respond better to UVA-1.

For ethical reasons some patients (mainly from the placebo group) could not be withheld from using topical corticosteroids after the 3 weeks of phototherapy. Six weeks after therapy the mean DASI in the UVA-1 treated group still showed a mean improvement of 10,85 points (SD 6,35). Although we could not properly evaluate the duration of the therapeutic effect, some patients probably need corticosteroid maintenance therapy to sustain the effect of UVA-1.

Apart from some minor erythemal reactions, no side-effects occurred. Three of the 13 patients in the placebo group prematurely discontinued therapy after 2 weeks because of exacerbation.

Discussion

UVA-1 radiation has been shown to be effective in the treatment of several skin diseases such as atopic dermatitis, localized scleroderma and mycosis fungoides.[6-8] Grattan *et al.* found topical PUVA and UVA to be equally effective in the treatment of dyshidrotic eczema.[1] However, UVA-1 and UVA have the advantage that no psoralens, with their side-effects and increased carcinogenic risk, are used.

We have shown that UVA-1 is significantly more effective than placebo, and is very well tolerated. According to literature there are two main modes of action of UVA-1. One of them

is induction of apoptosis of lymphocytes in the inflammatory infiltrate through generation of reactive oxygen species[9] and expression of FAS ligand on T lymfocytes.[10] Lymphoid cells have frequently been used for the investigation of UVA-mediated apoptotic responses because of their lower threshold for switching to the apoptotic program.[11] Secondly, *in vitro* UVA-1 irradiation of cultured keratinocytes resulted in increased interleukin (IL)-10 mRNA expression and protein secretion.[12] As IL-10 is a Th-2 derived anti-inflammatory cytokine known to inhibit pro-inflammatory interferon-γ, this may explain the decrease in inflammation observed with UVA-1.

In addition, UVA-1 appears to have a lower carcinogenic risk than PUVA and UVB. Compared with solar simulator light, UVA-1 induced less photodamage (pyrimidine dimers) in murine skin.[13] Likewise, in human skin 1 and 2 minimal erythemal doses from a solar simulator gave rise to twice the levels of p53 induced by UVA-1.[14] In another study, UVA-1 also induced less tumour suppressor gene p53 than "broad" UVA.[15] These observations indicate that UVA-1 causes less DNA damage. However, Lavker and coworkers have suggested that UVA-1 is capable of inducing dermal photo ageing.[16]

In conclusion, UVA-1 appears to be an effective therapy for dyshidrotic hand eczema, particularly on itch and affected area of skin. As no significant side-effects were observed, UVA-1 may constitute a promising therapy for an often recalcitrant skin disease.

Acknowledgements

The nursing personnel carried out the most of the daily irradiations. We are also grateful to Dr. M. Wintzen for her thorough reading of our manuscript.

References

1. Grattan CE, Carmichael AJ, Shuttleworth GJ, Foulds IS. Comparison of topical PUVA with UVA for chronic vesicular hand eczema. Acta Derm Venereol 1991;71:118-22.

2. LeVine MJ, Parrish JA, Fitzpatrick TB. Oral methoxsalen photochemotherapy (PUVA) of dyshidrotic eczema. Acta Derm Venereol 1981;61:570-1.

3. Schempp CM, Muller H, Czech W, Schopf E, Simon JC. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. J Am Acad Dermatol 1997;36:733-7.

4. Schmidt T, Abeck D, Boeck K, Mempel M, Ring J. UVA1 irradiation is effective in treatment of chronic vesicular dyshidrotic hand eczema. Acta Derm Venereol 1998;78:318-9.

5. Odia S, Vocks E, Rakoski J, Ring J. Successful treatment of dyshidrotic hand eczema using tap water iontophoresis with pulsed direct current. Acta Derm Venereol 1996;76:472-4.

6. Kerscher M, Dirschka T, Volkenandt M. Treatment of localised scleroderma by UVA1 phototherapy. Lancet 1995;346:1166.

7. Krutmann J, Czech W, Diepgen T, Niedner R, Kapp A, Schopf E. High-dose UVA1 therapy in the treatment of patients with atopic dermatitis. J Am Acad Dermatol 1992;26:225-30.

8. Zane C, Leali C, Airo P, De Panfilis G, Pinton PC. "High-dose" UVA1 therapy of widespread plaque-type, nodular, and erythrodermic mycosis fungoides. J Am Acad Dermatol 2001;44:629-33.

9. Morita A, Werfel T, Stege H, Ahrens C, Karmann K, Grewe M et al. Evidence that singlet oxygen-induced human T helper cell apoptosis is the basic mechanism of ultraviolet-A radiation phototherapy. J Exp Med 1997;186:1763-8.

10. Abeck D, Schmidt T, Fesq H, Strom K, Mempel M, Brockow K et al. Long-term efficacy of medium-dose UVA1 phototherapy in atopic dermatitis. J Am Acad Dermatol 2000;42:254-7.

11. Vowels BR, Yoo EK, Gasparro FP. Kinetic analysis of apoptosis induction in human cell lines by UVA and 8-MOP. Photochem Photobiol 1996;63:572-6.

12. Grewe M, Gyufko K, Krutmann J. Interleukin-10 production by cultured human keratinocytes: regulation by ultraviolet B and ultraviolet A1 radiation. J Invest Dermatol 1995;104:3-6.

13. Ley RD, Fourtanier A. UVAI-induced edema and pyrimidine dimers in murine skin. Photochem Photobiol 2000;72:485-7.

14. Burren R, Scaletta C, Frenk E, Panizzon RG, Applegate LA. Sunlight and carcinogenesis: expression of p53 and pyrimidine dimers in human skin following UVA I, UVA I + II and solar simulating radiations. Int J Cancer 1998;76:201-6.

15. Seite S, Moyal D, Verdier MP, Hourseau C, Fourtanier A. Accumulated p53 protein and UVA protection level of sunscreens. Photodermatol Photoimmunol Photomed 2000;16:3-9.

16. Lavker R, Kaidbey K. The spectral dependence for UVA-induced cumulative damage in human skin. J Invest Dermatol 1997;108:17-21.