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Extracorporeal photochemotherapy as systemic monotherapy of severe, refractory atopic dermatitis: results from a prospective trial†

Peter Wolf,^{*a} Dimitrios Georgas,^b Nordwig S. Tomi,^{‡b} Christoph M. Schempp^c and Klaus Hoffmann^b

Background: Previous work has indicated that extracorporeal photochemotherapy (ECP) may be a safe and effective treatment in patients with severe atopic dermatitis. **Methods:** We performed a prospective study to investigate the effect of a defined 20-week ECP protocol in patients with severe, refractory atopic dermatitis. The patient inclusion criteria included (i) disease duration of at least 1 year, (ii) SCORAD > 45, and (iii) resistance to first-line therapy, including topical steroids, topical calcineurin inhibitors, and one form of phototherapy (UVA, UVB, or PUVA) or one second-line therapy, including systemic steroids or cyclosporine. Ten patients (4 women and 6 men; age range 29 to 61 years) were enrolled and treated with two sessions of standard ECP in 2-week intervals for 12 weeks and 4-week intervals thereafter until week 20. The patients' clinical status and response was determined by SCORAD at baseline and every 2 weeks, and quality of life was assessed every 4 weeks using SKINDEX, SF-36, and FACT scores. **Results:** There was a statistically significant ($p = 0.015$) reduction of the mean SCORAD by 10.3 (95% CI, 2.5 to 18.0) from 64.8 at baseline to 54.5 (i.e., 15.9% reduction) at week 20. In a subset of patients (all of female sex), the relative reduction in SCORAD after ECP was more than 25% at week 20. Improvement in quality of life measured by SKINDEX, SF-36, and FACT did not reach statistical significance. **Conclusions:** We detected a small but significant therapeutic effect of ECP in patients with severe, refractory atopic dermatitis.

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Introduction

Atopic dermatitis (AD) is a common, chronically relapsing, inflammatory skin disease characterized by itchy eczematous skin lesions which can affect the entire body surface in severe cases.^{1–3} The exact pathogenesis of AD remains unclear. A multifactorial trait involving gene loci on different chromosomes with high correlations to mutations at the filaggrin gene have been found (cited in ref. 1). These mutations, predisposing to a disturbed epidermal barrier function and a simultaneous over-response of the immune system, characterized by a functional failure of regulatory T cells (Tregs)^{4,5} and an

abnormal Th2/Th17-driven immune response to exogenous and/or endogenous antigens most likely lead to the occurrence of the skin changes in the disease.^{6,7} Clinical studies have demonstrated a correlation between disease severity of AD and the levels of immunoglobulin (Ig)E, and surrogate markers such as eosinophil cationic protein or soluble E-selectin.^{8,9}

AD usually responds adequately to emollients, topical corticosteroids, calcineurin inhibitors, or phototherapy such as UVA-1, 311 nm UVB or broadband UVB, or psoralen plus UVA (PUVA) photochemotherapy.^{1–3,10–13} However, in some patients standard therapy remains unsatisfactory, in particular when they suffer from chronic disease with wide-spread skin involvement and/or erythroderma. These patients often require immunosuppression with systemic corticosteroids, azathioprine, cyclosporine or mycophenolate mofetil, or methotrexate to prevent severe disability (cited in ref. 1). More recently, systemic third line approaches leading to diminished T cell activation, including alefacept (fusion protein of lymphocyte antigen (LFA)-3 (anti-CD58) antibody), efalizumab (anti-CD11b antibody, no longer available), rituximab (anti-CD20 antibody) or intravenous IgG have been found effective in severe cases of the disease (cited in ref. 1). In addition, anti-TNF treatment

^aResearch Unit for Photodermatology, Department of Dermatology, Medical University of Graz, Graz, Austria. E-mail: peter.wolf@medunigraz.at; Fax: +43 316 385-12466; Tel: +43 316 385-12371

^bDepartment of Dermatology and Allergology, St. Josef Hospital, Ruhr University, Gudrunstrasse 56, D-44791 Bochum, Germany

^cDepartment of Dermatology, University Medical Center Freiburg, Freiburg, Germany

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‡Present address: Norderney Hospital, Allergy and Dermatology Clinic, Lippesstrasse 9-11, D-26548 Norderney, Germany.

with infliximab¹⁴ or anti-IL-12/23 antibody¹⁵ has been shown to have short term effects in single cases of severe AD. Treatment with the anti-IgE antibody omalizumab (cited in ref. 1) or the anti-IL-5 antibody mepolizumab¹⁶ has also revealed promising results in some moderate to severe cases of AD. However, these systemic therapies may be associated with significant risks of adverse effects. The administration of extracorporeal photochemotherapy (ECP; photopheresis) in AD as a safe and likely effective treatment was first described by Prinz *et al.*¹⁷ in 1994. Thereafter, several investigators have administered ECP in open trials to patients with severe AD.^{17–24} Rubegni *et al.*²⁵ recently reviewed those trials, some of them retrospective in nature and enrolling AD patients of different disease stages, together with a report on a AD patient series treated with ECP and concomitant systemic medication at their center. We herein report the results of a prospective ECP study with clearly defined treatment protocol and restrictive inclusion criteria of patients with severe, refractory AD.

Methods

Setting

This was a prospective trial conducted at the Department of Dermatology and Allergology, St. Josef Hospital, Ruhr University, Bochum, Germany; Department of Dermatology, University Medical Center Freiburg, Freiburg, Germany; and Department of Dermatology, Medical University of Graz, Graz, Austria.

Ethics

The study protocol was approved by the local ethical committees of the participating centers (Bochum: application no. 2284/2004; Freiburg: application no. 142/2004; and Graz: application no. 17-269 ex 05/06). The study was conducted according to the principles of the Declaration of Helsinki. All study participants provided informed written consent for study participation and reporting of results.

Patient inclusion and exclusion criteria

The inclusion criteria of the study were as follows: age above 18 years; body weight above 40 kg; adequate veins to provide intravenous access; diagnosis of severe, refractory atopic dermatitis (i) of at least 1 year duration, (ii) SCORAD > 45, and (iii) resistance in the last 12 months to all first-line therapies, including topical steroids, topical calcineurin inhibitors, and one form of phototherapy (UVA, UVB, or PUVA) or resistance to either systemic steroids or cyclosporine as second line therapy; willingness to abstain from therapeutic sunbathing and tanning beds for the duration of the study. Exclusion criteria were as follows: intolerance of extracorporeal volume loss (*e.g.*, due to severe cardiac disease or severe anemia or body weight below 40 kg); recent (within three months) deterioration of renal function with a serum creatinine level above 3.0 mg dL⁻¹, lipemic plasma above 500 ng dL⁻¹, or uncontrolled diabetes; history of liver damage (2.5 times normal aspartate

aminotransferase (AST), alanine aminotransferase (ALT)) or porphyria; positive testing for HIV antibody, HCV antibody or hepatitis B surface antigen; severe emotional, behavioral or psychiatric disease that may result in poor compliance with the treatment regimen; childbearing potential; pregnancy and lactation; idiosyncratic or hypersensitivity reactions to 8-methoxypsoralen, heparin, or citrate; treatment with PUVA, UVA or UVB within 4 weeks; systemic immunosuppressant therapy within 4 weeks; treatment with oral steroids above 10 mg unless necessary due to Addison's disease or adrenal insufficiency.

Interventions

Standard ECP treatment using UVAR XTS system (Johnson & Johnson, Therakos, Norderstedt, Germany)²⁶ and a standard dose of UVADEX (containing 20 µg 8-methoxypsoralen per 10 ml vial) (Ben Venue Laboratories, Bedford, USA) was administered. UVADEX was applied into the ECP treatment bag using the following formula: treatment volume of the collected plasma/buffy coat in ml multiplied by 0.017. ECP was administered with cycles consisting of treatment on 2 consecutive days every 2 weeks for 12 weeks; thereafter every 4 weeks to end of the study period at week 20. Additional treatment was restricted to the use of emollients, topical steroids, topical calcineurin inhibitors, and/or anti-histamines; no other concomitant treatment was allowed.

SCORAD assessment

The patient's clinical status and response was assessed every two week during the study period. The overall response of a patient was based on SCORAD, a validated clinical tool used to assess the severity of AD.^{1,27} The primary efficacy outcome assessment was SCORAD at week 20.

Quality of life

Quality of life was measured using SKINDEX,^{28,29} SF-36,^{30–32} and FACT³³ at baseline and every 4 weeks during the study period.

Laboratory investigations

For laboratory monitoring, blood was taken from each patient before the first ECP treatment of each treatment cycle to determine white and red blood counts, hemoglobin, mean corpuscular hemoglobin (MCH), and platelets; serum uric acid, total protein, bilirubin, alkaline phosphatase, AST, ALT, lactate dehydrogenase (LDH), gamma glutamyl transferase (GGT), BUN, creatinine, and electrolytes; and total serum IgE levels.

Statistics

For statistical analysis pretreatment values at baseline (before start of ECP) were compared to values at week 20 by two-tailed paired Student's *t* test. Normality testing was done by Kolmogoroff–Smirnov test. Ninety-five percent confidence intervals (95% CI) with lower and upper limits were calculated. The *p*-level of significance was set at ≤0.05. Bonferroni adjustment was made for multiple endpoint testing when appropriate.

Results

Patient characteristics

Ten patients (4 women and 6 men) were enrolled from the study centers (4 patients in Bochum; 3 patients in Freiburg; and 3 patients in Graz). The mean age of the patients was 49 years (range, 29 to 61 years). The mean SCORAD in the patients at baseline before ECP treatment was 64.8 (SD, 18.9; range, 46 to 97) (Table 1 and Fig. 1).

SCORAD

Although there was variability in SCORAD among patients and among treatment visits during the study period (Fig. 1 and 2), a statistically significant ($p = 0.015$) reduction of the mean SCORAD by 10.3 (SD 10.8; 95% CI, 2.5 to 18.0) from 64.8 at baseline to 54.5 at week 20 was evident (Table 1). This corresponded to an average reduction by 15.9% (95% CI, 3.9 to 27.8), comparing ECP pretreatment to after ECP SCORAD values. The relative SCORAD levels (normalized to 100% at baseline) are shown in Fig. 2. In three patients (no. 7, 8, and 9), the relative reduction in SCORAD after ECP was greater

than 25%. This effect was observed at several time points during the ECP treatment regimen and at week 20, as the primary endpoint of the study protocol (Fig. 2A). Remarkably, these well-responders were all of female sex and had the same age distribution (30, 48, and 60 years) as the remaining study population at study entry. As depicted in Fig. 3, significant improvement of skin lesions was observed in certain patients during the study period (Fig. 3A, patient no. 7) or after the 20-week study period under extended ECP treatment (Fig. 3B, patient no. 6).

Secondary clinical endpoints

Improvement of quality of life was observed after ECP but overall did not reach statistical significance for any of the scores, including SKINDEX,^{28,29} SF-36,^{30–32} or FACT³³ (Table 1). However, in individual patients substantial improvements were observed comparing baseline vs. after ECP treatment evaluations with these scores (data not shown). No serious side effects of ECP were observed in the study.

Table 1 Treatment effect of extracorporeal photochemotherapy in severe, refractory atopic dermatitis as determined by SCORAD and different quality of life scores, including SKINDEX, SF-36, and FACT. (A) Data at baseline and week 20. (B) Differences from baseline

(A) Data at baseline and week 20

	Week 0 (baseline)		Week 20	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
SCORAD	64.8 $\pm$ 18.9	46–97	54.5 $\pm$ 22.8	19–83
SF-36 physical sum	41.5 $\pm$ 3.6	37–48	43.9 $\pm$ 4.9	32–50
SF-36 psychological sum	42.9 $\pm$ 8.5	31–46	45.5 $\pm$ 8.7	35–52
SKINDEX (symptoms)	56.8 $\pm$ 10.7	36–75	48.5 $\pm$ 18.8	14–71
SKINDEX (emotions)	33.5 $\pm$ 15.8	13–70	30.0 $\pm$ 14.8	10–60
SKINDEX (function)	41.5 $\pm$ 16.2	19–67	35.5 $\pm$ 14.3	10–58
FACT-G (physical well-being)	22.4 $\pm$ 4.0	14–27	23.6 $\pm$ 3.3	17–28
FACT-G (social well-being)	18.2 $\pm$ 5.4	10–27	19.3 $\pm$ 4.5	13–26
FACT-G (emotional well-being)	19.3 $\pm$ 3.3	13–24	19.2 $\pm$ 3.5	13–24
FACT-G (functional well-being)	16.1 $\pm$ 5.7	9–25	17.8 $\pm$ 6.7	7–28
FACT-G	76.0 $\pm$ 13.4	58–97	79.9 $\pm$ 14.4	63–104

(B) Differences from baseline

Type of score	Mean difference from baseline	95% confidence interval		<i>p</i> -value
		Lower limit	Upper limit	
SCORAD	−10.3 $\pm$ 10.8	−18.0	−2.5	0.015
SF-36 physical sum	2.3 $\pm$ 5.3	−6.2	1.5	0.199
SF-36 psychological sum	2.6 $\pm$ 5.4	−6.4	1.3	0.167
SKINDEX (symptoms)	−8.3 $\pm$ 17.7	−21.0	4.4	0.172
SKINDEX (emotion)	−3.5 $\pm$ 11.2	−11.5	4.5	0.349
SKINDEX (function)	−6.0 $\pm$ 15.0	−16.8	4.8	0.240
FACT-G (physical well-being)	1.2 $\pm$ 2.3	−0.4	2.8	0.133
FACT-G (social well-being)	1.1 $\pm$ 2.6	−0.8	3.0	0.221
FACT-G (emotional well-being)	−0.1 $\pm$ 1.2	−1.0	0.8	0.798
FACT-G (functional well-being)	1.7 $\pm$ 5.5	−2.2	5.6	0.355
FACT-G	3.9 $\pm$ 7.5	−1.5	9.3	0.134

SD, standard deviation. SCORAD,^{1,27} (A) absolute lower values and (B) negative differences (from baseline) indicate better skin status. SF-36,^{30–32} (A) absolute higher values and (B) positive differences (from baseline) indicate better quality of life. SKINDEX,^{28,29} (A) absolute lower values and (B) negative differences (from baseline) indicate better quality of life. FACT,³³ (A) absolute higher values and (B) positive differences (from baseline indicate) better quality of life.

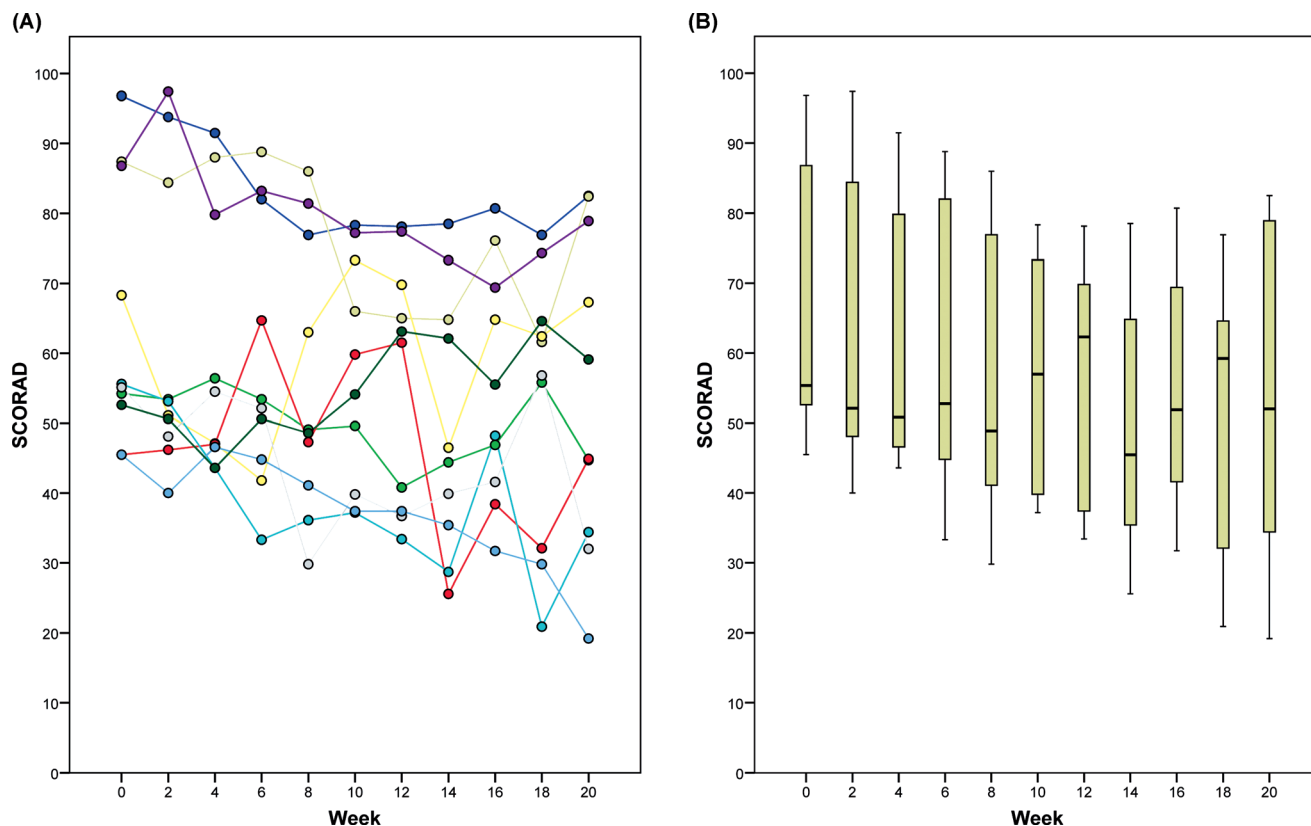


Fig. 1 Effect of extracorporeal photochemotherapy on SCORAD in patients with severe, refractory atopic dermatitis during the 20-week study period. (A) Absolute SCORAD values of individual patients and (B) box plots for all patients.

Laboratory observations

Laboratory monitoring revealed that leucocyte levels (7.1 ± 2.3 vs. $6.3 \pm 1.6 \times 10^9 \text{ L}^{-1}$; $p = 0.028$), MCH (30.0 ± 1.6 vs. 28.7 ± 1.2 pg; $p = 0.028$), and serum alkaline phosphatase (75 ± 20 vs. $66 \pm 14 \text{ U L}^{-1}$; $p = 0.028$) were significantly decreased, and potassium (4.1 ± 0.5 vs. $4.3 \pm 0.4 \text{ mmol L}^{-1}$; $p = 0.039$) was increased, comparing baseline levels vs. that at week 20. However, when adjusted for multiple endpoint testing by the Bonferroni method these differences were statistically not significant. Three patients had IgE levels increased above laboratory limits ($>5000 \text{ IU ml}^{-1}$) at the start of ECP and thereafter; two patients had lacking IgE levels from the visits during the study period; in the remaining five patients IgE levels (321 to 1213 IU ml^{-1} at baseline) decreased during the ECP treatment period, reaching at week 20 levels of approximately 20 to 40% below baseline (data not shown).

Discussion

In this prospective trial we observed a small though statistically significant effect of ECP in patients with severe refractory AD. Patients exhibited after ECP treatment a statistically significant reduction of SCORAD by 10.3 points (95% CI, 2.5 to 18.0) from 64.8 at baseline to 54.5 at week 20 (Table 1), corresponding to an average reduction of 15.9%. In a subset of three

patients the reduction of SCORAD was greater than 25% during the 20-week ECP study period and thereafter under extended ECP treatment (Fig. 3). This is consistent with reports by others, indicating that long-term application of ECP treatment can lead to satisfactory treatment results.^{18,20,25} Notably, on average an improvement in quality of life was not detectable with the standard scores we employed in the study, including SKINDEX,^{28,29} SF-36,^{30–32} and FACT³³ to the end of the study period at week 20. This indicates that a score such as SCORAD assessing the severity of disease by objective signs (*i.e.* extent and intensity of skin lesions) and subjective signs (pruritus and insomnia) can be more sensitive than quality of life scores to detect response to treatment.

The average response rate measured by SCORAD in this study was lower than that observed with similar ECP treatment protocols in previous studies, in which together more than 80 patients have been treated so far (reviewed in ref. 25). For instance, in the largest study Radenhausen *et al.*²¹ administered ECP to 35 patients with severe generalized AD over a period of 6 to 10 cycles. They observed that ECP led to a significant decrease in SCORAD from 74.4 before to 36.8 (*i.e.*, 50% reduction) after a mean of 10 cycles given in 2-weekly intervals. However, we observed, consistent with other reports,^{17,20} that ECP can be very effective in patients with (first-line-therapy-refractory) erythrodermic AD (Fig. 3) particularly when administered for longer periods of time. It is

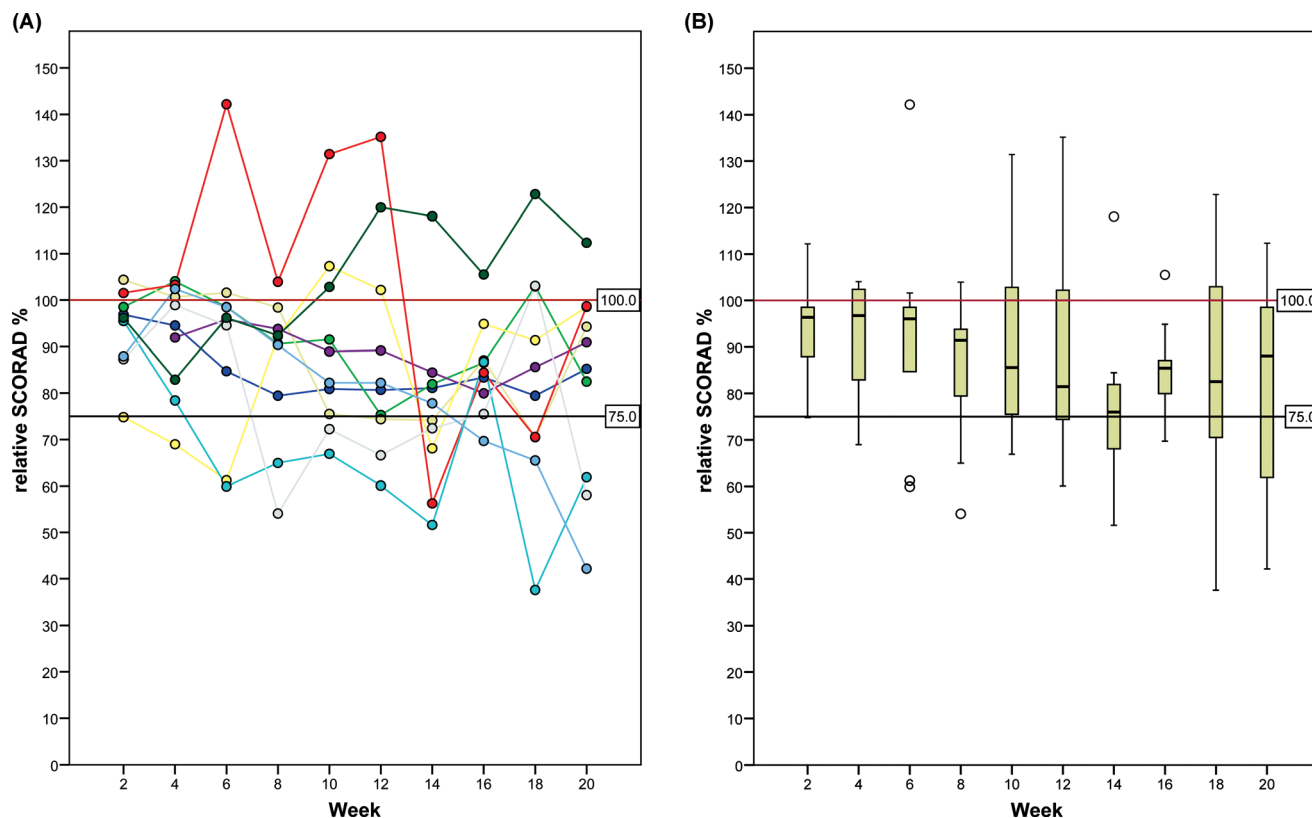


Fig. 2 Effect of extracorporeal photochemotherapy on SCORAD in patients with severe, refractory atopic dermatitis during the 20-week study period. (A) Relative SCORAD values (normalized to 100% at baseline) of individual patients and (B) box plots for all patients.

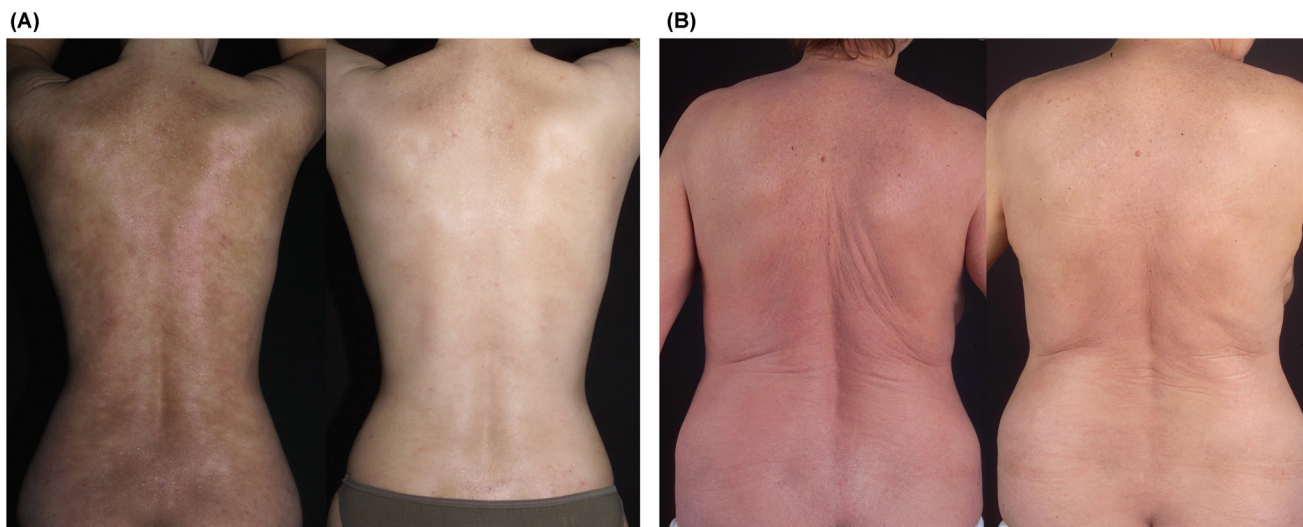


Fig. 3 Clinical treatment effect of extracorporeal photochemotherapy in patients with severe atopic dermatitis. (A) 30 year old woman (patient no. 7) with chronic poikilodermic atopic dermatitis before (left photograph) and after 18 weeks of ECP (right photograph). (B) 59 year old woman (patient no. 6) with erythrodermic atopic dermatitis before (left photograph) and 24 weeks after start of ECP (right photograph). Note in both patients a significant improvement of skin lesions was observed after ECP.

intriguing to note that, besides in Sezary syndrome,^{34,35} ECP has also been shown to be effective in erythroderma of other origin, such as red man syndrome,^{36,37} erythrodermic pityriasis rubra pilaris,³⁸ or photoaccentuated erythroderma associated with CD4+ T lymphocytopenia.³⁹

ECP has also been found to improve laboratory correlates of active AD including elevated levels of IgE, eosinophilic cationic protein, soluble interleukin-2 receptor (sIL-2R), or soluble E-selectin.^{20–22} However, Radenhausen *et al.*²¹ found no significant correlation between a decrease in these levels and

values of blood eosinophils. Compared to ECP responders, most non-responders had very high levels of total serum IgE before and during ECP therapy.²¹ In our study, we observed a trend for decreased IgE levels during and after ECP treatment. Consistent with previous studies, we found that ECP given to AD patients was safe and without any side effects.

The exact mechanisms of the therapeutic action of photochemotherapy⁴⁰ and ECP^{34,35,41} remain to be determined in AD. Tregs are crucial in the pathogenesis of AD.^{4,5} An experimental mouse model of contact hypersensitivity (CHS) revealed that ECP inhibited the induction of CHS and induced Tregs.⁴² In addition, ECP also inhibited the efferent phase of CHS although Tregs only inhibited sensitization. Similar as in CTCL, in which ECP has been shown to down-regulate peripheral Tregs,⁴³ an altered Treg function may be associated with the therapeutic response mechanism in AD. On the other hand, we have found in a TGF-beta transgenic mouse model of an inflammatory psoriasis-like disease that PUVA photochemotherapy does not only induce disease-suppressive Tregs but simultaneously suppresses the Th17 axis,^{44–46} a potential key pathway in psoriasis and AD.⁴⁷ In addition, photochemotherapy may also affect homing of Tregs to lymph nodes and the skin.⁴⁸ Moreover, we recently found that photochemotherapy down-regulated IL-9,⁴⁹ another cytokine that may play a role in AD by affecting mast cells.⁵⁰ In another previous study⁵¹ we discovered that photochemotherapy had proapoptotic and immunosuppressive properties and induced the formation of platelet-activating factor (PAF), a potent phospholipid mediator. The potential production of PAF in the flow chamber of the ECP apparatus, resulting in a cascade of downstream events,⁴⁴ may be involved in the therapeutic mechanisms in ECP-responsive diseases such as AD.

Taken together with previous reports,^{17–25} ECP seems to be effective in severe, refractory atopic dermatitis. However, the effect we detected in this study was on average rather small and not linked to an overall significant detectable improvement in quality of life in the short-term. Weaknesses of the study were that it was not a randomized controlled trial and the amount of additional local treatment was not quantified. Future studies will also have to identify potential predictive markers for AD patients responding favorably to ECP.

Abbreviations

ECP Extracorporeal photochemotherapy

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