A Retrospective Study of Six Cases of Severe Recalcitrant Atopic Dermatitis Treated with Long-term Extracorporeal Photopheresis

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Atopic dermatitis (AD) is a common, multifactorial inflammatory skin disease with a profound negative impact on quality of life of patients and their families. First-line treatments include topical steroids and topical calcineurin inhibitors (1). Treatment with ultraviolet (UV) radiation and oral antibiotics may be needed.

Second-line therapy includes immunosuppressive drugs, such as azathioprine, cyclosporine, systemic prednisolone, or methotrexate (2).

In some patients the disease takes a severe chronic course recalcitrant to these traditional first- and second-line therapies. In such cases, unconventional and less standardized third-line treatment regimes may be sought in order to ameliorate the disease effectively.

Extracorporeal photopheresis (ECP) is a leukapheresis-based therapy that uses 8-methoxypsoralen (8-MOP) and UVA irradiation (3). A series of small open-labelled studies have shown the effect of ECP in patients with severe, recalcitrant AD (4–7). The treatment seems to be safe, as no adverse events have been reported. Most of the studies are, however, based on relatively short-term application of ECP.

MATERIALS AND METHODS

The study was a retrospective follow-up based on a review of clinical files. Six patients, 3 men and 3 women, age range 33–63 (mean 46) years treated with ECP for more than one year were included (Table I).

All had a long history (mean 39 years) of severe recalcitrant AD. Five patients had a history of treatment with several first-line therapies (topical steroids, topical calcineurin inhibitors, UV therapy) and two or more of the second-line therapies, including systemic steroids, azathioprine, psoralen plus UVA (PUVA), cyclosporine and methotrexate. The patients had either been refractory to these treatments or they had been discontinued due to intolerable side-effects. One patient had been refractory to 3 first-line therapies and did not wish to receive systemic therapy, which is otherwise recommended in the European Task Force on Atopic Dermatitis (ETFAD) guidelines (8).

The patients were initially treated with oral 8-MOP, 0.6 mg/kg, followed by photopheresis 2 h later. This regime, however, resulted in inconsistent blood levels of psoralen. Furthermore, intolerable side-effects to the oral 8-MOP were noted in our group of patients. Owing to this, clinical policy on this area was revised, and administration of 8-MOP was changed to extracorporeal administration of methoxsalen (Uvadex®) in all patients.

The Uvar XTS photopheresis system (Therakos Inc., Exton, PA, USA) was used in the procedure.

The standard treatment was two ECP treatments on two consecutive days every fourth week. After the first year of treatment the intervals were adjusted individually in each patient in the range of 2–8 weeks according to clinical effect.

Clinical records were made at each visit, on the activity of the atopic dermatitis (flares, erythema, excoriations, etc.) and on the general state of the skin. Patient subjective remarks on activity of dermatitis, itch and general well-being was noted. Adverse events were also registered. A standardized skin scoring method was not part of the clinical files and therefore was not available.

Table I. *Patient data, history of pre-treatment and data on extracorporeal photopheresis (ECP)*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex/age (years)	F/63	M/46	M/38	F/33	F/46	M/47
Age at diagnosis	3 months	16 years	5 weeks	3 months	3 months	3 months
Treatment prior to ECP	Mtx, Az, Cy, SS, PUVA, TS, Tci, Tar	Az, Cy, SS, Ab, TS, Tci, Tar, UV	Ah, Az, Cy, Ab, TS, Tci, Tar, Ppb	Mtx, Az, Cy, SS, Ab, Ah, TS, Tci, Tar, UV	Ah, Ts, Tci, UV	Az, Cy, SS, Ab, TS, Tar, Ppb
Treatment during ECP*	TS	TS, Tci, Ab	TS, Tci, Ppb	TS, Tci, SS	TS	SS, TS
Duration of AD at initiation of ECP (years)	57	41	31	25	40	38
Length of ECP treatment(s) (months)	79	67	68	12 + 22 + 12	57	6 + 79
Adverse events	None	None	None	None	None	None
Effect on eczematous activity	Clearing	Slight to marked improvement	Slight to marked improvement	Slight to marked improvement	Slight to marked improvement	Marked improvement
Effect on pruritus	Clearing	Marked improvement	Marked improvement	Marked improvement	Clearing	Marked improvement
Remarks				Treatment paused due to pregnancies		Treatment paused due to good clinical effect.

*Intermittent

Ah: antihistamine; Ab: antibiotics; Mtx: methotrexate; Az: azathioprine; Cy: cyclosporine; SS: systemic steroids; PUVA: psoralen + UVA therapy; UV: conventional UVA or UVB light therapy; TS: topical steroids; Tci: topical calcineurin inhibitors; Tar: topical coal or pine tar; Ppb: potassium permanganate baths; F: female; M: male; AD: atopic dermatitis.

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The following data were registered in our review of the patient files: age, age at diagnosis of atopic dermatitis, gender, age at initiation of ECP, date and duration of each course of ECP treatment, dose of 8-MOP, and the date of change to extracorporeal administration of methoxsalen. At time 3, 6, 12 months, and every 12th month after this, data were recorded on any change to the treatment, along with key words from the clinical file on the activity of the atopic dermatitis and the effect on itch. The effect of ECP was graded in five categories on the basis of the clinical file data: worsening, unchanged, slight effect, marked effect, and clearing. The same grading was made regarding itch.

RESULTS

Clinical response was registered in all patients. In one patient (No. 1) clearing of the eczema was achieved. The rest of the patients were graded as having slight or marked effect (Table I). Two patients (Nos 1 and 5) reported clearing of the pruritus, while 4 patients reported marked improvement of the pruritic activity (Table I). There were, however, slight fluctuations in the clinical response over time.

ECP treatment was tolerated in all patients without any serological or objective clinical adverse reactions. Occasional difficulties in obtaining intravenous lines were not present to an extent that impeded the procedure. Subjective adverse effects, mainly in the form of gastrointestinal symptoms, were noted when the oral formulation of 8-MOP was administered. This was not registered when 8-MOP was administered extracorporeally. Some correlation between decreased eczematous activity and change from oral to extracorporeal 8-MOP was noted. This last observation is in accordance with the widely accepted fact, that the oral formulations of psoralen is subject to individual variations in pharmacokinetics and thus less stable blood levels of 8-MOP (9).

DISCUSSION

ECP is a therapeutic approach based on the biological effects of 8-MOP in combination with extracorporeal UVA radiation of white blood cells. The mechanism of action is not yet fully understood. It is, however, suggested that a combination of T-cell apoptosis and monocyte activation lead to an immune modulating effect with downregulation of pro-inflammatory cytokines (e.g. interleukin (IL)-12, interferon (IFN)-γ), upregulation of anti-inflammatory cytokines (eg. IL-10, transforming growth factor (TGF)-β) and generation of regulatory T-cells (9).

Six studies of patients with severe recalcitrant AD treated with ECP have been published (4–7, 10, 11). These studies have all indicated a beneficial effect of ECP, but the data are still limited.

Our data show an overall positive clinical effect of ECP, although only partial in some of the patients. In contrast to this, all patients reported good effect on pruritus. The patients expressed great satisfaction with the treatment and were reluctant to discontinue treatment in favour of other regimes. The course of ECP treatment has, in this group of patients, been extended up to more than 80 months. The effect of the treatment was stable and persistent. No signs or symptoms of severe adverse events have been recorded.

There are, however, some disadvantages to this treatment. It is costly and time-consuming for patients and personnel. In addition, it is a treatment that is so far based on a weak level of scientific evidence when it comes to efficacy in patients with atopic dermatitis, and is as such still considered experimental.

The obvious weakness of our study is the retrospective nature and the lack of a standardized skin scoring system. Furthermore, the study has a clear selection bias, in the sense that the treatment was continued on a long-term basis only in patients experiencing an effect.

The much extended period of time these individuals have been treated, with partial or complete remission, and the lack of serious adverse events is, in our opinion, nevertheless remarkable.

The authors declare no conflict of interest.

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