Sir,

Atopic dermatitis (AD) is a troublesome inflammatory skin disease characterized by severe pruritus, typical eczematous morphology and a chronic relapsing course often associated with increased IgE levels. The pathogenesis of AD remains unknown. Lesional skin in AD is characterized by a dermal mononuclear cell infiltrate composed of activated T cells, monocytes and eosinophils (1).

Studies have demonstrated a correlation between the disease severity of AD and the levels of eosinophil cationic protein (ECP), soluble interleukin-2 receptor (sIL-2R) and soluble E-selectin (2, 3). Especially E-selectin, a cell adhesion molecule on postcapillary endothelium, plays a pivotal role in the recruitment of circulating leukocytes into target tissues. After being expressed on the cellular surface, E-selectin is released into circulation through shedding (2, 4).

Extracorporeal photochemotherapy (ExP) was developed as an immunomodulatory therapy with particular efficacy in disorders with activation or proliferation of T cells (5). Recently, three open clinical trials have demonstrated that long-term ExP is effective in severe cases of AD (6–8). The purpose of our study was to determine whether improvement of AD after ExP is associated with a significant decrease of circulating inflammatory activation markers.

MATERIAL AND METHODS

Ten patients (6 males and 4 females, aged 35 – 67 years) with severe atopic dermatitis participated. Five were therapy-resistant and two had erythrodermia. Disease severity was measured using SCORAD (9) and only patients having an initial score above 45 points were included. A wash-out period of 2 weeks was established after UV phototherapy and systemic corticosteroid therapy. Besides ExP, additional therapy was restricted to emollients, antihistamine or short-term corticosteroid ointment as needed. The SCORAD score was assessed on admission and before the 11th ExP cycle. To evaluate the long-term effects of ExP, serum levels of ECP, sIL-2R and sE-selectin were determined before the 1st and 10th ExP cycles.

Soluble IL-2R was assessed using an enzyme-linked immunoassay kit (ELISA; R&D Systems Inc., Minneapolis, USA; sensitivity 5 pg/ml). Soluble E-selectin was determined by sandwich ELISA (R&D Systems; sensitivity 0.1 ng/ml) in accordance with the manufacturer’s instructions, and ECP levels were determined by a specific fluorimunnoassay (FEIA; Pharmacia-Upjohn, Freiburg, Germany). The differences between the pre- and post-treatment values were tested for significance using the t-test for paired samples (SCORAD score). Non-parametric statistics were used to evaluate differences between ECP, sIL-2R and sE-selectin (Wilcoxon rank sum test). P values less than 0.05 were considered as significant.

ExP was given using the UVAR XTS system (Therakos, London, GB). The patients were treated on 2 consecutive days at 2-week intervals for a total of 10 cycles. Two hours after ingestion of 8-MOP (0.6 mg/kg 8-MOP, Meladinine®; Galderma, Freiburg, Germany) leukopheresis was performed and leukocytes were additionally diluted with plasma and saline to yield a leukocyte-enriched fraction with a hematocrit of 1 – 2% in the presence of 50 – 200 ng/ml 8 MOP. This mixture was then irradiated by 1.5 J/cm² UVA. After exposure of the cells to UV the treated blood was re-infused.

RESULTS

ExP led to a significant decrease in SCORAD score from 87.3 ± 9.1 before treatment to 35.7 ± 12.3 after 10 ExP cycles (Table I). No adverse events were observed. Our results confirm that patients with severe AD have increased serum levels of ECP and sIL-2R reflecting the activation state of eosinophils and T lymphocytes as well as increased serum levels of sE-selectin. ECP levels decreased from 83.4 ng/ml before to 31.0 ng/ml after therapy. Furthermore, sIL-2R levels decreased from 1843 pg/ml before to 775 pg/ml after therapy, and sE-selectin levels from 84.3 ng/ml before to 32.1 ng/ml after therapy (Table I). After 10 cycles of ExP the concentrations of all three compounds were significantly lower than before ExP therapy (p < 0.05), which paralleled the decrease in SCORAD values (Table I). The decrease in soluble receptor molecules did not correlate with blood eosinophil count or lymphocyte count in patients with AD (data not shown).

Table I. SCORAD score (mean ± SE) and circulating activation markers (mean, range) before and after 10 cycles of extracorporeal photochemotherapy (ExP)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(normal values)</th>
<th>Before ExP therapy</th>
<th>After 10 ExP cycles</th>
<th>Degree of improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORAD</td>
<td>87.3 ± 9.1</td>
<td>35.7 ± 12.3*</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>ECP</td>
<td>83.4</td>
<td>31.0*</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>sIL-2R</td>
<td>(&lt;24 ng/ml)</td>
<td>(29.2 – 200)</td>
<td>(7.2 – 86.4)</td>
<td>62%</td>
</tr>
<tr>
<td>sE-selectin</td>
<td>84.3</td>
<td>32.1*</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>sIL-2R</td>
<td>(29 – 63 ng/ml)</td>
<td>(28.3 – 216)</td>
<td>(18.0 – 73.8)</td>
<td>58%</td>
</tr>
<tr>
<td>IL-2R</td>
<td>1843.4</td>
<td>775.8*</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>IL-2R</td>
<td>(676 – 1232 pg/ml)</td>
<td>(798 – 4488)</td>
<td>(303 – 2698)</td>
<td></td>
</tr>
</tbody>
</table>

p < 0.05; ECP: eosinophil cationic protein; sE-selectin = soluble E-selectin; sIL-2R = soluble interleukin-2 receptor.
DISCUSSION

Immunomodulatory treatment of severe AD consists almost exclusively of topical or systemic corticosteroid therapy, sometimes in combination with UV phototherapy. Long-term corticosteroid therapy and UV phototherapy are known to cause a variety of side effects, and alternative treatments such as ExP have been introduced. Our study confirms that ExP can be an effective treatment for severe AD, even in cases resistant to prior therapy (6–8). ExP led to partial or complete remission of AD among 65% of the patients within 10 cycles of ExP therapy.

An alternative treatment of severe AD is cyclosporine leading to an improvement in up to 80% of patients within a few weeks of therapy (10). Cyclosporine is well known as a potent T-cell inhibitor. However, it carries side effects that are present only during treatment.

ExP treatment is obviously capable of down-regulating augmented immune responses (5). As regards inhibition of T-cell proliferation, alterations in the cytokine production as well as expression of surface molecules are important events in 8-MOP photo-treated cells (11, 12).

It has been shown that serum markers such as ECP, sIL-2R and sE-selectin are useful in monitoring the activity in AD during therapy with topical or systemic steroids and/or UV phototherapy (3, 13–15). Our study demonstrated that after 10 ExP cycles, AD responds with a concomitant down-regulation of inflammatory markers accompanying the improved skin condition. Immunomodulatory changes of the inflammatory mediator pattern might be beneficial in the treatment of severe AD with ExP. Recent published data demonstrated in vitro that 8-MOP plus UVA might shift T-lymphocytes from Th2 to Th1 cells (11). In this context, further studies are required to evaluate changes in the T-helper cytokine pattern and the influence on lymphocytic subpopulation in the blood and skin after ExP.

REFERENCES