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Antipruritic Effect of Oral Cyclosporin A in Atopic Dermatitis

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The effect of ten days' treatment with cyclosporin A, 5 mg/kg/day, in 10 adults with atopic dermatitis was investigated using a double-blind, randomized, placebo-controlled, cross-over design. Evaluation was based on itch recording, clinical scoring and immunohistochemical examination of skin biopsy specimens. Cyclosporin A significantly reduced the itch intensity, the eczema score and the consumption of topical hydrocortisone. A significant decrease in serum magnesium and in the total number of blood eosinophils was seen. No other laboratory abnormalities were observed. In lesional skin, Cyclosporin A induced a relative decrease of CD3+ T cells in 5/10 patients, of HLA-DR+ cells in 6/10, and of interleukin-2-receptor positive (CD25+) cells in 4/10. However, these changes in phenotype expression did not seem necessary for itch relief. Relapse of clinical symptoms was seen within 2–30 days of completion of the Cyclosporin A course. The mechanism of the antipruritic effect remains unclear, but the present findings may support the hypothesis that 'pruritogenic cytokines', whose production is inhibited by Cyclosporin A, may be important in the pathogenesis of itch in atopic dermatitis. ***Key words: Ciclosporin; Itch; T lymphocytes; Eosinophils; Skin biopsies; Symtrack.***

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Itch is the dominating symptom in atopic dermatitis (AD). However, its pathogenesis remains unknown. Histamine does not seem to play an important role as pruritogen in AD (1). Several pharmacophysiological (2) and immunological abnormalities have been identified, and during the last ten years several publications have focused on the altered T lymphocyte subpopulations in peripheral blood (e.g. 3, 4, 5) and in skin (e.g. 5) in AD patients.

Recently, several case reports concerning the beneficial effect of oral cyclosporin A (CSA) in AD have been published (6–10). In these cases, where CSA was given for 1 to 12 months in doses of 1–6 mg/kg/day, eczema and pruritus improved remarkably but temporarily, as relapses were seen within 3 days to 3 weeks after discontinuation. In a randomized, double-blind, placebo-controlled study of 20 subjects with AD, two weeks of topical CSA (100 mg/g) gave a significant improvement on treated sides when compared with placebo (11). As CSA primarily inhibits lymphokine production, such as interleukin-2 (IL-2) from the T-"helper" lymphocytes (12), it may be assumed that T lymphocytes play an important role in AD; but the mechanism is obscure.

The aim of the present investigation was to use CSA as a tool in an attempt to elucidate the mechanism of itch in AD. The effects of CSA were evaluated by itch recording, clinical scoring and skin biopsy specimens.

MATERIAL AND METHODS

Subjects

Ten adults (7 men and 3 women; median age 24; range 22–42 years) with stable and moderate or severe AD, fulfilling the criteria of Hanifin & Rajka (13) were included in the study. Median age at onset of eczema was 6 months (range 3 months – 10 years). All subjects suffered from a distressing pruritus, frequently disturbing sleep at night, and with a duration exceeding the previous 12 months. Nine had a past or present history of respiratory atopy, but none required regular pharmacotherapy because of this. The median serum IgE-level before the study was 2550 (range 60–8600) kU/l.

Exclusion criteria were age below 18, pregnancy or lactation, fertile female without contraception, earlier or present history of any other disease than atopy, acute uncontrolled infection, internal pharmacotherapy, internal corticosteroids for the previous 3 months, UV therapy during the previous month, pathological routine laboratory tests, drug or alcohol abuse, or suspicion of insufficient patient compliance. The study, which was approved by the Ethics Committee of Karolinska sjukhuset and the National Board of Health and Welfare, was performed during March–April.

Experimental design

All subjects were treated with CSA oral solution (100 mg/ml) in a dosage of 5 mg/kg/day and placebo (both kindly supplied by Sandoz AG, Basel, Switzerland), according to

a randomized double-blind cross-over design. Each period included 10 days' treatment separated by a 2–3-week washout interval. One week before, and during, each treatment period no topical corticosteroids more potent than hydrocortisone 1% were allowed. Indifferent emollients were permitted.

Clinical investigation

The patients were examined two days before (day −2), and twice during, each treatment period (days 5 and 10), i.e. on 6 occasions. Safety and efficacy variables were checked. The safety variables included medical history concerning AD and the exclusion criteria, physical examination, body weight, blood samples (hemoglobin, total blood-cell count, albumin, electrolytes, magnesium, creatinine, urea, uric acid, bilirubin, liver enzymes, alcaline phosphatases and finally CSA level in whole blood assessed with a specific monoclonal RIA technique [CYCLO-Trac® SP-Whole Blood, Incstar Corp., USA, (14)]), urine samples (protein, glucose, bacteria) and recording of side effects.

The efficacy of CSA was evaluated by recording itch intensity, scoring eczema, weighing of hydrocortisone cream tubes and examination of punch biopsies from involved and uninvolved skin.

Recording of itch intensity

Itch intensity was recorded using two different sampling methods, Symtrack® on days −2 to 5 and 9 to 10, and retrospective visual analogue scale (VAS) forms on days −2 to 10. The assessments from the first 2 days (days −2 and −1) constituted the subjects' baseline ('before') values.

Symtrack®, a new version developed from Pain-Track® (Autenta AB, Uppsala, Sweden), is a system for self-recording of subjective symptoms. It consists of portable VAS data-loggers for patients' use, a terminal unit and a software package for storage, analysis and presentation of data (for details, see refs. 1, 15). The technique is valid for the recording of clinical and experimental itch (15, 16). The main difference between the Pain-Track® and the new Symtrack® is that the seven-stepped scale has been replaced by a lever sliding along a 100-mm VAS (0 = no itch, 100 = maximal itch) for rating the itch intensity (at least every hour but also whenever desired). When the recording is completed, the data in the logger are transferred to a personal computer. The compliance of the recording can be calculated as the percentage of the patient's responses to a buzzer every hour. As an arbitrary choice, all days with a compliance below 70% were excluded. The clinical itch variables analysed were median and average itch intensity and percentage of time awake without itch.

At night before going to sleep the patient also rated retrospectively the 'global' itch intensity of that day, making a pen marking on a 100-mm VAS. The compliance was calculated as the proportion of forms completed.

Scoring of eczema

The extension and intensity of AD were scored by the same investigator (CFW) according to a 'twenty-area severity chart' (3), where the severity of eczema in each of 20 areas is assessed semiquantitatively by a 0–3 grading (no, mild, moderate or severe), giving a total score of 0–60.

Skin biopsies

Before, and on the last day of, each period, 4-mm punch biopsies were taken under local anesthesia (lidocain 20 mg/ml with epinephrine 12.5 μg/ml) from involved and uninvolved skin, i.e. 8 biopsies in total per subject. The biopsy specimen was divided into two parts, one for routine histological examination (hematoxylin-eosin staining) and one for immunohistochemical investigation. The lesional biopsies were taken from symmetrical lichenified plaques (posterior axillary fold, arm and/or buttocks), i.e. 'before' on one side and 'after' on the contralateral. The non-lesional biopsies were obtained from the same regions. The biopsies were taken with a minimum distance of 5 cm and an intervening period of 3–4 weeks from the preceding biopsies.

Immunohistochemical examination

The biopsy specimens were kept in Histocon® (Histolab, Gothenburg, Sweden) at +4°C (for less than 24 h) until they were snap-frozen in chilled isopentane and stored at −70°C. Acetone-fixed cryostat sections, 6 μm thick, were stained with a 3-stage monoclonal antibody peroxidase-anti-peroxidase (PAP) technique (17). The panel of monoclonal mouse antibodies (all from Becton Dickinson, Sunnyvale, CA, USA) included Leu-4 (working dilution: 1:256; cluster determinants: CD3; main cellular reactivity: pan T cells), Leu-3a (1:256; CD4; T-"helper/inducer" cells, some macrophages and Langerhans' cells), Leu-2a (1:32; CD8; T-"cytotoxic/suppressor" cells), anti-IL-2r (1:16, CD25; interleukin-2 receptor β-chain), Leu-6 (1:64; CD1a; Langerhans' cells) and anti-HLA-DR (1:128; activated T cells, B cells, macrophages, monocytes, Langerhans' cells). The peroxidase reaction was developed with 3-amino-9-ethylcarbazole and the sections were counterstained with Mayer's hematoxylin. The dilutions of antibodies were determined using sections from normal lymph nodes and skin. Specificity tests included omission of the primary antibodies, and staining was not observed in these tests. The examination was performed separately by two investigators (CFW, AS) under coded conditions. A minimum of two sections per antibody and biopsy were examined. Estima-

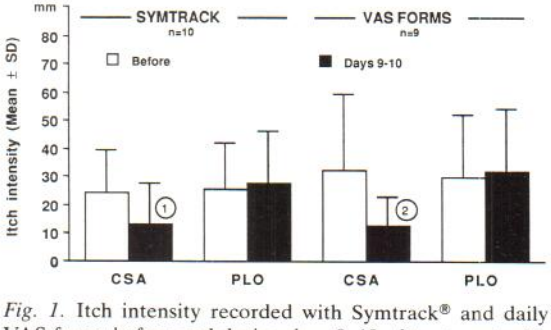


Fig. 1. Itch intensity recorded with Symtrack® and daily VAS forms before and during days 9–10 of treatment with cyclosporin A (CSA) 5 mg/kg/day or placebo (PLO) in patients with atopic dermatitis. (1) = significant decrease in relation to CSA 'before' ($p = 0.01$) and to PLO days 9–10 ($p < 0.05$). (2) = significant decrease in relation to CSA 'before' ($p = 0.02$) and to PLO days 9–10 ($p < 0.01$).

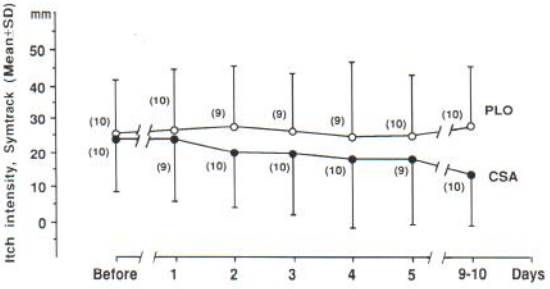


Fig. 2. Itch intensity day by day recorded with Symtrack® during treatment with cyclosporin A (CSA) 5 mg/kg/day or placebo (PLO) in patients with atopic dermatitis. Numbers of subjects in brackets.

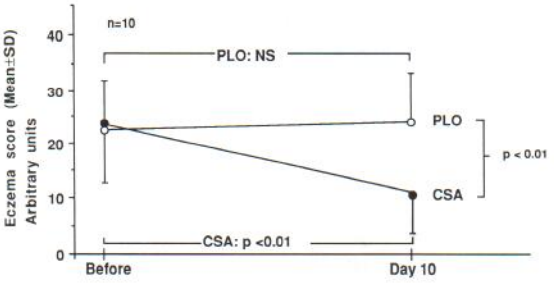


Fig. 3. Eczema scores before and on the 10th day of treatment with cyclosporin A (CSA) 5 mg/kg/day or placebo (PLO) in patients with atopic dermatitis. NS = not significant.

tion of the total amount of cells per section reactive with the different monoclonal antibodies was based on a semi-quantitative scale (0 = no, + = few, ++ = moderate, +++ = many). After uncodifying the specimens, the relative changes between 'before' and 'after' were expressed in terms of increase, decrease or no change of reactive cells per section.

Statistical analysis

Itch intensity, eczema score, hydrocortisone consumption, serum magnesium and number of blood eosinophils were analyzed using the non-parametric Wilcoxon signed-rank test.

RESULTS

Itch recording

Compliance. All 10 subjects completed the study. In total, 180 days were recorded with the Symtrack® system. The subjects' average compliance was 91±7% (range 80–99%). Five persons had one or more days with a compliance less than 70%, which meant that a total of 10/180 (5.6%) days were excluded. On 70/180 days (38.9%) the compliance was 100%. The VAS forms were completed for 220/240 days (91.7%), as 4 subjects failed to fill in their forms for a total of 20 days.

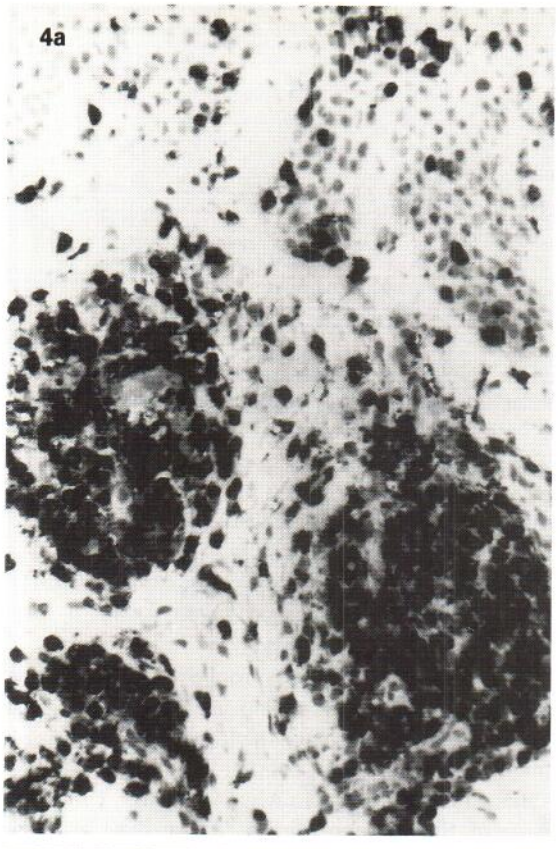
Itch intensity. The results from Symtrack® and the VAS forms were similar and are shown in Fig. 1. CSA significantly reduced the itch intensity on treatment days 9–10, when compared with the baseline value ('before') and also when compared with days 9–10 of the placebo period. An analysis of time awake without itch on days 9–10 of CSA therapy revealed that 4 subjects were completely free from itch, 2 had more than 90% of the day without itch, while 4 were never free from itch. With placebo, 9/10 patients were never free from itch. Fig. 2 shows the average itch intensity level day by day, as recorded by Symtrack®. The onset of the antipruritic effect of CSA varied. Six patients had an effect within days 2–4, whereas in 3 others the decrease in itch was

Table I. *Relative changes of reactive cells, as determined by immunoperoxidase staining of cryostat sections of skin biopsy specimens from lesional skin of 10 adults with atopic eczema, treated for 10 days with cyclosporin A (5 mg/kg/day) or placebo.*

Figures denote numbers of subjects.

Cluster determinants[a]	Cyclosporin A[b]			Placebo[b]		
	Decrease	Increase	Unchanged	Decrease	Increase	Unchanged
CD3	5	0	5	1	2	7
CD4	5	0	5	2	4	4
CD8	3	0	7	0	1	9
CD25	4	0	6	0	2	8
CD1a	3	3	4	3	4	3
HLA-DR	6	1	3	2	2	6

[a] See Material and Methods. [b] Comparison of values 'before' and 'after' the period.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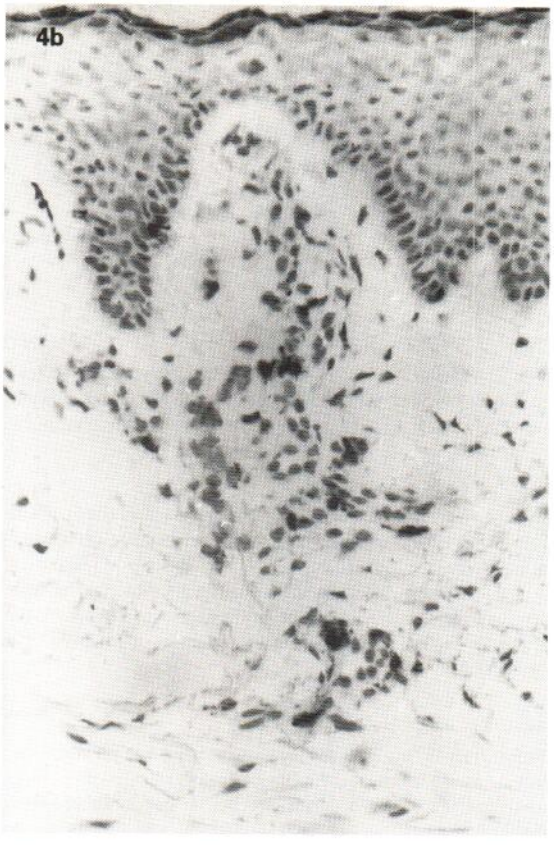
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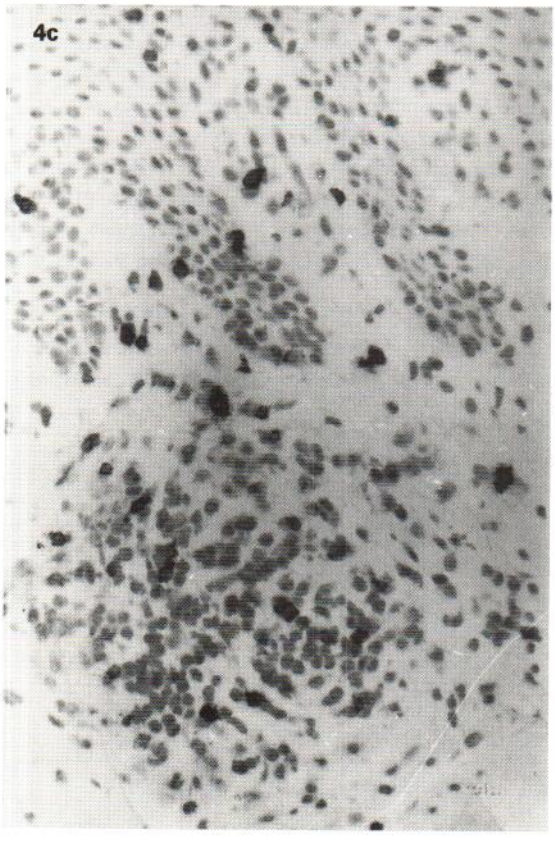
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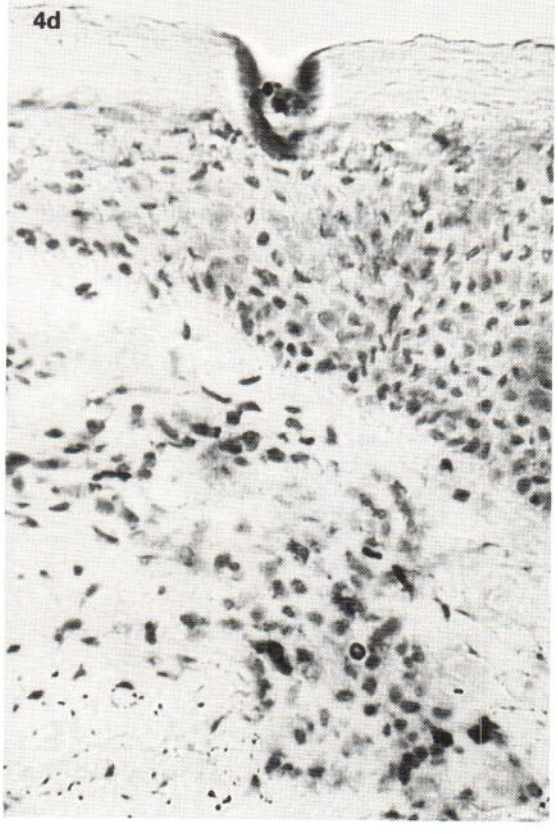
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Fig. 4. Immunoperoxidase staining of cryostat sections of skin biopsy specimens from lesional skin obtained before [*a, c*], and on the 10th day [*b, d*] of treatment with cyclosporin A 5 mg/kg/day in one patient. Monoclonal antibodies Leu-4 (CD3) [*a, b*] and anti-IL-2r (CD25) [*c, d*] were applied, respectively. The sections were counterstained with hematoxylin.

recorded on days 8–10. In one subject, however, the itch remained unchanged with no tendency to decrease.

Eczema

The eczema scores are shown in Fig. 3. CSA therapy improved all patients, including the one where no itch relief was achieved, and the eczema score was reduced significantly on the 10th day of treatment, when compared with the baseline value ('before'), and also when compared with the placebo value on day 10. No significant change was seen with placebo. Consistent with this, the consumption of topical hydrocortisone was significantly less ($p < 0.01$) with CSA (48.5 ± 47.3 g) than with placebo (90.7 ± 70.0 g).

Side effects and laboratory findings

After some days with CSA, 2 patients noticed a slight hand tremor and another felt a mild burning sensation in the hands and feet, the latter being also reported by a person while on placebo. Heart rate and blood pressure were unaffected. CSA induced a non-symptomatic, temporary but significant, decrease in serum magnesium ($p < 0.01$; baseline value: 0.79 ± 0.065 mmol/l, day 10: 0.65 ± 0.032 mmol/l, reference value: 0.75–1.00 mmol/l). Also, the total number of blood eosinophils decreased significantly ($p < 0.01$) with CSA, from the baseline value of $514.6 \times 10^6 \pm 211.6 \times 10^6$/l down to $279.5 \times 10^6 \pm 185.1 \times 10^6$/l on day 10 (reference value: $40 \times 10^6 - 540 \times 10^6$/l); whereas no significant change was seen during the placebo period. No significant alterations occurred in serum creatinine or urea. All subjects had taken CSA and no toxic CSA blood level was found. The average CSA whole-blood concentration 9–21 h after drug intake was 106.5 ± 43.6 ng/ml. No CSA was found in the samples from the placebo period.

Immunohistochemical examination

In the lesional skin biopsy specimens there were small-to-large cell infiltrates mainly perivascularly, as judged from hematoxylin-eosin-stained sections, except for one patient who displayed almost no cell infiltrates in 3 of 4 specimens. The majority of the infiltrating cells were CD3, CD4 and HLA-DR positive. The treatment results, presented as relative changes between 'before' and 'after' each course, are shown in Table I. CSA induced a relative decrease in the number of CD3+ cells in 5/10 subjects (Figs. 4 a and b). In these cases the reduction of CD4+ cells was more frequent than the reduction of CD8+ cells. CSA reduced the HLA-DR+ cells in 6/10 subjects. These patterns were not seen after the placebo period. The CD1a+ cells showed no distinct pattern of alteration during the 2 periods. The keratinocytes were all HLA-DR negative. The number of interleukin-2 receptor positive cells (CD25+) was decreased in 4/10 cases during CSA therapy (Figs. 4 c and d), but in no case with placebo. On the contrary, a 'rebound phenomenon' occurred during placebo in 2/5 patients previously on CSA.

The non-lesional skin biopsy specimens revealed a few scattered perivascular lymphocytes. Here neither CSA nor placebo induced any major changes of the phenotype expressions.

Clinical follow-up

In all cases a gradual relapse was seen 2–30 days after the discontinuation of active therapy. On follow-up investigations 2 and 8 months after CSA treatment, when most subjects were using potent topical corticosteroids and UV therapy, the average eczema score was 14.6 ± 6.3 (May–June) and 16.6 ± 9.8 (Nov–Dec), respectively. Repeated routine laboratory tests on these occasions revealed increased total blood eosinophils in some patients, but no other abnormality.

DISCUSSION

In this placebo-controlled short-term study we confirmed the previous reports (6–10) of the beneficial effects of oral CSA on itch and eczema in adult AD. Nine of 10 subjects had a decrease in itch intensity level within 10 days, the majority even within 2–4 days of the start of active therapy. The eczema scores decreased in all subjects, even in the one who did not experience any itch relief. The clinical impression was that the effect on erythema seemed more pronounced than the effect on induration, li-

chenification or scaling. This association between erythema and itch accords with the results of Graham & Wolf (18), who found that erythema followed by itch occurred in dermatitic sites in AD patients subjected to experimental stress interviews.

The baseline immunohistochemistry fitted well with earlier reports on the phenotype expressions in lesions of AD (e.g. 5). No correlation was found between the magnitude of change in itch intensity and the alterations in skin phenotype expression. A reduction of the cell infiltrate or any of the phenotype expressions examined did not seem to be necessary for itch relief during CSA therapy.

The exact mechanism of the antipruritic effect of CSA cannot be established by our study. CSA inhibits the production of IL-2 from T-"helper" cells, but also affects other cytokines, e.g. interleukin-1, colony-stimulating factor, macrophage-activating factor, macrophage-inhibiting factor, leukocyte-derived chemotactic factor and gamma-interferon (12, 19). A CSA-induced inhibition of 'pruritogenic cytokines' may be postulated, but hitherto no such substances have been identified. In a case of therapy-resistant Sézary syndrome, prompt suppression of intolerable pruritus was achieved using CSA (20). In an experimental study of the possible pruritogenic effect of cytokines (unpublished), we stimulated peripheral mononuclear cells with concanavalin A. After culture for 24–120 h in autologous serum, lymphocyte activation was confirmed with [^{3}H]-thymidine incorporation. When the sterile-filtered, dialyzed and ultracentrifugated supernatants from stimulated or non-stimulated cultures were injected intradermally back to the donor, no clinical reaction or itch was observed. In leprosy patients, however, intradermally injected human recombinant IL-2 (30–90 kU) provoked induration (21) and also localized pruritus (Kiessling R, personal communication). Further, Gaspari et al. (22) investigated cancer patients (e.g. metastatic renal or colonic cancer) receiving intravenous IL-2 therapy (30–100 kU/kg/8h). After 2–3 days of treatment, erythema with burning sensations and pruritus of the skin frequently developed, followed by desquamation after cessation of infusion of IL-2. Immunohistochemistry of lesional skin biopsies in Gaspari's study showed perivascular activated (HLA-DR+) T cells in papillary dermis. Moreover, a peripheral blood eosinophilia was observed in association with IL-2 infusion (22). In vitro studies suggest that human T lymphocytes from eosinophilic patients can produce interleukin-5 (IL-5) on IL-2 stimulation (23). IL-5 stimulates eosinophil colony formation (e.g. 23). Experiments in the rat show that CSA can abolish hypereosinophilia (24). As IL-2-provoked erythema and itch are not reduced by indomethacin or antihistamines, prostaglandins or histamine are unlikely to be the major cause of these symptoms (22). We do not consider histamine to be of any major importance in the pathogenesis of itch in AD (1). CSA increases the skin response to intradermally injected histamine (25) and does not inhibit the cutaneous response to prick test with house dust mite antigen in AD (9).

The mechanism of the antipruritic effect of CSA still remains unclear, as CSA may have widespread pharmacological actions (26). However, since it is known that human IL-2 therapy provokes itch as a side-effect (22) and that CSA inhibits the production of cytokines (12, 19), we suggest the existence of 'pruritogenic cytokines' that are of importance, directly or indirectly, in the pathogenesis of itch in AD.

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