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Long-term Follow-up of Eczema Patients Treated with Cyclosporine

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Cyclosporine is efficacious in short-term treatment of various eczematous disorders. In a follow-up study we have evaluated the long-term efficacy of cyclosporine in 75 patients, who in previous studies had been treated with cyclosporine for chronic actinic dermatitis (6 patients), atopic dermatitis (42 patients) and chronic hand eczema (27 patients), 4, 2 and 1 year after the initial treatment, respectively. Three out of 6 patients with chronic actinic dermatitis showed long-term efficacy. Two years after the initial treatment with cyclosporine (5 mg/kg/day for 1–2 treatment periods of 6 weeks) for atopic dermatitis the mean disease activity was significantly lower compared to baseline (58% decrease), and compared to the time of treatment stop no significant change had occurred. Of 37 evaluable patients 35 were still in remission. One year after the initial treatment with cyclosporine (3 mg/kg/day for 6 weeks) for chronic hand eczema the mean disease activity was significantly lower than at baseline (54% decrease), and compared to the time of treatment stop no significant change had occurred. Of 27 evaluable patients 21 patients were still in remission. The study suggests that long-term remissions are possible in eczematous diseases treated with cyclosporine, even for a relatively short treatment period. It must be stressed, however, that we did not have control groups for any of the studied patient groups. *Key words: chronic actinic dermatitis; atopic dermatitis; contact dermatitis; long-term efficacy*.

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Cyclosporine has proved to be effective in the induction of remission in various eczematous diseases, like atopic dermatitis (1, 2), chronic hand eczema (3, 4) and chronic actinic dermatitis (5). Usually the relapse of the disease after stopping cyclosporine is rather rapid in a majority of the patients (6). However, there are also data suggesting long-term efficacy of cyclosporine in atopic dermatitis (6, 7).

The natural course of various eczematous diseases in adults is not very well known. Nor is the influence of various treatments on the course of the disease well documented. To evaluate the possibility of long-term efficacy of cyclosporine we have evaluated, in a follow-up study, the clinical status of patients who took part in three previous studies on short-course cyclosporine treatment in chronic eczematous diseases (4, 5, 6).

METHODS

Patients

Patients who had participated in previous clinical studies were studied. Altogether 75 patients had been treated with cyclosporine in 3 different studies on cyclosporine treatment of eczematous diseases: 4 patients with chronic actinic dermatitis (CAD), 42 patients with atopic dermatitis (AD) and 27 patients with chronic hand eczema. Two patients with CAD, who were treated after the publication of the study on cyclosporine in CAD (5), were also included in this study.

The patients with CAD were examined 4 years after the initial treatment. They had been treated with an initial cyclosporine dose of 2.5 mg/kg/day, which was adjusted according to clinical response (mean dose 1.9 mg/kg/day) for 4 to 26 weeks (mean duration 6 weeks) (5). The patients with AD were examined 2 years after the initial treatment. All these patients had been treated with a fixed dose of 5 mg/kg/day in one or two cycles of 6 weeks (6). The patients with hand eczema were examined 1 year after the initial treatment. They had participated in a study (4) where they had been treated with 3 mg/kg/day of cyclosporine for 6 weeks.

Assessments

CAD. The present disease signs and symptoms as well as a history of clinical status and treatments were recorded. The treatment was judged as having long-term efficacy if the disease did not require retreatment with cyclosporine within 1 year after the initial treatment.

AD. A history of treatments (topical or systemic corticosteroids, cyclosporine or other immunosuppressive agents, UV treatments, antimicrobic agents, antihistamines) and the appearance of new diseases since the last visit were recorded. Disease activity, extent of disease, itch and sleep disturbances were assessed as described in the primary study (6). Briefly, for the assessment of disease activity six regions (head and neck, trunk, hands, feet, elbows and knees) were assessed for erythema, pus, excoriation/crusting, dryness/scaling, cracking/fissuring and lichenification on a scale from 0 (none) to 3 (severe). The maximum possible score was 108. For the assessment of the extent of the disease the total body area was divided into nine regions, in which the affected area was estimated to comprise none, a third, two thirds, or all of the region. The symptoms of itch and sleep disturbances were documented using a visual linear analogue scale (0–100 mm). The patients were also asked to judge whether their disease and perception of itch were worse, unchanged or better compared to the previous visit 1 year earlier.

Chronic hand eczema. A history of treatments and the appearance of new diseases were recorded, as in the patients with AD. Disease activity, extent of disease, itch and sleep disturbance were assessed as described in the primary study (4). Briefly, for the assessment of disease activity each hand was scored for signs of erythema, scaling, infiltration, excoriation, crusting and vesicles on a scale from 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe), giving a maximum possible score of $6 \times 3 \times 2 = 36$. For the assessment of the extent of disease the area of each aspect of each hand was considered as 25% (100% = both aspects of both hands). The symptoms of itch and sleep disturbances were documented using a visual linear analogue scale (0–100 mm). As for the AD patients the patient were also asked to judge whether their disease and perception of itch were worse, unchanged or better compared to the previous visit 1 year earlier.

Statistics

Results for patients with CAD were tabulated and for patients with AD and chronic hand eczema given as the mean (±SD; 95% CI). The main efficacy variable in AD and chronic hand eczema patients was the disease activity. Statistical analysis for continuous variables was made with the use of a Wilcoxon signed rank test, as all variables did

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not have a strictly normal distribution. Categorical data were analysed with McNemar's test. *P*-values <0.05 were considered significant.

RESULTS

CAD

Three out of 6 patients were considered to have experienced long-term efficacy (Table I). Of these one patient had had a new treatment cycle with cyclosporine but not until 4 years after the initial treatment and another patient had been treated twice with cyclosporine during the follow-up period. Two of those 3 patients who did not achieve long-term efficacy were successfully treated with cyclosporine every summer.

AD

As 4 patients were unavailable for examination, 38 patients of those 42 initially enrolled were evaluable. Two years after the initial treatment with cyclosporine all assessed variables were significantly ($p<0.001$) lower compared to baseline (data for disease activity and itch are shown in Fig. 1). The mean ($\pm$SD; 95% CI) change in the disease activity from baseline was -18.1(9.9; -14.8 to -21.3). On the other hand, compared to the time of treatment stop there was no significant change in any of the efficacy variables. The slight deterioration noted at 1 year after treatment had reversed, as shown by a decrease in the disease activity ($p<0.001$) and itch ($p<0.05$). Using the same criteria for relapse as in the initial study (disease activity $\geq$75% of the patient's own baseline value), 35 patients were in remission. In the overall assessment 79% of the patients thought they were in better condition than the year before, and 74% considered that their itch was less severe (Table II). Compared to both baseline and 1 year after treatment a significantly smaller number of patients had been treated with UV therapy and antimicrobic agents. The use of systemic steroids and antihistamines had slightly decreased. However, a switch to the use of more potent topical corticosteroids had occurred. Both findings were significant. During the first year after treatment stop 14% but during the second year only 8% of the patients had been treated with cyclosporine.

Chronic hand eczema

Twenty-seven of the enrolled patients with chronic hand eczema had been treated with cyclosporine and all were evaluable. One year after the initial treatment with cyclosporine all assessed variables were significantly lower compared to baseline (data for disease activity and itch are shown in Fig. 2). The mean

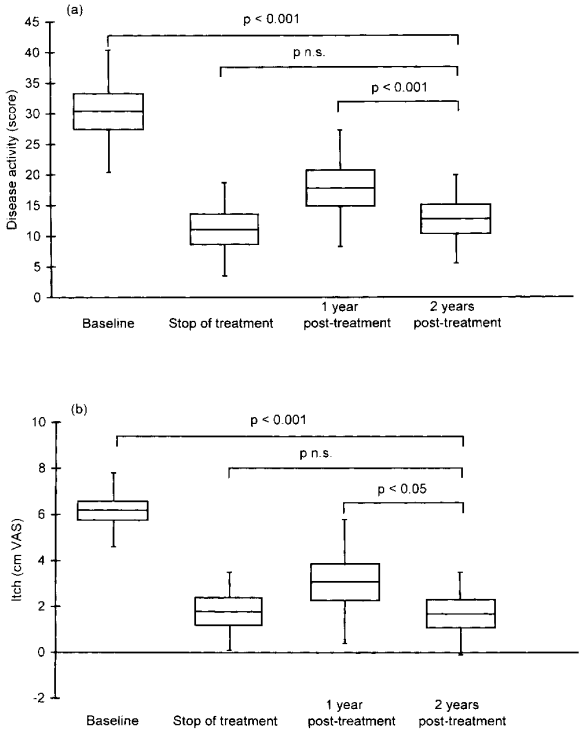

Fig. 1. Disease activity and itch in patients with atopic dermatitis treated with cyclosporine (old formulation) for 6 weeks at a dose of 5 mg/kg/day. *Boxes* indicate 95% confidence intervals and *bars* $\pm$SD.

($\pm$SD; 95% CI) change in the disease activity from baseline was -7 (5; -5 to -9). Compared to the situation immediately after treatment there was no change in disease severity measured with any of the efficacy variables. Using the same criteria for relapse as in the initial study (disease activity $\geq$75% of the patient's own baseline value), 21 patients were in remission. A significantly smaller proportion of the patients had required treatment as in-patients or had been on sick leave during the year after treatment, compared to the situation 1 year before treatment (Table II). There had also been a switch to the use of less potent topical corticosteroids. No patient had been treated with cyclosporine during the follow-up period.

DISCUSSION

This study suggests that long-term remissions are possible in eczematous diseases treated with cyclosporine even for a short

Table I. *Long-term efficacy in patients with chronic actinic dermatitis treated with cyclosporine*

			Response			
Case	Dose mg/kg/day	Duration weeks	Overall	Initial relapse	Follow-up (4 years)	Long-term efficacy
1	2.5→1.5	14	Good	1 week	Need for retreatment after 4 years, treated with success	Yes
2	2.5→3.0	8	Good	2 weeks	Retreated with success 2 summer seasons, symptomless – 94	Yes
3	2.5→1.5	8	Moderate	1 month	Retreated several summer seasons with moderate success	No
4	2.5→1.5	4	Good	6 months	Slight relapse after 10 months, manages now without cyclosporine	Yes
5	2→3	5	Poor	N.A.	N.A.	N.A.
6	3→4	26	Good	4 months	Retreated every year from March to October	No

Table II. *Characteristics of patients*

Values number of patients (% of study population).

Characteristic	Atopic dermatitis			Hand eczema	
	Baseline	1 year	2 year	Baseline	1 year
Number of patients	42	42	38	37	37
Disease activity compared to baseline judged by the patient					
Better		32 (76)	30 (79)		20 (74)
Unchanged		3 (7)	1 (3)		1 (4)
Worse		7 (17)	7 (18)		6 (22)
Itch compared to baseline judged by the patient					
Less		27 (64)	28 (74)		17 (63)
Unchanged		2 (5)	1 (3)		2 (7)
More		13 (31)	9 (24)		8 (30)
Treated as in-patient	7 (17)	4 (10)	0 (0)***,‡	2 (7)	0 (0)*
On sick leave within 1 year	ND	ND	ND	13 (48)	7 (26)**
Treatments used					
Topical corticosteroids					
Mild (e.g. hydrocortisone)	30 (71)	37 (88)	21 (55)*,¶	0 (0)	7 (26)***
Moderate (e.g. desonide)	18 (43)	8 (19)	4 (11)***	4 (15)	1 (4)**
Strong (e.g. betamethasone)	5 (12)	4 (10)	8 (21) †	27 (100)	12 (44)***
Very strong (e.g. halsionide)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Systemic corticosteroids	5 (12)	5 (12)	2 (5)	2 (7)	2 (7)
PUVA	ND	0 (0)	0 (0)	1 (4)	4 (15)
UVB	ND	1 (2)	0 (0)	1 (4)	0 (0)
SUP	13 (30)	21 (50)	3 (8)***,¶	2 (7)	1 (4)
Antimicrobic agents	19 (45)	23 (32)	5 (13)***,‡	11 (41)	5 (19)**
Antihistamines	15 (36)	27 (64)	18 (47) †	ND	7 (26)
Other	ND	6 (14)	3 (8)	3 (11)	0 (0)***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to baseline (McNemars test).
† $p<0.05$, ‡ $p<0.01$, ¶ $p<0.001$ compared to 1 year follow-up (McNemars test).

treatment period of 4–26 weeks. Half of the patients with CAD experienced long-term efficacy for 1 to 4 years, and a great majority of the patients with AD and chronic hand eczema were in remission (as initially defined) 2 and 1 year, respectively, after a relatively short course of cyclosporine. The mean disease activity was lower than before treatment, whether assessed by the investigator (disease activity score, extent of disease) or the patient (itch, sleep disturbances). Four AD patients had at least once used a more potent topical corticosteroid between 1 and 2 years of follow-up than during the year before. As the actual amount of used corticosteroid was not measured, the impact of this switch on the outcome is not possible to predict. However, the number of patients was small and calculation of the mean disease activity without these patients did not change the outcome in a significant way. At follow-up all patients were seen by the same dermatologist as in the original study, ensuring continuity in assessments but also a possibility for bias because of the open design. It must also be stressed that we did not have appropriate control groups for any of the studied patient groups.

The natural courses of these diseases are not well known. In AD most of the available data on natural course concerns the fate of atopy in the transition from child to adolescense (8–10). According to these follow-up studies 40–91% of children with AD still have dermatitis in adolescense. However, we do not know much about the further natural course of the disease in these patients who continue to have dermatitis as adults. Spontaneous remissions even for several years do occur (11), which must be remembered when conclusions concerning long-term efficacy are drawn from uncontrolled studies like the present study. All our patients had severe AD, i.e. a disease severity scoring of at least 8 out of maximal 9 scores according to Rajka & Langeland (12). Chronic hand eczema is a long-lasting disease with relapsing course. In a survey from Sweden the mean duration of hand eczema was 12 years, but 66% of the patients had eczema-free intervals (13, 14). Only about a third of patients with contact dermatitis clear completely (15–18). CAD is generally long-lasting but may occasionally slowly remit (19). Toonstra et al. followed up 16 patients for 11 years (20). Nine patients required continuous treatment with UVB radiation and all 6 patients who stopped maintenance treatment relapsed.

However, these data on the "natural course" of the disease include patients who actually have been treated with conventional methods. The influence of treatment in this sense is impossible to estimate. In clinical trials there is a possibility to evaluate the influence of the treatment on the course of the disease. Unfortunately few clinical trials are extended by follow-up to measure the time to relapse and to estimate a possible long-term efficacy. PUVA-treated patients with hand eczema have been followed up for various time periods (3 weeks to 5 years) in a number of small-sized studies (21–23). In these studies the disease relapsed within 1–8 months in a majority of the patients. Nevertheless, it would be important to evaluate the possible long-term efficacy of various treatments as we are dealing with chronic diseases and treatments with potentially serious side-effects. A diminished disease activity even without complete clearance after a short course of treatment can be of considerable importance for the patient.

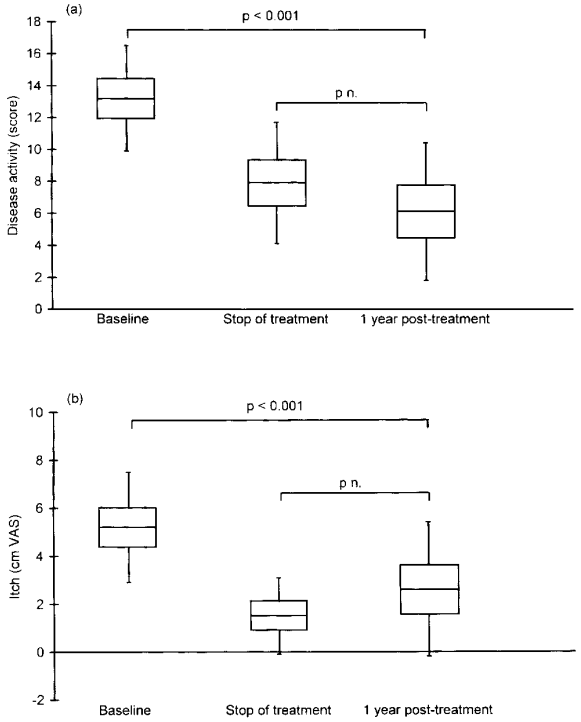

Fig. 2. Disease activity and itch in patients with chronic hand eczema treated with cyclosporine (old formulation) for 6 weeks at a dose of 3 mg/kg/day. *Boxes* indicate 95% confidence intervals and *bars* ±SD.

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