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CLINICAL REPORT

Comparison of Cyclosporin and UVAB Phototherapy for Intermittent One-year Treatment of Atopic Dermatitis

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Although cyclosporin is effective for the treatment of severe atopic dermatitis, phototherapy is the standard second-line treatment for this disease. An open, randomized, controlled, parallel-group study was conducted to compare the efficacy, influence on quality of life and safety of cyclosporin and UVAB phototherapy during 1 year of intermittent treatment of atopic dermatitis in adult patients. The main endpoints of the study were the number of days in remission and the influence on quality of life. Seventy-two patients were treated, 36 in each group. Cyclosporin produced significantly more days in remission than UVAB phototherapy during the 1-year study period. At the end of the study no difference between the 2 groups was noted in terms of quality of life. A significant increase in serum creatinine occurred in 2 patients and 7 patients developed mild or moderate hypertension during cyclosporin treatment. It can be concluded that intermittent cyclosporin seems to be more effective than UVAB and is reasonably safe for the treatment of atopic dermatitis over a 1-year treatment period. ***Key words: cyclosporin; UVAB; atopic dermatitis; quality of life.***

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Atopic dermatitis generally responds well to treatment with topical corticosteroids. If adequate topical therapy fails, phototherapy constitutes the standard second-line treatment. UVAB seems to be the most suitable form of phototherapy for treatment of atopic dermatitis (1). However, phototherapy is time-consuming as it requires regular treatment visits. It is contraindicated in patients with photosensitivity and is ineffective in some patients.

Cyclosporin has shown efficacy in the treatment of severe atopic dermatitis (2–4). Usually the disease relapses rapidly on withdrawal of cyclosporin, but not in all patients (4). Furthermore, cyclosporin maintains its efficacy when re-instituted, which makes intermittent treatment a possible treatment approach (4). Intermittent treatment with short courses of cyclosporin might decrease the incidence of cyclosporin side effects.

Cyclosporin has not been compared with standard secondary treatment, i.e. phototherapy, which is the natural preceding treatment before the institution of cyclosporin. The objectives of this study were to compare the efficacy, safety, tolerability and influence on quality of life of cyclosporin and UVAB in the treatment of adult atopic dermatitis.

MATERIAL AND METHODS

The study was an open, randomized, controlled, parallel-group study with 2 treatment limbs and was conducted as a multicentre study in 1 Finnish (Helsinki University Central Hospital, Helsinki) and 4 Norwegian centres (Rikshospitalet Oslo, Ullevål, Haukeland, Bodø). The study protocol was approved by the Ethics Committee at each centre. The study was conducted in compliance with good clinical practice guidelines (CPMP Working Party on Safety in Medicinal Products, Brussels, 1990; U.S. Code of Federal Regulations dealing with clinical studies) and the Declaration of Helsinki ("Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects", Helsinki, 1964). Written informed consent was obtained from all patients after the study had been fully explained to them.

Study population

Adult patients aged between 18 and 70 years with atopic dermatitis diagnosed according to the criteria outlined by Hanifin & Rajka (5) and with a disease severity of 7–9 according to Rajka & Langeland (6) were considered eligible for the study. Patients who had been treated with systemic corticosteroids, cyclosporin or UVAB within the 2 weeks prior to entry into the study were excluded, as were patients with photosensitivity or skin type I and patients using drugs known to be photosensitizers. In addition, other standard exclusion criteria for patients undergoing cyclosporin treatment were used (4, 7–8).

Study protocol

Patients were randomly allocated to either the cyclosporin or UVAB treatment arms. In both arms, the treatment was administered intermittently with a treatment period of 8 weeks (treatment phase) followed by a period of only topical treatment (remission phase). The remission phase continued until relapse, or at least for 2 weeks. One treatment phase and the following remission phase constituted a treatment cycle. The total study time was 12 months and contained as many treatment cycles as needed to keep the patient in remission.

In the first treatment cycle visits were made biweekly, and during subsequent cycles monthly. However, in the remission phase the first visit was made after 2 weeks and then every 4 weeks in all following cycles.

Assessments of clinical efficacy

Clinical efficacy was assessed using the SCORAD method (9). This scoring index combines clinical signs (disease intensity, extent of disease) and symptoms (itching, sleep disturbance) giving a maximum score of 103 and has been validated for inter-observer variability (10). SCORAD assessments were made at each visit. Remission was

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defined as a reduction in disease activity assessed by SCORAD to $\leq 50\%$ of the patient's baseline value. Relapse was defined as an increase in SCORAD to $>50\%$ of the patient's baseline value.

The primary efficacy variable was the number of days in remission based on SCORAD values and was estimated by counting days following remission visits until the next visit (method A) or days proceeding a remission visit since the previous visit (method B). The area under the curve of number of days in remission vs. time was calculated by linear trapezoidal summation.

Secondary clinical efficacy assessments were measurements of the use of emollients and topical corticosteroids and an overall assessment of efficacy made by both the patient and investigator at the end of each treatment phase on a scale from 1 to 5 (1= very good, 2= good, 3= moderate, 4= slight, 5= none).

Assessment of quality of life

The Eczema Disability Index (EDI) (11) was used to measure the influence on quality of life. This questionnaire consists of 15 questions answered on a combined categorical and linear analogue scale from 0 to 6, representing grades from "not at all" to "very much". The questions represent 5 different dimensions of quality of life: daily activity (5 items), work and school (3 items), personal relationships (2 items), leisure (4 items) and treatment (1 item). The EDI has been externally validated against the United Kingdom Sickness Impact Profile, a general quality-of-life instrument, and also against clinical variables (11). Measurements were performed at baseline, at weeks 4 and 8 in the first treatment cycle and at the end of the study.

Safety assessments

The evaluation of safety involved physical examination, recording of vital signs and laboratory examinations. The following laboratory examinations were performed at baseline and at the end of the study: serum creatinine, potassium, urea, uric acid, aspartate aminotransferase, total bilirubin, haemoglobin, thrombocytes, leukocytes, sedimentation rate, total IgE and absolute eosinophils. In the cyclosporin group, serum creatinine was controlled 5 times during the first cycle and 3 times during the subsequent cycles and the rest of the biochemical variables were controlled 3 and 2 times during the first and subsequent cycles, respectively. In the UVAB group the recording of vital signs and laboratory examinations were performed only at baseline and at the end of the study.

Subjective and objective signs and symptoms of adverse events were recorded at each visit. The severity (assessed as mild, moderate or severe), frequency of occurrence, relation to and influence on treatment were recorded by the investigator. At the end of each treatment phase the overall tolerability to treatment was recorded separately by both patient and investigator on a scale of 1–5, identical to that used for overall efficacy.

Treatments

The new microemulsion form of cyclosporin was used, with an initial dose of 4 mg/kg/day. During the first 2 treatment cycles the dose was either increased or decreased at each scheduled visit in increments of 1 mg/kg/day according to the response. The lowest dose used was 1 mg/kg/day and the maximum dose was 4 mg/kg/day. The second treatment phase was initiated using the lowest effective dose from the first treatment phase. The lowest effective dose in the second cycle was chosen as a constant maintenance dose in subsequent cycles.

In the case of significant adverse events, the dose of cyclosporin was decreased or treatment discontinued in agreement with protocols used in earlier studies (4, 7, 8).

A Waldmann UV 8001 K phototherapy cabin was used as the source of UV radiation. The initial dose depended on the patient's skin type and on previous experience with UVAB therapy. Successive dose increments were performed at every other treatment visit according to a standard treatment schedule, up to maximal doses of 15 J/cm^2 of UVA and 0.26 J/cm^2 of UVB. If remission occurred before the maximal dose was achieved no further dose increments were performed. If erythema appeared the dose was reduced to the preceding dose. Treatment was administered 2–3 times a week. It was intended that patients should have at least 16 visits/cycle and no more than 1 cycle was allowed to be incomplete. The same treatment schedule was used in all treatment phases. UVAB treatment was stopped in cases of inefficacy, if relevant side effects were observed, at the wish of the patient, in cases of lack of compliance and if the investigator believed that continuation was detrimental to the patient's health.

Topical non-halogenated corticosteroids not stronger than hydrocortisone-17-butyrate were allowed in order to keep patients in remission. The patients were encouraged to use emollients as needed.

Statistics

For statistical evaluations all patients who received at least 1 dose of cyclosporin or at least one UVAB treatment, and those patients who had at least one efficacy or safety evaluation after baseline constituted the "safety" and "intention-to-treat" populations, respectively. All patients who were evaluated at baseline and at least at week 8 in the first cycle constituted the "Cycle 1 treatment phase completers" population.

The primary efficacy endpoint was the number of days in remission. The results are expressed as the mean ($\pm$SD; 95% CI) and mean change ($\pm$SD; 95% CI) from baseline. Baseline characteristics, overall outcomes and assessments and relapse rates were expressed as proportions.

A sample size of 32+ 32 patients was calculated based on a binomial distribution assuming $\beta = 0.20$ (power= 80%) and $\alpha = 0.05$ with a directed hypothesis, ensuring at least 26+ 26 patients at the end of the study. All analyses were made on an intention-to-treat basis. Analysis of continuous variables (SCORAD, remission days, use of emollients and topical corticosteroids, EDI) was performed using Student's *t*-test for between-group comparisons based on mean values and a paired *t*-test for intergroup comparisons based on mean change values. The dichotomous variables (baseline characteristics, overall assessments of efficacy and tolerability) were tested using a χ^2 test or Fisher's exact test depending on the hypothesis.

RESULTS

Of 79 patients screened, 72 were eligible for randomization into 2 treatment groups: 36 in each. Seven screened patients did not meet the inclusion criteria at randomization and were excluded. One patient randomized to the UVAB group never appeared for treatment and was excluded.

Twenty-four patients discontinued treatment prematurely: 4 in the cyclosporin group and 20 in the UVAB treatment group. Treatment failure was the main reason for withdrawal and all 6 cases occurred in the UVAB group. Adverse events caused withdrawal in 4 patients: 1 on cyclosporin and 3 on UVAB. Other reasons for withdrawal were mostly protocol violations due to lack of adherence to the treatment schedule or other practical difficulties with treatment. These occurred in 3 patients on cyclosporin and 11 on UVAB.

Major protocol deviations not resulting in premature withdrawal occurred in 13 patients (8 in the cyclosporin group and 4 in the UVAB group). In most cases the reason was a delay in the initiation of new treatment cycles on relapse. However, the delay was usually short, i.e. 2–4 weeks, and was judged not to have any great impact on the evaluation.

Baseline demographics and background characteristics

Except for concomitant asthma, which was more common in the cyclosporin group, no significant differences in demographics, previous therapy or severity grading were noted at baseline (Table I).

Induction of remission

In all cycles, except for the last, the disease activity measured by changes in SCORAD decreased significantly more rapidly in the cyclosporin group compared to the UVAB group (Table II). In the first 2 treatment cycles cyclosporin maintained its superiority over UVAB at the termination of treatment. However, in subsequent cycles the difference in disease activity between the 2 treatment groups disappeared towards the end of each cycle, although cyclosporin was still significantly more rapid at inducing remission than UVAB. At the first post-treatment visit (week 10) in each cycle, no significant difference in disease activity could be seen between the treatment groups, indicating a similar relapse rate in both groups. Including only "Cycle 1 treatment phase completers" in the analysis did not change the results in the first treatment cycle.

Table I. *Baseline demographics and characteristics. The values are expressed as mean ± SD unless otherwise stated*

Characteristic	Cyclosporin	UVAB
Age (years)	33.3 ± 12.2	33.2 ± 10.6
No. of males/females	21/15	14/21
No. (%) of patients with other atopic disorders		
Allergic conjunctivitis	24 (67)	22 (63)
Allergic rhinitis	25 (69)	20 (57)
Asthma bronchiale	14 (39)	6 (17)*
No. (%) of patients with family history of atopy	24 (69)	28 (80)
No. (%) of patients with positive prick test[a]	17 (63)	20 (77)
Duration of disease (years)	30.3 ± 11.8	30.0 ± 10.9
Severity score[b]	7.8 ± 0.8	7.7 ± 1.0
SCORAD	48.5 ± 12.7	46.8 ± 15.3
Total EDI[c]	30.5 ± 13.5	32.4 ± 18.9
No. (%) of patients using		
Topical corticosteroids		
group I[d]	10 (28)	11 (32)
group II	9 (27)	10 (34)
group III	14 (42)	11 (38)
group IV	0 (0)	0 (0)
Systemic corticosteroids	6 (17)	5 (14)
SUP	23 (64)	24 (69)
UVB	0 (0)	2 (6)
PUVA	1 (3)	0 (0)
Antihistamines	3 (8)	7 (20)

*$\chi^2 = 4.148$, $p < 0.05$ (cyclosporin versus UVAB).
[a]Number of patients with available data: 27 in the cyclosporin group and 26 in the UVAB group.
[b]According to Rajka and Langeland (6).
[c]Eczema Disability Index (11).
[d]Classification of topical corticosteroids: Group I = mild, group II = moderate, group III = strong, group IV = very strong. The patient was classified according to the most potent corticosteroid used.
SUP = selective ultraviolet phototherapy; UVB = ultraviolet-B therapy; PUVA = photochemotherapy.

Table II. *Changes in SCORAD from baseline (± SD)*

Time point of assessment	Cyclosporin		UVAB		p*
	No. of patients	Mean change	No. of patients	Mean change	
Cycle 1					
Week 2	36	−26 ± 11	34	−8 ± 9	<0.001
Week 4	36	−27 ± 10	34	−11 ± 12	<0.001
Week 6	36	−26 ± 12	31	−14 ± 14	<0.001
Week 8	35	−26 ± 13	30	−16 ± 13	<0.01
Week 10[a]	33	−12 ± 15	27	−19 ± 13	n.s.
Cycle 2					
Week 4	33	−25 ± 12	20	−14 ± 14	<0.01
Week 8	32	−27 ± 14	18	−18 ± 10	<0.05
Week 10[a]	31	−16 ± 17	16	−21 ± 14	n.s.
Cycle 3					
Week 4	28	−25 ± 13	111	−12 ± 15	<0.01
Week 8	27	−28 ± 12	10	−19 ± 16	n.s.
Week 10[a]	27	−11 ± 16	9	−20 ± 11	n.s.
Cycle 4					
Week 4	24	−25 ± 11	6	−13 ± 13	<0.05
Week 8	24	−30 ± 9	6	−18 ± 16	<0.05
Week 10[a]	24	−14 ± 13	6	−10 ± 18	n.s.
Cycle 5					
Week 4	17	−24 ± 15	2	−32 ± 0	n.s.
Week 8	16	−27 ± 14	2	−27 ± 5	n.s.
Week 10[a]	14	−18 ± 14	2	−29 ± 7	n.s.
End of study	36	−18 ± 17	34	−16 ± 16	n.s.

*Student's t-test.
[a]Two weeks off treatment.

Number of days in remission

Patients on cyclosporin had significantly more days in remission than patients on UVAB, regardless of the calculation method used (Table III). However, there were more treatment cycles and therapy visits in the cyclosporin group, which reflects the much larger number of withdrawals in the UVAB group. A corollary of this was the significantly longer participation in the study by patients in the cyclosporin group. In order to exclude the impact of the early withdrawals

Table III. *Time in remission. Values are given as mean ± SD*

	Cyclosporin (n = 36)	UVAB (n = 30)	p*
No. of remission days	186 ± 84	114 ± 118	<0.01
Total no. of days in study	354 ± 70	237 ± 141	<0.001
Percent days in remission A[a]	55 ± 23	38 ± 32	<0.05
Percent days in remission B[b]	60 ± 24	37 ± 32	<0.01
No. of therapy visits	17 ± 3	12 ± 6	<0.001
No. of remission visits	9 ± 4	5 ± 5	<0.001
AUC[c]	22 ± 8	30 ± 14	<0.01

*Student's t-test.
[a]Estimated by counting days following remission visits until the next visit.
[b]Estimated by counting days proceeding a remission visit since the previous visit.
[c]Area under the curve; calculated by linear trapezoidal summation.

on the results the same calculations were performed for the "Cycle 1 treatment phase completers" population. This did not change the significance of the result (data not shown).

Use of emollients and topical corticosteroids

The change in the use of emollients and topical corticosteroids was calculated for cycle 1. While the use of emollients decreased in the cyclosporin group (mean change -75 ± 166 g at week 8) it increased in the UVAB group ($+41 \pm 287$) ($p < 0.01$). The use of topical corticosteroids decreased in both groups: -45 ± 74 and -43 ± 99 g in the cyclosporin and UVAB groups, respectively.

Overall assessment of efficacy

In the first treatment cycle the overall effect of treatment was rated as "very good" or "good" by 86% and 60% of the patients in the cyclosporin and UVAB groups, respectively. Corresponding rates given by the investigators were 91% and 44%. Both results are significant ($p < 0.001$; Wilcoxon). In subsequent cycles no significant differences in overall ratings were observed.

Quality-of-life assessment

During the first 4 weeks of treatment the improvement in quality of life as measured by the EDI was significantly more pronounced in the cyclosporin group compared to the UVAB group (Table IV). However, at the end of the study no difference in the perception of the quality of life was seen between the treatment groups, although it must be noted that the patients reached the end of the study at different stages of the study, i.e. some immediately after a treatment phase and others after a variable time lag. This probably reduced the possibility to note significant differences. Including only "Cycle 1 treatment phase completers" in the analysis did not change the result in cycle 1.

Treatment dosage

The rapid reduction in SCORAD in the first treatment cycle resulted in a lowering of the cyclosporin dose to a mean of 2.7 ± 0.89 mg/kg/day (Table V) without loss of efficacy. The initiation dose in subsequent cycles also decreased to a mean of 2.6 (range 2.3–2.8) mg/kg/day. In contrast, the mean total dose of UVAB tended to increase with time (Table VI). The maximum UV dose remained relatively unchanged throughout the study (data not shown).

Table IV. *Changes in total eczema disability index score from baseline ($\pm$SD)*

Time point of assessment	Cyclosporin		UVAB		p*
	No. of patients	Mean change	No. of patients	Mean change	
Week 4	29	-17 ± 11	31	-9 ± 9	<0.01
Week 8	32	-17 ± 11	27	-12 ± 13	n.s.
End of study	34	-13 ± 11	32	-12 ± 12	n.s.

*Student's t-test.

Safety assessments

Adverse events were reported in 35 patients on cyclosporin and 32 patients on UVAB. A total of 212 adverse events were registered (139 and 73 in the cyclosporin and UVB groups, respectively), but only 4 patients stopped treatment due to an adverse event (1 and 3 in the cyclosporin and UVAB groups, respectively). No serious adverse events were reported. Gastrointestinal (gastroenteritis, pain, vomiting, nausea, diarrhoea), neurological (headache, paraesthesias) and musculoskeletal (myalgia, arthralgia) problems accounted for the more frequently reported adverse events in the cyclosporin group. Sunburn and visual disorders were more frequent in the UVAB group. Infections were reported equally often in both groups (29 and 25 in the cyclosporin and UVAB groups, respectively); for example, herpes simplex was reported in 2 patients on cyclosporin and 4 on UVAB. The longer participation in the study of patients in the cyclosporin group must be taken into consideration when comparisons are made.

There was no significant difference between the mean baseline and endpoint values for the vital signs and laboratory parameters between the groups. The mean systolic and diastolic blood pressure increased significantly during cyclosporin treatment, but returned to normal after each treatment phase. Accordingly, at the endpoint the change from baseline was not significant. Seven patients on cyclosporin developed mild or moderate hypertension after 3–5 cycles. The hypertension was controlled by dose reduction in all patients, with the exception of 1 patient who received antihypertensive medication.

Serum creatinine increased significantly during cyclosporin treatment, but returned to normal after each treatment phase. Accordingly, at the endpoint the change from baseline was not significant. Two patients in the cyclosporin group had an increase in their serum creatinine value to 30% above their baseline value during the fifth treatment cycle. The values returned to normal after the treatment was stopped.

In the first treatment cycle the overall tolerability of treatment was rated as "very good" or "good" by 86% and 63% of the patients in the cyclosporin and UVAB groups, respectively. Corresponding rates given by the investigators were 86% and 70%. Both results are significant ($p < 0.05$; Wilcoxon). In subsequent cycles this significance disappeared.

DISCUSSION

This clinical study is the first to compare cyclosporin with a conventional, second-line treatment in atopic dermatitis. It is also one of the few studies to have assessed efficacy and safety

Table V. *Mean dose of cyclosporin (mg/kg/day) in each cycle*

Cycle	No. of patients	Mean $\pm$ SD
I	35	2.7 ± 1.0
II	31	2.5 ± 1.0
III	27	2.5 ± 0.9
IV	24	2.6 ± 0.9
V	16	2.8 ± 1.0
VI	3	2.3 ± 1.2

Table VI. *Mean total UVA and UVB dose in each cycle (±SD)*

Cycle	No. of patients	UVA (J/cm^2)	UVB (J/cm^2)
I	35	116±64	1.5±0.9
II	19	128±70	1.7±0.9
III	11	119±59	1.5±0.8
IV	6	167±47	2.2±0.6
V	2	176±54	2.3±0.8

of intermittent long-term treatment of the disease. Although a double-blind design is preferable in clinical trials, an open study design was chosen because of the disparate treatment modalities, i.e. a drug compared with a physical therapy. Blinding of UV therapy is difficult; it would require the use of visible light as a placebo and was thus abandoned on ethical and practical grounds. It would not have been ethically sound to expose patients to visible light for the expected long treatment periods over the course of a 1-year trial. The typical adverse event profiles of the treatments could also have easily unblinded the study. The open design makes it possible to evaluate the practicability of the 2 treatment modalities.

UVAB was chosen as the UV source because it has shown better efficacy than several other conventional phototherapy modalities for the treatment of atopic dermatitis (1) and is widely available in the Nordic countries. The washout period for phototherapy before the start of treatment was probably too short, i.e. 2 weeks instead of 4 weeks, but if this had any influence on the results it presumably would have diminished the efficacy difference between the treatment groups in the first cycle. Newer modalities such as high-dose UVA1 have shown superiority to UVAB for the treatment of acute atopic dermatitis (12) but are still offered only at a very few centres. In addition, published evidence for UVA1 is available only for short-term treatment. The purpose of this study was to compare cyclosporin with a standard UV treatment modality that is available for most patients.

For comparison of efficacy only, in terms of induction of remission and short-term safety, a shorter study design would have been acceptable. The number of withdrawals may also have been lower with a shorter design. However, for several reasons we chose to conduct a 1-year study. The evaluation of intermittent treatment regimens requires a long study duration and seasonal variations in disease activity can thus be excluded.

Although both cyclosporin and UVAB were shown to be effective in the treatment of atopic dermatitis, cyclosporin produced a significantly more rapid and pronounced induction of remission in several subsequent treatment cycles and significantly more remission days than UVAB therapy. This is also reflected in the diminished use of emollients and topical corticosteroids, as well as in an improved quality of life. The superiority of cyclosporin is also seen in the significantly greater number of withdrawals due to both treatment failure and protocol violations in the UVAB group. Six patients stopped UVAB treatment due to treatment failure, but none in the cyclosporin group. Several withdrawals occurred in the UVAB group because the patients could not attend for regular treatment visits, a requirement of UVAB therapy. It is also important to note that the efficacy of cyclosporin was maintained with a mean dose of 2.6 mg/kg/day, while the total dose of UVAB increased slightly towards the end of the study. The fact that patients could be treated successfully with a lower initial dose in subsequent cycles also suggests that the cumulative dose of cyclosporin will be lower with intermittent treatment compared with continuous treatment. This is important as the cumulative dose of cyclosporin is probably the most important factor predicting renal damage.

No significant difference in disease activity between the treatment groups could be observed 2 weeks after termination of treatment. This suggests that, at least when measured in terms of mean disease activity, the relapse of the disease was similar in the 2 treatment groups. Patients on cyclosporin needed more treatment cycles, but this observation is obscured by the more frequent withdrawals in the UVAB group.

Several efficacy variables which showed a significant difference between cyclosporin and UVAB in favour of cyclosporin lost their ability to detect any difference towards the end of the study. This is probably due to a decreasing number of patients. The study design, which allowed dose reduction in the cyclosporin group but not in the UVAB group, probably also influenced the disappearance of significant differences.

The adverse event profile of cyclosporin was not unexpected, minor gastrointestinal and musculoskeletal complaints, headache, paraesthesias and hypertension all occurring. Regarding the long duration of the study, the development of hypertension and functional renal impairment was very low (7% and 3% of patients, respectively) and only 1 patient (1%) stopped treatment because of an adverse event. In continuous long-term treatment with cyclosporin for 10–12 months, 5–14% of patients developed hypertension, 6–45% experienced functional renal impairment and 14–21% withdrew due to adverse events (13, 14). It should be noted that in this study the mean serum creatinine value did not change from baseline to the endpoint. Taken together, these results suggest that intermittent treatment is safer and better tolerated than continuous treatment in atopic dermatitis. In the case of psoriasis treated with continuous administration of cyclosporin, the number of patients who have to stop treatment due to side effects increases steadily with time (15). With intermittent treatment it would probably be possible to treat the same patients for a longer time. This must be compared with the very small risk of long-term side effects with UVAB treatment.

Cyclosporin seems to be a more efficacious alternative to UVAB treatment for adult patients with atopic dermatitis who fail on conventional treatment with topical corticosteroids. Cyclosporin is also more convenient to administer and less time-consuming for the patient. With an intermittent regimen the most severe side effects of cyclosporin seem to be manageable over a 1-year treatment period. However, the long-term safety of cyclosporin is still the main concern; it needs to be continuously followed up and the drug should be used according to guidelines (16). Cyclosporin is an expensive drug and the cost-effectiveness of different treatment modalities should be compared by taking into consideration both direct and indirect costs. In conclusion, UVAB remains the main second-line treatment for atopic dermatitis, but cyclosporin offers an alternative when phototherapy is either ineffective or unavailable.

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REFERENCES

1. Jekler J. Phototherapy of atopic dermatitis with ultraviolet radiation. Acta Derm Venereol 1992; Suppl. 171: 1–37.
2. Wahlgren C, Scheynius A, Hägermark Ö. Antipruritic effect of oral cyclosporin A in atopic dermatitis. Acta Derm Venereol 1990; 70: 323–329.
3. Sowden JM, Berth-Jones J, Ross JS, Motley RJ, Marks R, Finlay AY, et al. A multicentre, double-blind, placebo-controlled crossover study to assess the efficacy and safety of cyclosporin in adult patients with severe refractory atopic dermatitis. Lancet 1991; 338: 137–140.
4. Granlund H, Erkko P, Sinisalo M, Reitamo S. Cyclosporin A in atopic dermatitis: time to relapse and effect of intermittent therapy. Br J Dermatol 1995; 132: 106–112.
5. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl. 1980; 92: 44–47.
6. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol Suppl. 1989; 144: 13–14.
7. Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. N Engl J Med 1991; 324: 277–284.
8. Reitamo S, Erkko P, Remitz A, Lauerma AI, Montonen O, Harjula K. Cyclosporine in the treatment of palmoplantar pustulosis. A randomized, double-blind, placebo-controlled study. Arch Dermatol 1993; 129: 1273–1279.
9. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: The SCORAD index. Consensus report of the European task force on atopic dermatitis. Dermatology 1993; 186: 23–31.
10. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. Dermatology 1997; 195: 10–19.
11. Salek MS, Finlay AY, Luscombe DK, Allen BR, Berth-Jones J, Camp RDR, et al. Cyclosporin greatly improves the quality of life of adults with severe atopic dermatitis. A randomized, double-blind, placebo-controlled trial. Br J Dermatol 1993; 129: 422–430.
12. Krutmann J, Diepgen TL, Luger TA, Grabbe S, Meffert H, Sonnichsen N, et al. High-dose UVA1 therapy for atopic dermatitis: results of a multicenter trial. J Am Acad Dermatol 1998; 38: 589–593.
13. Zonneveld IM, De Rie MA, Bos JD. The long-term safety and efficacy of cyclosporin A in severe refractory atopic dermatitis: a comparison of two dosage regimens. Br J Dermatol 1996; 135: 15–20.
14. Berth-Jones J, Graham-Brown RAC, Marks R, Camp RDR, English JSC, Freeman K, et al. Long-term efficacy and safety of cyclosporin in severe adult atopic dermatitis. Br J Dermatol 1997; 136: 76–81.
15. Grossman RM, Chevret S, Abi-Rached J, Blanchet F, Dubertret L. Long-term safety of cyclosporine in the treatment of psoriasis. Arch Dermatol 1996; 132: 623–629.
16. Camp RDR, Reitamo S, Friedmann PS, Heule F. Cyclosporin A in severe, therapy-resistant atopic dermatitis: report of an international workshop, April 1993. Br J Dermatol 1993; 129: 217–220.