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Comparison of Cyclosporine and Topical Betamethasone-17,21-dipropionate in the Treatment of Severe Chronic Hand Eczema

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Topical corticosteroids are the standard treatment for hand eczema. However, in chronic forms of the disease they are often ineffective or lose their efficacy due to tachyphylaxis. In a previous open study cyclosporine showed efficacy in chronic hand eczema. The aim of this study was to compare oral cyclosporine at 3 mg/kg/day with topical 0.05% betamethasone-17,21-dipropionate (BDP) cream in the treatment of chronic hand eczema. In a randomized, double-blind study 41 patients with chronic hand eczema resistant to conventional treatment were assigned to either cyclosporine or BDP for 6 weeks. Both cyclosporine and BDP improved the eczema. The total disease activity score decreased to 57% of baseline in the cyclosporine group (mean change −6, SD 4.3; $p<0.001$) and to 58% of baseline in the BDP group (mean change −5.7, SD 4; $p<0.001$) at the end of treatment. However, between the groups there was no significant difference. Adverse events occurred in 68% of the patients during cyclosporine and in 56% during BDP treatment. With cyclosporine no case of hypertension or increase in serum creatinine above normal levels was recorded. In two patients the serum creatinine levels increased to values 30% above their own baseline values. Relapses occurred to the same extent in both groups. Cyclosporine at 3 mg/kg/day is as effective as topical BDP in the treatment of chronic hand eczema. Low-dose cyclosporine could be useful as an alternative treatment for severe chronic hand eczema in patients unresponsive to conventional treatment. ***Key words: topical corticosteroids; contact dermatitis; occupational skin disease; immunomodulation.***

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Eczema is a distinctive pattern of skin inflammation which can be induced or maintained by a variety of environmental or intrinsic factors, e.g. contact allergens and irritants, infective agents and atopy. Hand eczema, a defined clinical variant of eczema with different aetiologies, is a common skin disease with a point prevalence of 2–5.4 % and a considerable socioeconomic impact (1–3). It is often chronic, as only a third of the patients clear completely (1, 4–6), and it is the most important occupational skin disease (1, 5, 7–9), accounting for the greatest part of all temporary or permanent working disability (10) and change of occupation (1, 5, 6) due to skin disease.

Severe chronic hand eczema is, in addition, often difficult to treat. Topical corticosteroids are the mainstay of eczema therapy, but they are, however, sometimes insufficient or lose their efficacy due to tachyphylaxis in the more chronic forms of the disease. A preliminary open study suggested that cyclosporine is effective in the treatment of chronic hand eczema (11). In this study we have compared standard topical corticosteroid treatment, i.e. 0.05% betamethasone-17,21-dipropionate (BDP) cream, with oral low-dose cyclosporine in a double-blind, controlled manner.

MATERIAL AND METHODS

Patient selection

Patients of either sex, aged 18–70 years, with hand eczema causing significant disability, were considered eligible for the study. The patients were recruited from a university hospital dermatological outpatient clinic between April 1992 and August 1993. Before entry a histopathological examination was conducted in all patients to help to exclude other skin disorders, e.g. psoriasis. For inclusion, the patients were required to have had hand eczema continuously for at least 6 months, significant disability and an inadequate response to conventional treatment, i.e. topical halogenated corticosteroids for at least 3–4 weeks and/or oral psoralen photochemotherapy (PUVA) and avoidance of relevant contact allergens. All patients had been evaluated with standard and other appropriate patch tests. Patients treated with systemic corticosteroids within 4 weeks and topical corticosteroids or ultraviolet radiation within 2 weeks before the study were excluded. In addition, other standard exclusion criteria for patients undergoing cyclosporine treatment were used (12–14).

Study protocol

The study protocol was approved by the ethics committee of the Department of Dermatology, Helsinki University Central Hospital. The study was a double-blind, randomized, controlled parallel-group study with two treatment limbs and was conducted as a single-centre study. Informed consent was obtained from all patients after the study had been fully explained to them.

The following variables were used to monitor the efficacy of treatment.

Disease activity score–Each hand was evaluated separately. The signs of erythema, scaling, infiltration, excoriation, crusting and vesicles were graded on a scale of 0–3 (0 = none; 1 = mild; 2 = moderate; 3 = severe), giving a maximum possible score of $2 \times 6 \times 3 = 36$.

Extent of the disease–The area of each aspect of each hand was considered as 25% (100% = both aspects of both hands).

Use of emollients–Throughout the study the patients were allowed to use their own emollients, recording their use on diary cards which were returned at each visit.

Itch and sleep disturbances–At each visit, the patient recorded the intensity of these symptoms for the final 2 weeks on a visual linear analogue scale (VAS) from 0 to 100 mm.

Overall assessment of efficacy–Both the patient and the investigator assessed the overall efficacy of the treatment at the end of each part. The assessment was made on a scale of 1–5 (1 = very good, 2 = good, 3 = moderate, 4 = slight, 5 = none).

The patients were always assessed by the same investigator. Only two investigators performed the assessments. Prior to starting the study the assessments were tried together in several patients with hand eczema. Treatment success was defined as a decrease in the disease activity score to $\leq 50\%$ of the patient's own baseline score. During

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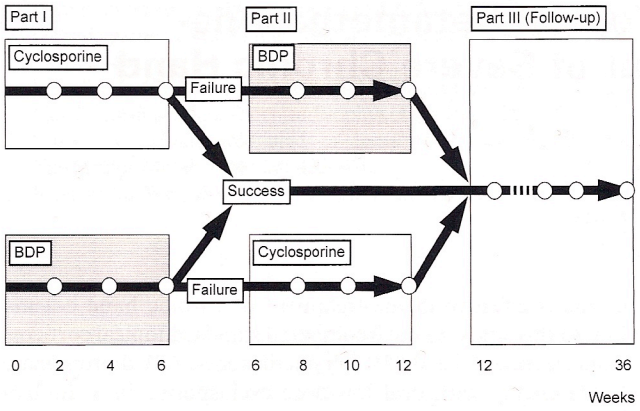


Fig. 1. Study design. BDP = betamethasone-17,21-dipropionate.

follow-up, a relapse was defined as an increase in the disease activity score and/or extent of the disease to >75% of the patient's own baseline value.

The patients were given numbers 1–41 in consecutive order; each number had been reassigned to treatment with oral cyclosporine 3.0 mg/kg/day and topical placebo cream or capsules containing vehicle without oral cyclosporine and BDP cream topically. After a run-in period of 4 weeks the study was conducted in three parts (Fig. 1). In Part I the patients were treated for 6 weeks with either medication. In Part II, patients with treatment failure in Part I were transferred to the other treatment for another 6 weeks. Patients with success in Part I proceeded directly to Part III. In Part III patients were followed until relapse or for a maximum of 6 months. The patients were examined biweekly, except during the last 4 months of Part III, when those patients still in follow-up were assessed monthly. The codes were not opened until all patients had finished all parts of the study.

Soft gelatine capsules containing cyclosporine 25, 50 or 100 mg and identical placebo capsules were supplied by Sandoz Pharma AG. BDP cream (Diproderm, 0.05%) and the corresponding plain cream (Diprobase cream) serving as placebo were both purchased from Schering-Plough Co. Identical 100 tubes were used for the creams. The daily oral dose was taken in two separate doses with meals and the creams were applied at the same time. Compliance with oral treatment was monitored and the consumption of creams was recorded by weighing the tubes at each visit.

Safety and tolerability

On inclusion patients underwent full clinical history and physical examination. Safety assessments based on vital signs (blood pressure, weight) and laboratory and physical examinations were made at each visit. All adverse events observed by the investigator or reported by the patient were recorded. The severity (assessed as mild, moderate or severe), frequency of occurrence, reaction to therapy, and the disease course were also recorded by the investigator. At the end of each part 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.

In case of significant adverse events in which cyclosporine treatment was thought to play a role, cyclosporine had to be discontinued or the dose reduced according to standard protocols used in earlier studies (12–14).

Statistics

Results are given for the efficacy variables as the mean (SD; 95% confidence interval [CI]) and mean change (SD; 95%CI) from baseline in Part I and from week 6 of Part I in Part II. Proportional values are used for overall assessments. Results were analyzed on an intention to treat basis. Statistical analysis of continuous variables (disease activity score, extent of disease, linear analogue scale) was performed with Student's t-test for between groups comparisons based on mean values and with paired t-test for intergroup comparisons based on mean change values. Discontinuous data were analyzed by Fisher's exact test (overall assessments, proportions of successes and failures), chi-square test (baseline characteristics, cumulative relapse rate), and Mann-Whitney U-test (proportions of successes and failures, overall assessments, cumulative relapse rate), respectively. All p values reported are two-sided except those with Fisher's exact test. A p value less than 0.05 was considered significant.

RESULTS

Forty-one patients were recruited and randomized. In Part I, 6 patients withdrew prematurely, either before or at the first visit; reasons for withdrawal were protocol violation, adverse events and treatment failure (2 patients each). The patients excluded due to protocol violation were both randomized for cyclosporine and withdrawn because of inability to attend; one had already withdrawn during the run-in period. Withdrawals due to adverse events and treatment failures were distributed equally between the two groups. As one patient withdrew in Part II, because of inability to keep appointments, a total of 34 patients completed the trial: 16 in the cyclosporine group and 18 in the BDP group.

The baseline characteristics of the patients are shown in Table I. Except for the number of patients treated with antibiotics before the study ($p<0.05$) no significant differences were found between the two treatment groups. No apparent differences were noticed between the patients who withdrew and those who remained in the study (data not shown).

Efficacy in Part I

Of the patients who completed Part I, 50% in the cyclosporine group and 32% in the BDP group were classified as treatment successes; this difference was not, however, significant (Fisher's exact test, $p=0.233$).

The total disease activity score decreased significantly and to the same degree in both groups (Fig. 2), i.e. from the mean value of 12.9 to 7.3 in the cyclosporine group (57% of baseline; mean change −6, SD 4.3, 95% CI −8.2 to −3.8; $t=5.392$, df = 14, $p<0.001$) and from 13.7 to 7.9 in the BDP group (58% of baseline; mean change −5.7, SD 4, 95%CI −7.6 to −3.7, $t=6.172$, df = 16, $p<0.001$) at the end of treatment. As indicated, both treatments showed almost maximum efficacy within the first 2 weeks. The decrease in the extent of the disease, occurrence of itch and use of emollients from baseline was also significant in both groups, but the decrease in sleep disturbance was significant only in the cyclosporine group. However, the difference between the groups at week 6 was not significant irrespective of used variable, e.g the difference in mean disease activity score was 0.6 (SD 3.6, 95% CI −3.2 to 1.9). Analysis with the last available assessment did not indicate any bias due to withdrawals (data not shown).

In the overall assessment made at the end of treatment, a slight preference for cyclosporine was noted, although not significant. Efficacy was considered very good or good by 60% of the patients in the cyclosporine group and by 48% in the BDP group; when evaluated by the investigator the values were 60% and 31%, respectively.

For comparisons between subgroups of hand eczema the numbers of patients were in general too small to allow meaningful conclusions. Thus, 7 patients with established

Table I. *Baseline comparisons of study population according to assigned treatment*

Variable	Cyclosporine ($n=20$)	Betamethasone-17,21-dipropionate ($n=21$)
Mean (SD; 95%CI) age (yr)	36 (9; 32 to 40)	40 (11; 35 to 45)
Male/female (No)	7/13	11/10
Mean (SD; 95% CI) duration of hand eczema (yr)	5 (6; 2 to 8)	8 (8; 5 to 11)
Coexistence of foot eczema (No)	6	12
Mean (SD; 95% CI) duration of foot eczema (yr)	7.6 (9.6; −0.8 to 16)	4 (3; 2 to 6)
Own or family history of atopy (No)	11	10
Positive reactions in prick tests (No)	11	5
Diagnosis (No)		
Irritant contact	6	5
Allergic contact	6	4
Unclassified	8	12
Positive reactions in patch tests (No)	13	14
Previous treatments with systemic steroids (No)	2	3
Previous treatments vid PUVA (No)	2	4
Previous treatments with antibiotics (No)*	7	15
Sick leave within 1 year before entry (No)	8	10
In-patient treatment within 1 year before entry (No)	1	4
Type of eczema (No)		
Dry and/or hyperkeratotic	16	16
Vesicular	4	5
Mean (SD; 95% CI) disease activity score (score)	12.9 (3.7; 11.3 to 14.6)	13.7 (3.3; 12.2 to 15.2)
Mean (SD; 95% CI) extent of disease (%)	33 (21; 24 to 43)	48 (32; 33 to 62)
Mean (SD; 95% CI) itch (VAS mm)	54 (29; 41 to 67)	48 (21; 39 to 58)
Mean (SD; 95% CI) sleep disturbance (VAS mm)	24 (27; 12 to 37)	23 (19; 14 to 31)
Mean (SD; 95% CI) use of emollients (grams/2 weeks)	134(147; 66 to 201)	123 (134; 62 to 185)

*chi-square test; $X^2=5.467$, $p<0.05$.

contact allergies and 6 patients with treatment failure to PUVA were evaluable. In the cyclosporine group, 1/4 patients with known contact allergies had treatment success, compared to 7/12 patients without contact allergies. Respective numbers in the BDP group were 2/3 and 4/16. Of 2 patients who had failed on PUVA treatment and who were subsequently treated with cyclosporine, one patient failed and the other patient had to stop treatment after 2 weeks due to adverse events. Correspondingly in the BDP group, one had to stop treatment due to failure, one failed, and 2 were successfully treated.

Efficacy in Part II

In this part, only patients with failure in Part I were treated (8 patients from the cyclosporine group switched to BDP and 12 from the BDP group to cyclosporine). Treatment success was obtained in 67% of patients on cyclosporine and in 62% of patients on BDP, a non-significant difference.

The patients treated with cyclosporine showed an improvement in all efficacy variables at the end of treatment, compared to week 6 in Part I (Fig. 2). The improvement was significant for the disease activity score (mean change −3.3, SD 3.4, 95%CI −5.2 to −1.4; $t=3.430$, $p<0.01$) and sleep disturbance (mean change −16, SD 21, 95%CI −28 to −4); $t=-2.668$, $p<0.05$). In contrast, patients who switched to BDP showed a deterioration of their disease as measured with all the efficacy variables except for a non-significant decrease in the disease activity score; however, the number of patients in Part II was too small to make the difference between groups significant.

In the overall assessment, the efficacy was considered very good or good by 50% of patients on cyclosporine and by 38% of those on BDP. Correspondingly, the investigators rated the efficacy as very good or good in 75% of patients treated with cyclosporine and in 51% of those treated with BDP, although these differences were not significant.

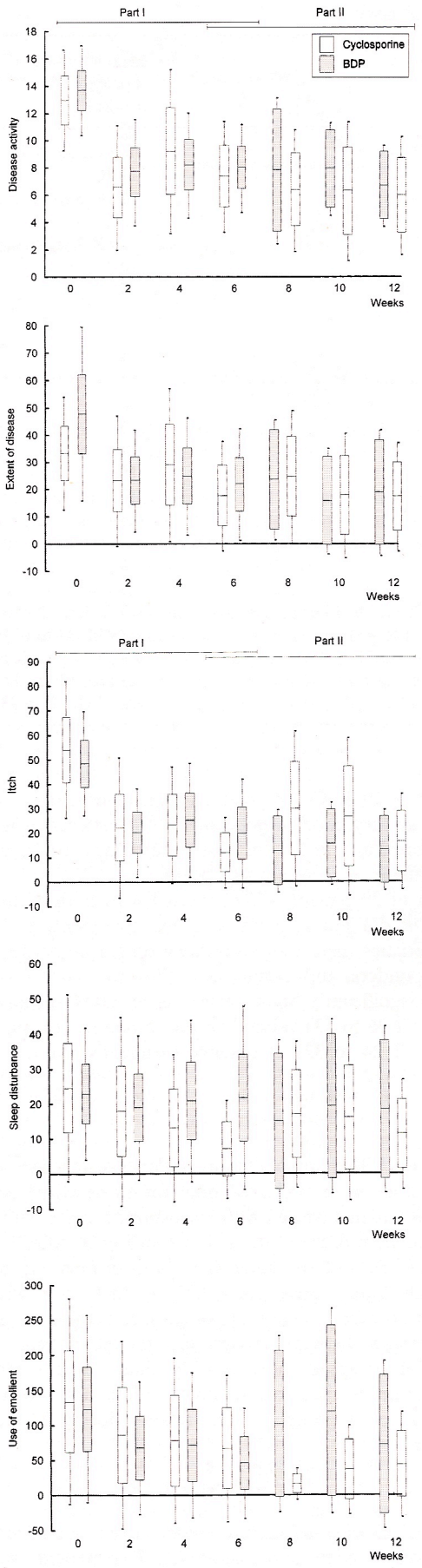
Seven of 20 patients (35%) treated with both cyclosporine and BDP did not respond to either treatment. In baseline characteristics there was no notable difference between these non-responders and responders. However, non-responders showed significantly higher mean serum GOT (mean 40, SD 18, 95%CI 26 to 53) value than the responders (mean 28, SD 10, 95%CI 24 to 32) at baseline (Student's t test, $t=2.457$, $p<0.05$).

Relapse

As patients with treatment failure in Part I switched treatments, relapse rates were evaluated only for those with success in Part I (8 patients treated with cyclosporine and 6 with BDP); the cumulative relapse rate is shown in Fig. 3. After a 2-week follow-up, 50% of the patients in both groups had relapsed (X^2 with Yates' correction $=0.92$, p n.s.). Nor when last treatment is taken as base for comparison is there any significant difference between the groups, though patients treated with BDP relapsed more quickly than patients who had cyclosporine as their last treatment (data not shown). One patient in each group did not relapse during 24 weeks of follow-up.

Safety

Data on all 41 randomized patients were included in the evaluation of safety and tolerability. Two patients withdrew



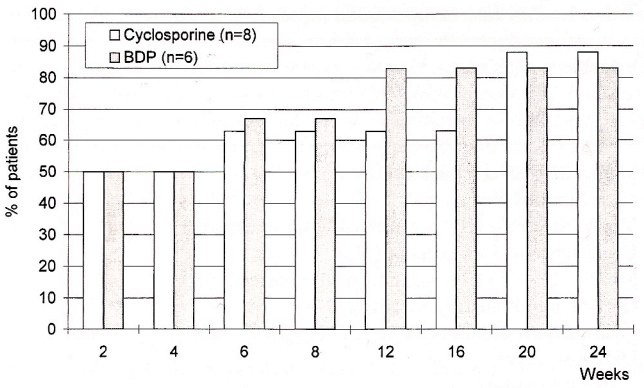


Fig. 3. Cumulative relapse rate (% of relapsed patients) of patients with treatment success in Part I. BDP = betamethasone-17,21-dipropionate.

due to adverse events; one patient on cyclosporine stopped treatment because of dizziness, vomiting and facial oedema and one patient on BDP experienced severe insomnia. Nineteen of 28 patients on cyclosporine and 15 of 27 on BDP experienced some kind of adverse event. No hypertension or increase in serum creatinine levels above the normal range was recorded. In 2 patients on cyclosporine the serum creatinine levels increased to values 30% above their own baseline values. However, the serum creatinine normalized before the doses were reduced. The treatments were equally well tolerated when assessed by the patients at the end of treatment, i.e. 80% in the cyclosporine and 89% in the BDP group graded the tolerance of the treatment as "good" or "very good" in Part I. Corresponding numbers for Part II were 92 and 88%. The investigators' assessments were in accordance with these figures.

DISCUSSION

With every efficacy variable used, cyclosporine at 3 mg/kg/day was as effective as BDP cream in the induction of remission in severe, chronic hand eczema. It is to be noted that BDP is a potent topical corticosteroid and that the cyclosporine dose used in this study was lower than doses required for induction of remission in several dermatoses as indicated in controlled efficacy studies (12, 15). A higher initial cyclosporine dose would certainly have enhanced efficacy, but for safety reasons we decided to use the lowest effective dose, which in our experience could be expected to be about 3 mg/kg/day (11). Despite the low dose, half the patients were successfully treated with cyclosporine and 60% considered the treatment as very good or good. By comparison, in our study on patients with atopic dermatitis 73% of patients treated with cyclosporine 5 mg/kg/day considered the treatment good or very good (14). Patients who, after treatment failure, changed to cyclosporine managed slightly better than those who switched to BDP. The

Fig. 2. Efficacy variables in Part I ($N_{Cyclosporine}=20$ and $N_{BDP}=21$) and II ($N_{Cyclosporine}=8$ and $N_{BDP}=12$). The values in Part II are based on the population continuing in Part II, except the mean values at week 6 Part I, which are based on the whole group. *Boxes* indicate 95% confidence intervals and *bars* ±SD. BDP = betamethasone-17,21-dipropionate.

number of patients treated in this second part of the study was, however, too small to allow any conclusions to be drawn.

A response to BDP was noted though non-responsiveness to topical halogenated corticosteroids was an inclusion criterion. This inclusion criterion concerned different kinds of halogenated corticosteroids. It is possible that some patients who had failed on earlier non-BDP corticosteroids in this study, for reasons related to BDP itself or the base, responded to treatment with BDP. It also possible that some patients had been non-responders to PUVA, another inclusion criterion, but not to corticosteroids. It cannot, however, be ruled out that the thorough follow-up with regular controls and monitoring elementary for clinical studies had an influence on the management of the patients.

After the treatment was stopped, patients treated with cyclosporine and BDP relapsed at the same rate. In about a third of the patients the eczema relapsed within 2 weeks, which is in agreement with our findings for cyclosporine in atopic dermatitis (14). A rebound effect was not noted after cyclosporine or BDP.

Seven patients did not respond to either treatment, showing how difficult these patients are to treat. The higher serum GOT levels at baseline in the non-responders might show a difference important for treatment success, i.e. difference in alcohol consumption. This, however, cannot be stressed in this study.

Hand eczema is not a strictly defined entity. However, we decided not to differentiate between eczema types because, although the majority of hand eczemas can be classified into irritant and allergic contact dermatitis (1), there is no reliable test differentiating irritant contact dermatitis from endogenous eczema (9), and a significant proportion (45%) of endogenous hand eczemas are unclassifiable (9). In this study about half the patients in both groups were considered to have either allergic or irritant contact dermatitis and a third had atopic diathesis. These figures roughly correlate with the findings in epidemiological studies (2, 16). The number of patients with established contact allergies was too small to allow conclusions to be drawn as to differences between patients with or without contact allergies. Non-responsiveness to conventional treatment was required for inclusion to assure that only patients with severe disease were recruited. Although this could have introduced a selection bias, we used this definition of disease severity to include only patients with severe disease.

When compared to efficacy of cyclosporine in psoriasis (12, 17), the present study suggests that cyclosporine 3 mg/kg/day is as effective in the treatment of chronic hand eczema as in plaque psoriasis. Disease activity decreases by 50% in both diseases, but does so within 2 weeks in hand eczema, while plaque psoriasis requires 6 weeks to achieve this resolution. The PASI score takes account of both disease activity and extent of disease. In the present study we assessed disease activity and extent of the disease separately, but both decreased to the same extent.

The adverse events observed were mild and almost equally frequent in both treatment groups. Paresthesias were the only side-effects more common in the cyclosporine group than in the BDP group. When compared with other studies with low cyclosporine doses, i.e. 3 mg/kg/day in psoriasis (12) and 2.5 mg/kg/day in pustulosis palmoplantaris (13), the profile of adverse events was similar, with a predomination of gastrointestinal symptoms, paresthesias and headache. The adverse events were well tolerated. The most important side-effects of cyclosporine, i.e. renal dysfunction and hypertension, are dose-dependent and usually recorded when >3 mg/kg/day-doses are used. In this study, 2 patients on cyclosporine had a temporary increase in serum creatinine above the recommended upper limit of 30% above baseline; however, no patient needed to stop treatment owing to hypertension or renal insufficiencies.

Since their introduction in 1952 (18), several new and more potent topical corticosteroids have come on the market. Their efficacy in eczematous diseases has been demonstrated in studies, which almost exclusively have been comparative (19, 20). This also applies to BDP (21), which was introduced in the early 1970s and is a standard treatment for eczemas in many countries. Few studies on topical corticosteroids have dealt specifically with hand eczema (22). Hand eczema is difficult to treat and its treatment with topical agents is troublesome because they are greasy and interfere with daily life and work. More potent therapies have consequently been sought. Experimental therapies for hand eczema include PUVA (23–26), topical PUVA (27), UVB (28), Grenz-ray (29) and superficial radiotherapy (27, 30). These modalities have their own side-effects, and the radiation therapies are often time-consuming and thus interfere with the work of patients already disturbed by the disease, which can lead to poor compliance (27). There is clearly a need for an effective, safe and easily administered alternative to topical corticosteroids in the treatment of hand eczema.

We are not aware of any conclusive data on the efficacy of PUVA, radiotherapy or other treatments in hand eczema. Therefore, topical steroids remain the primary treatment of this condition. In the present study the majority of topical steroid-unresponsive patients improved when switched to cyclosporine treatment. Therefore, a reasonable approach to treatment might be an initial use of potent topical steroids followed in unresponsive patients by cyclosporine as a secondary treatment if the severity of eczema justifies it. Future studies should aim at determining the optimal dosage and treatment time for cyclosporine.

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