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Comparison of the Influence of Cyclosporine and Topical Betamethasone-17,21-dipropionate Treatment on Quality of Life in Chronic Hand Eczema

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In a randomized, controlled parallel group study we have shown that cyclosporine at 3 mg/kg/day is as effective as topical betamethasone-17,21-dipropionate in the treatment of chronic hand eczema. In this study we compared the influence of these therapies on the quality of life. Forty-one patients were treated with either treatment for 6 weeks, after which patients with failure were switched to the other treatment for another 6 weeks. Quality of life was assessed with the Eczema Disability Index (EDI) at baseline and at the end of both treatment periods. The total EDI score decreased significantly and to the same degree in both groups, i.e. from the mean value of 30.5 to 20.9 in the cyclosporine group and from 27.2 to 18.9 in the betamethasone-17,21-dipropionate group. Irrespective of the dimension of the EDI (daily activity, school/work, personal relationship, leisure, treatment), the difference between the treatment groups at the end of the first treatment period was not significant. In the second part of the study a slight further decrease in total score was observed, but without any difference between the groups. There was a significant correlation between changes in the total EDI score and changes in all the clinical assessments, i.e. disease activity, extent of the disease, itch, sleep disturbances and use of emollients. Though the significant correlation between the total EDI and clinical assessments makes quality of life assessments in hand eczema questionable, the missing correlation between some clinical assessments and dimensions of the EDI suggests that EDI views aspects of the disease not covered by clinical measures. ***Key words: topical corticosteroids; contact dermatitis; occupational skin disease; immunomodulation.***

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Hand eczema is a disease with a great socio-economic impact. It is often chronic in course (1–6) and occupational in origin (1, 7) and consequently causes a considerable part of all working disability (8, 9). In accordance with this, eczematous diseases are recognized as diseases having a detrimental effect on the quality of life (9–11). Thus, the measurement of quality of life in the assessment of new therapies can, besides conventional clinical descriptions of disease activity, provide an important insight into the efficacy of the therapy. However, the assessment of patients' well-being is often neglected in medical interventions. In dermatology, disease-specific indices of disability have been developed for atopic eczema (11), psoriasis (12) and acne (13), and a common index for all skin diseases has also been described for routine clinical use (14).

Cyclosporine provides a treatment alternative in several eczematous diseases of severe grade (15–18). In a comparative, double-blind study we have shown that cyclosporine at 3 mg/kg/day for 6 weeks is as effective as topical betamethasone-17,21-dipropionate (BDP) in the treatment of chronic hand eczema (19). In the present study, we evaluated the impact of both treatment modalities on the quality of life of the patients.

METHODS

Patient selection

Forty-one patients of either sex, aged 18–70 years, with hand eczema, were recruited from the dermatological outpatient clinic of Helsinki University Central Hospital between April 1992 and August 1993. Details of patient selection, inclusion and exclusion criterias have been reported elsewhere (19). Briefly, the inclusion criteria were: a continuous disease duration of at least 6 months; significant disability and inadequate response to conventional treatment. Treatment with systemic corticosteroids within 4 weeks and topical corticosteroids or ultraviolet radiation within 2 weeks before the study were not allowed and, in addition, other standard exclusion criteria for patients undergoing cyclosporine treatment were used.

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 patients were randomized to treatment with either oral cyclosporine at 3 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 patients were treated for 6 weeks with either medication in the first part of the study. Only patients with treatment failure in this first part were retreated and transferred to the other treatment for another 6 weeks. Clinical and safety assessments were made biweekly. Quality of life assessments were collected at the beginning of the study (baseline) at the end of the first (week 6) and the second part (week 12). After the last treatment, all patients were followed until relapse or for a maximum of 6 months, but assessments of quality of life were not made in this part of the study.

Assessments of quality of life

The Eczema Disability Index (EDI) (8) 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 15 questions represent five different dimensions of quality of life: daily activity (five items), work and school (three items), personal relationship (two items), leisure (four items) and treatment (one item). EDI has been externally validated against UKSIP, a general quality of life instrument and also against clinical parameters (8). When completing the EDI, patients were asked to consider the condition as it had appeared during the last 2 weeks. The questionnaire was self-administered under the supervision of the investigators or a registered nurse involved in the study. A self-administered method may be more valid and reliable than the interviewer-administered (20). During the

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course of the study, the investigator, nurses and patients were unaware of the specific drugs which the patients were taking. A total EDI score is calculated by summing the scores for each question.

Clinical assessments

The clinical efficacy of treatment was monitored by a set of five different assessments. A specific disease activity score designed for the study was used as the main clinical variable. In this score 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) separately for both hands, giving a maximum possible score of $2 \times 6 \times 3 = 36$. Other assessments of efficacy were extent of the disease, use of emollients, and the symptoms of itch and disturbances of sleep. The intensity of the symptoms were recorded by the patient on a visual linear analogue scale (VAS) from 0 to 100 mm. Details of the clinical assessments are published elsewhere (19).

Statistics

Results are given for the total EDI and its different dimensions as the mean (±SD; 95%CI). Both a per protocol and intention to treat analysis was performed, as this is particularly appropriate in quality of life trials (21). The given p-values are based on the intention to treat analysis. Statistical analyses were made for between groups comparisons with both Student's t-test based on mean values and Mann-Whitney U test based on median values and for intergroup comparisons with paired t-test based on mean change values. All p-values reported are two-sided and based on the parametric tests. P-values <0.05 were considered significant. Correlations between the dimensions of quality of life and clinical assessments were analysed both on mean values and changes in mean values using Spearman rank correlation coefficients (r_s).

RESULTS

Forty-one patients were recruited and randomized. Thirty-four patients completed the trial; 16 in the cyclosporine group and 18 in the BDP group. Except for the number of patients treated with antibiotics before the study (7 and 15 patients in the cyclosporine and the BDP group, respectively) ($p<0.05$), no significant differences were found between the two treatment groups at baseline. The basic characteristics of the patients in the cyclosporine and the BDP group, respectively, were as follows: mean age 36 and 40; males/females 7/13 and 11/10; diagnosis of irritant/allergic/unclassifiable eczema 6/6/8 and 5/4/12. Of those who completed the trial 6 patients in the cyclosporine group and 3 in the BDP group had missing answers.

EDI

The total EDI score decreased significantly and to the same degree in both groups (Fig. 1). The mean change±SD was -10.4 ± 14.8 in the cyclosporine group ($p<0.05$) and -8.4 ± 12 in the BDP group ($p<0.01$). For the different dimensions of EDI the mean change from baseline was significant for personal relationship and treatment in the cyclosporine group and for daily activity and work/school in the BDP group. However, irrespective of the dimension of EDI, the difference between the treatment groups at week 6 was not significant, e.g. the difference in the mean total EDI was 2.0 (±SD 14.3) (p n.s.).

In the second part of the study, only patients with failure in the first part were treated (8 patients switched to BDP and 12 patients to cyclosporine). A slight further decrease in total score was observed in both groups (Fig. 1). The decrease was significant in the BDP group for the total score and daily activity ($p<0.001$). Between the groups there was no significant difference at the end of treatment.

In order to evaluate the contribution of different dimensions of quality of life in hand eczema, we calculated mean changes for the whole study population. For the whole study population the mean change (±SD) from baseline to week 6 in the first part was significant in the dimensions of daily activity $-4.1(5.9)$ ($p<0.001$), work/school $-2.3(3.7)$ ($p<0.01$) and treatment $-0.8(1.6)$ ($p<0.01$).

When patients at work were compared to those who for various reasons did not work, there was a difference both at baseline and in the response to treatment. The mean (±SD) total EDI score decreased from 26.7 (16.5) to 16.9 (13.7) in patients who worked (mean change -10.8, $p<0.01$) and from 33.7 (12.2) to 26.9 (13.1) in patients not at work (mean change -4.8; p n.s.). The proportion of patients at work was 75% in the cyclosporine group and 63% in the BDP group.

Relation between clinical assessments and EDI

Correlations between mean values of clinical assessments, i.e. disease activity, extent of the disease, itch, sleep disturbances and use of emollients and different dimensions of EDI were assessed for the whole study population at baseline and at week 6 (Table I). At baseline the total EDI strongly correlated to the disease activity score ($r_s>0.56$, $p<0.001$) and significantly also to the analogue score of sleep disturbance ($r_s>0.40$, $p<0.05$) but not to the other clinical assessments. However, at week 6 the total EDI correlated to all clinical assessments except the use of emollients. Of the different dimensions of EDI all showed correlations to at least one clinical assessment. The dimensions of personal relationship and treatment, however, poorly related to many of the clinical assessments. Of the different clinical assessments, the extent of disease and the analogue scale of itch did not correlate to any dimension of EDI at baseline, but after treatment itch correlated to several dimensions of EDI. After treatment there was a weak correlation between the total EDI score and the overall assessment of efficacy, both judged by the patient ($r_s=0.365$, $p<0.05$) and by the investigator ($r_s=0.381$, $p<0.05$) (data not shown).

Also the mean changes in the EDI and the clinical assessments were analysed for correlation (Table II). There was a significant correlation between changes in the total EDI score and changes in all the clinical assessments. Of the different dimensions of EDI daily activity showed the most pronounced correlations.

DISCUSSION

This study shows that treatment with cyclosporine at 3 mg/kg/day or topical BDP significantly and to the same extent improves the quality of life in patients with chronic hand eczema. The improvement in quality of life was comparable to the efficacy measured with clinical assessments. This was also reflected by the near correlation between assessments of changes in quality of life and the clinical assessments.

When the whole study population was evaluated, significant changes after treatment were noted in the total EDI and the dimensions of daily activity, work/school and treatment. The responsiveness of the questionnaire used in this study, a crucial requirement for measures of quality of life in clinical trials

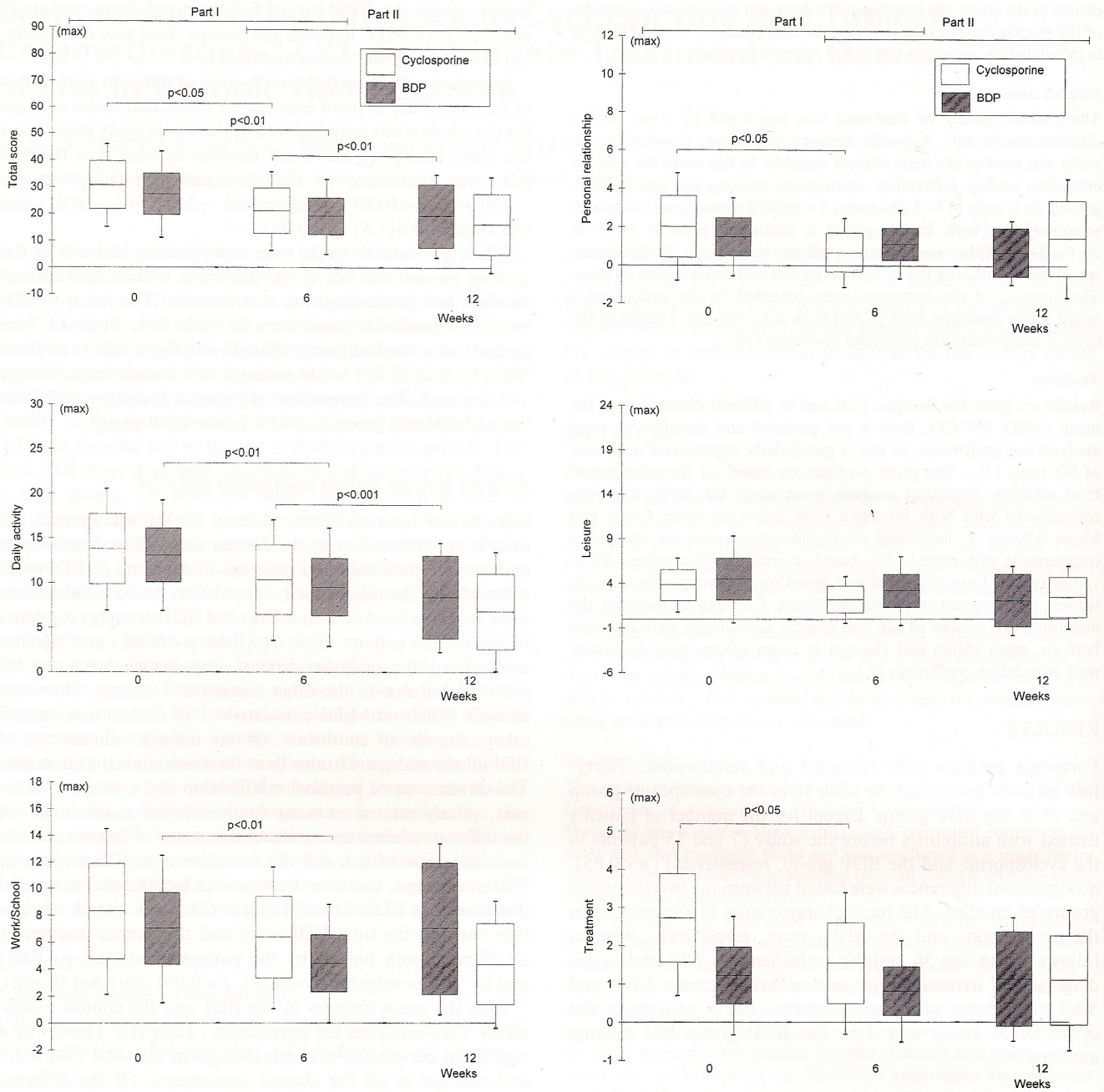

Fig. 1. Total and different dimensions of EDI in both treatment parts. *Boxes* indicate 95% confidence intervals and *bars* ±SD. The top of the *Y* axis indicates the maximum possible score. *BDP* = betamethasone-17,21-dipropionate. The *p* values correspond to the mean change from baseline or week 6, respectively.

(22), can thus be considered good. This was also shown by the significant correlations between the mean changes in many dimensions of EDI and the clinical assessments, as association between changes in quality of life scores and clinical scores suggests that the index adequately distinguishes changes over time (22).

Overall there was a clear correlation between quality of life and clinical assessments both when mean values and mean changes were considered. However, of the clinical assessments the extent of disease and itch showed the weakest relationship to EDI at baseline. This is not surprising, since itch in hand eczema is seldom of that magnitude experienced in atopic dermatitis and improvements in the extent of the disease are often of the all or none type. The weak correlation should rather be taken as a suggestion of leaving out assessments of disease extent and itch in medical intervention of hand eczema rather than incapacity of the EDI to recognize efficacy of the intervention.

In contrast to the experience in atopic dermatitis (8), we found no proof that measuring quality of life would measure different aspects of the disease or the medical intervention when compared to clinical assessments. This could be due to differences between atopic dermatitis and chronic eczema of the hands. Such a difference is suggested when baseline values

Table I. *Correlations† between quality of life and clinical assessments at baseline and at the end of treatment in the first part of the study*

	Clinical assessments at baseline (33 observations)					Clinical assessments at week 6, Part I (33 observations)				
Quality of life assessments	Disease activity	Extent of disease	Sleep	Itch	Use of emollient	Disease activity	Extent of disease	Sleep	Itch	Use of emollient
Daily activity	0.539**	0.115	0.193	0.117	0.209	0.481**	0.412*	0.273	0.380*	0.281
Work/School	0.389*	0.103	0.527**	0.111	0.226	0.312	0.352	0.543**	0.364*	0.065
Personal relationship	0.148	0.091	0.211	0.191	0.272	0.359*	0.340	0.213	0.256	−0.053
Leisure	0.508**	0.215	0.194	0.195	0.442*	0.520**	0.533**	0.311	0.421*	−0.095
Treatment	0.174	0.006	0.403*	0.149	0.213	0.042	0.155	0.21	0.083	0.611***
Total EDI	0.559***	0.086	0.400*	0.125	0.302	0.446*	0.443*	0.438*	0.425*	0.194

†Spearman correlation coefficients (r_s) tested against zero using two-tailed interpretation.
*$p<0.05$, **$p<0.01$, ***$p<0.001$.

Table II. *Correlations† between changes in quality of life and clinical assessments in the first part of the study*

	Clinical assessments				
Quality of life assessments	Disease activity	Extent of disease	Sleep	Itch	Use of emollient
Daily activity	0.480***	0.478***	0.365*	0.444**	0.280
Work/School	0.347*	0.226	0.280	0.127	0.399**
Personal relationship	0.351*	0.305*	0.084	0.246	0.430**
Leisure	0.327*	0.165	0.126	0.460**	0.383*
Treatment	0.014	0.318*	0.027	−0.118	0.229
Total EDI	0.481***	0.355*	0.335*	0.491***	0.453**

†Spearman's correlation coefficients (r_s).
*$p<0.05$, **$p<0.01$, ***$p<0.001$.

in the cyclosporine-treated group are compared to the corresponding values of the cyclosporine/placebo group in the study of atopic dermatitis by Salek et al. (11). Although the total EDI score was almost identical in the two studies (34 and 33.2%, respectively, of maximum score), the score for the dimensions of work/school (46 and 20.2%), personal relationship (17 and 32.8%) and leisure (16 and 26.3%) differed. Furthermore, in the present study treatment mainly affected the dimensions of daily activity and work /school (75% and 76% decrease, respectively), when cyclosporine treatment in atopic dermatitis seems to affect the different dimensions to the same degree. The difference between the two forms of eczema is also reflected in the present study, in which changes in the leisure dimension of the quality of life strongly correlated with itch, a fundamental symptom in atopic dermatitis. These differences in the various dimensions of the quality of life index emphasize the recommendation by Fitzpatrick et al., not to sum up various dimensions in a quality of life index because contradictory trends for different aspects of quality of life are missed (20).

Quality of life should measure a dimension not covered by the clinical score because medical views of severity often do not correlate well with patients' views. The strong correlation between the total score of EDI and clinical assessments in this study could be taken as a proof that clinical assessments in medical interventions in chronic hand eczema give enough strength to have a complete picture of the outcome. However, the missing correlation between some clinical assessments and both the total EDI and its dimensions shows that EDI views aspects of the disease not covered by these clinical measures. It is also possible that the EDI should be modified when used in other eczematous diseases than atopic dermatitis. Probably the dimensions of work/school and treatment should be emphasized. A modified EDI for chronic hand eczema could pick up subtle differences in a patient's state of well-being.

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