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INVESTIGATIVE REPORT

Treatment with a Barrier-strengthening Moisturizer Prevents Relapse of Hand Eczema: An Open, Randomized, Prospective, Parallel Group Study

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Hand eczema influences the quality of life. Management strategies include the use of moisturizers. In the present study the time to relapse of eczema during treatment with a barrier-strengthening moisturizer (5% urea) was compared with no treatment (no medical or non-medicated preparations) in 53 randomized patients with successfully treated hand eczema. The median time to relapse was 20 days in the moisturizer group compared with 2 days in the no treatment group ($p = 0.04$). Eczema relapsed in 90% of the patients within 26 weeks. No difference in severity was noted between the groups at relapse. Dermatology Life Quality Index (DLQI) increased significantly in both groups; from 4.7 to 7.1 in the moisturizer group and from 4.1 to 7.8 in the no treatment group ($p < 0.01$) at the time of relapse. Hence, the application of moisturizers seems to prolong the disease-free interval in patients with controlled hand eczema. Whether the data is applicable to moisturizers without barrier-strengthening properties remains to be elucidated. ***Key words: long-term management/treatment; maintenance treatment; urea; emollients; skin barrier function; topical corticosteroids; disease-control; prevention; randomized clinical trial.***

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Hand eczema is a common and persistent disease with a relapsing course and variable disease duration (1). Approximately half of cases of hand eczema develop into a chronic disease and symptoms may persist for many years or recur after disease-free intervals (1, 2). The one-year prevalence is approximately 10% and the lifetime prevalence is approximately 20% (3–5).

Treatment is avoidance of irritants and allergens that could worsen the eczema. Suppressive treatments are topical corticosteroids, irradiation with ultraviolet (UV) light or X-rays and chemotherapy (6). Moisturizers are considered useful treatment adjuncts, with those containing humectants being typically more efficacious than those without humectants (7). Efforts to improve the efficacy of moisturizers have included using skin-related lipids (e.g. ceramides) in formulations. However, no superiority of a ceramide cream over an ordinary petrolatum emollient was observed in patients with chronic hand dermatitis (8) or in experimentally irritated skin (9).

Long-term disease-control of hand eczema can be achieved by intermittent treatment with topical corticosteroids (10). Moisturizers are also suggested to be a vital part of the management when the skin condition is under control (11, 12). However, moisturizers have different effects on the skin. Furthermore, the majority of commercially available moisturizers are cosmetics, which according to the European Union (EU) legislation, cannot be recommended for treatment of skin diseases. More rigorous data on the preventive effectiveness of moisturizers are required (11), as some formulations deteriorate skin barrier function, with possible negative consequences for the eczema (13–17). Repairing the barrier or preventing barrier dysfunction are important strategies for reducing the risks for eczema (18).

One 5% urea-containing moisturizer has repeatedly been shown to improve skin barrier function in dry atopic skin (19, 20), as well as in normal skin (13). This urea-containing moisturizer was recently found to prevent relapse of flares in patients with controlled atopic eczema (21). The efficacy of the same urea-containing moisturizer to prevent eczema-relapse in patients with treated hand eczema was evaluated in the present study.

MATERIALS AND METHODS

Patients and study design

The study was conducted in accordance with the Declaration of Helsinki and was approved by an independent ethics committee and the national Competent Authority in Norway. A total of 53 patients (19 men and 34 women, mean age 46 years (age range 22–76 years) with a clinically proven history of hand eczema were recruited at four clinics in Norway (48 patients were enrolled by general practitioners and 5 by dermatologists). The mean time since their first diagnosis of hand eczema was 10 years. At inclusion the grading of the hands showed a controlled state of the eczema (the Hand Eczema Extent Score (HEES) was ≤ 3, see below). The patients also considered their eczema to be controlled

and they used moisturizers daily. Patients with a possible allergy to ingredients in the study medication and patients with active psoriatic lesions, active atopic eczema lesions or active bacterial, fungal or viral infection of the hands were excluded.

The patients were randomized to either the moisturizer (Canoderm cream 5% urea, ACO Hud, Upplands Väsby, Sweden) or to no treatment in a 1:1 ratio using a computerized procedure. The moisturizer was an oil-in-water emulsion containing 5% urea, fractionated coconut oil, emulsifying wax, hydrogenated canola oil, propylene glycol, carbomer, dimethicone, hard paraffin, glycerol polymetacrylate, propyl- and methyl parahydroxybenzoate, sodium lactate solution, lactic acid, glyceryl stearate, polyoxyethylene stearate and purified water. The lipid content of the cream was approximately 20% and pH 5. Patients randomized to moisturizer treatment were instructed to apply the moisturizer at least twice daily. The application frequency had to be noted daily in the patient diary for the first 28 days, thereafter weekly. Concomitant topical treatment of the hands was not permitted during the study. Patients randomized to no treatment were instructed to abstain from using moisturizers or other topical treatments on their hands during the study period. The flow of patients in the study is shown in Fig. 1. The intention to treat (ITT) population consisted of all randomized patients who applied the study moisturizer at least once, i.e. 53 patients in the present study. The per-protocol (PP) population (i.e. all patients who fulfilled all the major protocol criteria) consisted of 44 subjects in the analysis of visit 2 data and 45 subjects in the analysis of diary data.

The patient made a note of each application in the patient diary. Clinic staff weighed each tube before dispensing them to patients and upon return by the patients.

Evaluation

At recurrence of eczema the patients were instructed to contact the investigator and to have the lesion documented in a clinic visit. The date of eczema recurrence was noted in the patient diary. At inclusion in the study and at recurrence of eczema the patient reported the severity of their eczema on a 100-mm visual analogue scale (VAS), where 0 mm denoted no eczema and 100 mm extremely severe eczema. At inclusion in the study and upon eczema relapse the patient also assessed the influence of the skin disease using the Dermatology Life Quality Index (DLQI) (22). The questionnaire consists of 10 questions and covers items such as symptoms and feelings, leisure, daily activities, work and school. Each item is scored from 0 to 3, where higher scores indicate more problems. The individual items are summed to generate an overall score, where the maximum possible score is 30.

The investigator also scored the presence of eczema at inclusion and upon recurrence using the Hand Eczema Extent Score (HEES) method. HEES is the sum of the scores of the two hands and the maximum possible score is 74. Eczema on the entire dorsum of the hands scores 4, part of the dorsum scores 2, entire palm scores 4, part of palm scores 2, on the finger dorsum, edge, volar part, fingertip, nail, and finger-web score 1 each (23).

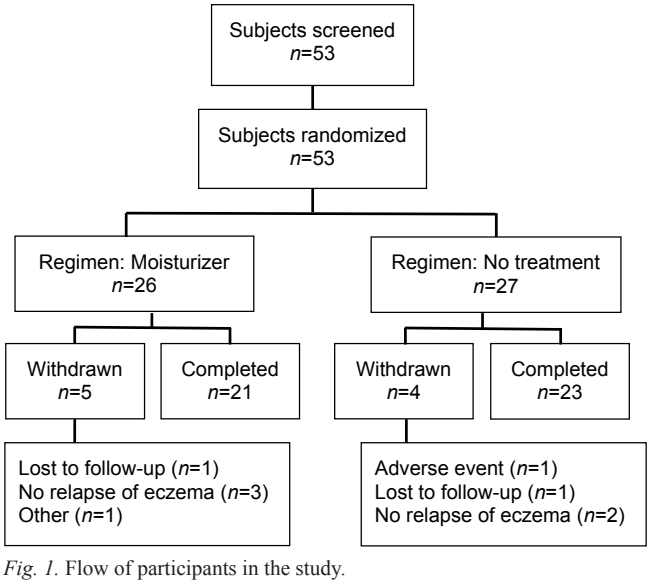

Fig. 1. Flow of participants in the study.

Calculations and statistical analysis

The main outcome measure was number of days to relapse of eczema, calculated as the time from entry into the maintenance phase until a relapse of eczema occurred. The Kaplan-Meier method was used in order to estimate the distribution of time to relapse in the two groups (24). Data for subjects who withdrew from the study or who were lost to follow-up were included in the analysis as censored observations, with the time of withdrawal or last time of study contact as time of censoring. The null hypothesis to be tested on a 5% significance level was that time until reappearance of eczema is equal in the patient group treated with the moisturizer compared with the patient group receiving no treatment. The hypothesis was tested using the log-rank test on the ITT population. Confirmatory analyses were also made on PP populations.

In the secondary analysis of eczema assessment on the VAS, HEES and DLQI, missing data were treated as missing. Patients who did not have a reappearance of the hand eczema during the study were not included in the analyses.

The non-parametric Spearman's correlation coefficient between different variables was calculated and tested for significance, where $p < 0.05$ was considered significant.

RESULTS

Fifty-three patients were included and 44 patients fulfilled all major protocol criteria (Fig. 1). The subject diary showed that 92% of the patients in the treatment group applied the moisturizer in accordance with the instructions on more than 75% of the days. The daily median consumption of cream was 5.9 g (mean ± SD 11.0 ± 12.6).

The primary efficacy variable showed that the median and 25/75 percentiles of the number of days from inclusion in the study to reappearance of eczema was 20 (6/92) days in the moisturizer group and 2 (1/15) days in the no treatment group (Fig. 2) ($p = 0.04$). The difference in time to relapse was also significant in the PP group, $p = 0.007$. Five persons did not experience any eczema relapse during the 6-month study period; 3 of these belonged to the moisturizer group (12%) and 2 were in the no treatment group (7%) (Fig. 1).

At the time of relapse of eczema, the mean increase in HEES was 8.8 in the moisturizer group and 13.0 in the no treatment group (Table I). There were no differences in the degree of eczema at the time of relapse between the two groups ($p = 0.28$). Nor were there any differences between the patients' estimation of their degree of eczema at relapse. The degree of eczema on the 100 mm

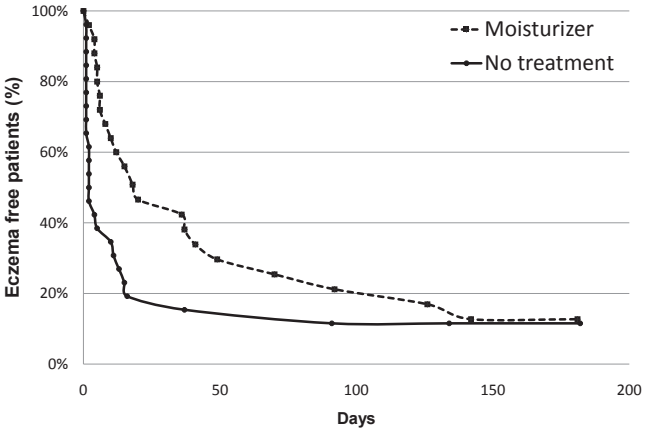

Fig. 2. Relapse of hand eczema in the moisturizer and no treatment groups. Median time to relapse was 20 days in the moisturizer group and 2 days in the no treatment group. The 95% confidence interval was 8–19 days in the moisturizer group and 1–11 days in the no treatment group. $n = 53$; 19 men and 34 women, mean age 46 years (age range 22–76 years).

VAS was 2.5 mm lower with the moisturizer treatment than with no treatment ($p = 0.66$) (Table I). The results of the corresponding analyses of the PP populations were similar to the ITT populations.

The two treatment groups had similar DLQI scores at inclusion (Table I). At recurrence of eczema the mean scores had increased significantly in the two groups ($p < 0.01$) from 4.7 to 7.1 in the moisturizer group and from 4.1 to 7.8 in the no treatment group (Table I).

There was a positive correlation between the assessment of eczema made by the clinician (HEES) and patients assessment of DLQI at relapse of eczema (Spearman's rank correlation coefficient r = 0.39, $p = 0.0085$, $n = 44$). DLQI and patient assessment of eczema (on the VAS) also correlated significantly (r = 0.52, $p = 0.0003$, $n = 44$), and there was also significant correlation between HEES and patient assessment of eczema (on the VAS) (r = 0.42, $p = 0.0042$, $n = 44$).

DISCUSSION

As long ago as 1943 a urea-containing moisturizer was found to be superior to a urea-free cream in inducing softer, smoother, and even whiter, hands in 225 hospital personnel (25). Since then, a large number of studies on the efficacy of moisturizers in the treatment of dry skin have been published. However, to our knowledge this is the first study in which the potential of a moisturizer to prevent relapse of hand eczema in patients with a controlled state of their eczema has been examined.

The adherence to the treatment was satisfactory in the present study, as the median consumption of cream was 5.9 g/day. A recent cost-utility analysis estimated the daily cream consumption on adult hands to be 2 g/day (26).

In the present study, as well as in our previous study on atopic dermatitis (21), the eczema relapse was simply detected by the patients themselves and then confirmed by the clinician. This approach is considered relevant based upon a systematic review of the literature and experience in running clinical trials (27). Furthermore, answering the question "do you have hand eczema" has high sensitivity and specificity and is less complicated to the lay individual than identification of skin signs used for clinical diagnosis of eczema (28).

Clinical diagnosis of hand eczema includes several scoring systems for measuring severity and no widely accepted standardized scoring system exists (29). The HEES system used in the present study is simple and straightforward, since it focuses only on the presence of eczema at different locations on the hands. The system was developed in the 1980s to study epidemiological changes in hand eczema (23) and has been found to be useful to predict the long-term prognosis of hand eczema (30). Furthermore, a clear association between the presence of eczema and morphology was also proven, where widespread eczema tended to be more polymorphic than eczema at low extent, and vice versa; polymorphic hand eczema also tended to be more widespread than hand eczemas with fewer morphological characters (29).

In the present study the HEES at relapse of eczema correlated significantly with the patient assessment of DLQI and the VAS. A significant correlation between hand eczema severity score and DLQI was reported recently using a new scoring system also addressing the severity of the hand eczema (Hand Eczema Severity Index, HECSI) (31).

The findings of the present study demonstrated that patients with hand eczema could delay their next ec-

Table I. *Hand Eczema Extent Score (HEES) assessed by the physician at inclusion to the study and the patients scoring of the eczema on the visual analogue scale (VAS) and using the Dermatology Life Quality Index (DLQI) scoring system. Mean values and standard deviation (SD)*

	Moisturizer			No treatment		
	HEES	VAS	DLQI	HEES	VAS	DLQI
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Time	$n = 21$	$n = 20$	$n = 21$	$n = 23$	$n = 23$	$n = 23$
Inclusion	2.2 (0.9)	22.1 (23.6)	5.3 (3.8)	2.3 (0.8)	24.6 (20.6)	4.4 (4.7)
Relapse	11.0 (8.7)	54.2 (24.9)	7.1 (4.3)	15.3 (13.9)	58.1 (18.9)	7.8 (5.0)
Change	8.8 (8.8)	32.2 (20.0)	1.8 (4.4)	13.0 (14.1)	33.6 (21.0)	3.3 (3.0)

zema relapse by the use of the urea-containing cream. The median time to eczema-relapse showed a ten-fold difference between the moisturizer and no treatment groups; 20 days vs. 2 days, respectively. In our previous study on patients with controlled atopic dermatitis, we showed that moisturizer treatment prolonged the time to eczema-relapse from 30 days in the untreated group to more than 180 days in the moisturizer group (21). The shorter time to relapse of eczema in the hands than in atopic body areas, is probably due to the high vulnerability of the hands. Hands are easily exposed to external stressors.

The definition of the primary outcome in the present study depended on an action initiated by the participants. Hence, it is possible that the subjects in the no treatment group alerted the clinicians earlier about a flare than those in the moisturizer group. However, the results from patient's assessments of eczema on a VAS-scale and physician's assessment by use of the HEES-system, showed no significant differences in severity of eczema between the treatment groups at relapse. The results tended to indicate more severe eczema on untreated hands compared with moisturizer-treated hands.

The ten-fold difference in time to relapse of eczema between treated and untreated hands made it possible to reject the null hypothesis on a 5% significance level without including more than 53 subjects in the present study. A larger number of patients would probably have been required to demonstrate superiority of the present moisturizer to its placebo, since its cream-base is also expected to contribute to the advantageous results. The use of a humectant-free lipid-rich moisturizer has been found to be of general benefit to control dryness in cleaners and kitchen workers during everyday exposure to water and detergents (32). However, whether a similar delay in the flare-up of eczema would have been noted with a moisturizer without barrier-improving properties has yet to be studied. Increasing evidence of functional differences in effects on skin barrier function between creams may bring into question the suitability of barrier-deteriorating moisturizers for treatment and prevention of dry skin disorders (13, 15, 17, 33–35).

In conclusion, this clinical study demonstrated that maintenance treatment with a barrier-strengthening moisturizer significantly reduces the time to relapse of hand eczema. At the time of relapse of eczema no difference in severity was noted between the groups.

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