

ORIGINAL ARTICLE

Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial

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Abstract

Background Standard treatment of atopic dermatitis (AD) is based on topical glucocorticosteroids or calcineurin inhibitors to treat flares combined with moisturizer treatment to alleviate dry skin symptoms. Patients with AD have an abnormal skin barrier function, and strategies for reducing the risks for eczema would be to repair the barrier or prevent barrier dysfunction.

Objectives The objective of this study was to explore the time to relapse of eczema during a 26-week maintenance treatment with a urea containing moisturizer compared to no treatment (neither medical nor non-medicated preparations) after successful clearing of atopic lesions. The moisturizer has previously been shown to improve skin barrier function.

Methods Patients applied betamethasone valerate (0.1%) on eczematous lesions during a 3-week period. Those with cleared eczema entered a 26-week maintenance phase, applying the moisturizer or left the previously affected area untreated. Upon eczema relapse, patients were instructed to contact the clinic and to have the relapse confirmed by the investigator.

Results Fifty-five patients entered the study and 44 patients were included in the maintenance phase (22 using moisturizer twice daily and 22 using no treatment). Median time to relapse for patients treated with moisturizer was > 180 days (duration of the study) compared with 30 days for the no-treatment group. Sixty-eight per cent of the patients treated with the moisturizer and 32% of the untreated patients remained free from eczema during the observation period.

Conclusions Maintenance treatment with a barrier-improving urea moisturizer on previous eczematous areas reduced the risk of relapse to approximately one third of that of no treatment.

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Keywords

disease control, emollients, long-term management/treatment, maintenance treatment, prevention, skin barrier function, topical corticosteroids, urea

Conflicts of interest

None declared.

Introduction

Atopic dermatitis (AD) is a chronic relapsing and remitting disease characterized by exacerbations or flares over years. AD has a profound effect on the quality of life for both sufferers in childhood and their families. In addition to the effects of stubborn itching, skin damage, soreness, sleep loss and the social stigma of

a visible skin disease, other factors such as frequent visits to doctors, special clothing and the need to constantly apply topical applications all add to the burden of disease.¹

AD is a multifactorial disease which is increasingly being considered a primary disorder of stratum corneum barrier failure, where major predisposing factors for the eczema are mutations in

the *filaggrin* gene.²⁻⁴ Filaggrin plays a key role in epidermal barrier function as it aggregates keratin filaments and adds to the bulk of natural moisturizing factor (NMF) in the stratum corneum.⁴⁻⁷ Mutations in the gene leads to reduced level of NMF.⁸ The barrier abnormality enables enhanced penetration of environmental noxious substances, which may favour not only the development of eczema, but is also suggested to predispose patients to asthma.³ The impaired skin barrier function is measured as elevated transepidermal water loss (TEWL), both in the rough and clinically normal skin.^{9,10}

Conventional long-term therapy for AD is based on anti-inflammatory drugs, usually topical glucocorticosteroids or topical calcineurin inhibitors, combined with moisturizer treatment.¹¹ Most trials in AD have been concentrated on short-term disease control, whereas more recent trials have begun to consider the issue of long-term control, with particular emphasis on the prevention of flares using intermittent treatment with corticosteroids or early treatment with calcineurin inhibitors.¹²⁻¹⁶

Moisturizers alleviate dry skin symptoms and reduce the need for corticosteroids.^{17,18} However, evidence to make recommendations on moisturizers is scarce, and more rigorous data on their preventive effectiveness have been requested.¹¹ Clinical differences between treatments are found and some moisturizers may actually deteriorate the skin barrier function.¹⁹⁻²³ Important strategies for reducing the risks for eczema would be to repair the barrier or prevent barrier dysfunction.²⁴

The objective of this study was to explore the efficacy of a moisturizer applied daily after successful clearing of atopic lesions with topical treatment with betamethasone valerate (BV) 0.1% cream. The time to relapse of eczema was measured during a 26-week maintenance therapy. The moisturizer chosen for this study has previously been shown to improve skin barrier function in dry atopic skin,^{25,26} as well as in normal skin.¹⁹

Methods

Patients and treatments

This was a randomized, controlled, parallel-group, prospective, multicentre study conducted at five dermatology outpatient clinics centres in Sweden. Included patients (55 Caucasians; 18–65 years) were either known to the clinic for their chronic atopic disease, or were consecutively diagnosed as patients with AD according to Hanifin and Rajka.²⁷ Patients receiving any concomitant medications that might have affected the study's outcome were excluded. Patients eligible for the study had a typical lesion on an easily inspected body area, such as arms, legs, chest, abdomen or back, in addition to possible eczema elsewhere. The degree of eczema on the identified area had to have an initial score of at least 6 according to the Atopic Dermatitis Severity Index (ADSI;²⁸ see below).

The patients were randomized to treatment with one of two 0.01% BV creams (Betnoderm® ACO HUD AB, Upplands Väsby, Sweden or Betnovat® GlaxoSmithKline, Solna, Sweden) on the

Table 1 Patient demographics in the maintenance phase

	Moisturizer (n = 22)	No treatment (n = 22)
Age (years), mean ± SD	34.0 ± 14.4	33.1 ± 13.4
Female : Male (%)	68.2 : 31.8	77.3 : 22.7
Study area (number of patients)	Arm (14)	Arm (15)
	Back (4)	Back (4)
	Leg (2)	Leg (2)
	Abdomen (1)	Abdomen (1)
	Chest (1)	Chest (0)

identified area for 3 weeks: week 1, twice daily; week 2, once daily; week 3, once daily every other day. One of the BV creams was a new generic medicinal whose skin compatibility should be confirmed in the study. After the treatment period, the patients were clinically evaluated by a dermatologist and those with cleared eczema, and only signs of lichenification, were considered eligible to take part in the maintenance phase. These patients were randomized to either moisturizing treatment (Canoderm cream 5%, ACO HUD NORDIC AB, Upplands Väsby, Sweden) or to no treatment in the previously corticosteroid-treated area. The moisturizer was an oil-in-water emulsion containing 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, purified water. The lipid content of the cream was c. 20% and pH 5. The demographic characteristics of patients randomized to maintenance treatment and disposition to identified body sites are given in Table 1.

Patients allocated to the treatment group were instructed to apply the moisturizer on the identified area twice daily, whereas the other group had to abstain from using any topical formulation on the area. Concomitant treatment of other body areas with other topical preparations (e.g. cosmetics and corticosteroids) was allowed throughout the study. Both patient groups were instructed to inspect the identified area daily for the presence of possible recurrence of eczema. They should note the date in the patient diary and immediately contact the investigator, who confirmed the relapse of eczema. The study lasted until recurrence of eczema or at the most 6 months (180 days). Patients that did not experience relapse of eczema were clinically evaluated after 6 months. The definition of eczema relapse was simply defined as an episode requiring additional medical treatment based upon the patients' judgement of the worsening in skin condition,²⁹ which is in agreement with a previous proposal based upon a systematic review of the literature and experience in running clinical trials.²⁹

The study was planned and carried out in accordance with Helsinki Declaration II and the good clinical practice guidelines of the EU. The protocol was approved by the local ethics committee and by the Swedish Medicinal Products' Agency.

Evaluation

The degree of eczema was scored at inclusion in the study and after treatment for three weeks in accordance to the ADSI,²⁸ which is based upon a cumulative 0–3 point scale (0 denotes none/absent; 1, mild; 2, moderate; and 3, severe) for the five parameters erythema, pruritus, exudation, excoriation and lichenification in the defined area. The maximum score is 15.

Instrumental measurement of the integrity of the skin barrier (TEWL) was conducted at inclusion to the study start, after treatment with BV for 3 weeks and then after additional 3 weeks of the maintenance phase. Patients were instructed to abstain from cream treatment in the morning before attending the clinic. Measurements of TEWL were performed using DermaLab (Cortex Technology, Hadsund, Denmark; open chamber). After the probe was applied on to the skin, TEWL values were automatically transferred into a computer during the subsequent 60 s, and the mean value from the latest 20 s was recorded and used for further calculations.

Calculations and statistical analysis

The main outcome measure was time to relapse of atopic eczema, calculated as the time from entry into the maintenance phase until a relapse occurred. The Kaplan-Meier method was used in order to estimate the distribution of time to relapse.³⁰ The null hypothesis to be tested on a 5% significance level was that the time until reappearance of eczema is equal in the patient group treated with the moisturizer compared to the patient group receiving no treatment. The hypothesis was tested using the log-rank test on the intention to treat population (all patients were included in the analysis if they were randomised and applied the study moisturizer at least once). The hazard ratio was estimated as the ratio of the hazard rate in the treated vs. the untreated group. The hazard rate is the probability that if the eczema relapse has not already occurred, it will occur in the next time interval, divided by the length of that interval. In addition, absolute and relative risk reduction as well as the number needed to treat for 6 months to prevent one event of eczema relapse were calculated. Confirmatory analyses were also conducted on per protocol populations (all patients who fulfilled all the major protocol criteria); however, they are not shown in this paper.

Secondary efficacy variable was TEWL after 3 weeks of the maintenance phase and was presented in a box plot. In the text, median values are given for non-parametric data with lower (Q1) and upper (Q3) quartiles in brackets. Mann-Whitney *U*-test was used for analysis of the efficacy variables between the groups.

Results

Fifty-four of the 55 included patients completed the first part of the study, and one patient withdrew due to reasons not related to the treatment. A flow diagram of patients and treatment outcomes are shown in Fig. 1. Both BV creams improved the degree of eczema and decreased TEWL significantly (Fig. 1). There were no

Table 2 Time to relapse in the maintenance phase

	Group using moisturizer (n = 22)	Group using no treatment (n = 22)
No. (%) of patients having a relapse	7 (32%)	15 (68%)
Median time to relapse (days)	> 180	30
Hazard ratio (no treatment:moisturizer)	3.2 (95% CI 1.3 to 7.8 <i>P</i> = 0.01)	
Absolute risk reduction (%)	36%	
Number needed to treat (NNT)	2.8	
Relative risk reduction (%)	53%	

statistically significant differences between the treatment outcomes. Forty-four patients were eligible for the maintenance phase, and no differences between the groups were noted with respect to demography, body site treated or skin condition at start of the maintenance therapy (Table 1).

In the maintenance therapy, 68% of the patients treated with the moisturizer and 32% of the untreated patients experienced no relapse in the eczema during the 180 days of observation. The median time to relapse of the patients treated with the moisturizer was > 180 days (the duration of the study) and 30 days without moisturiser treatment (Table 2, Fig. 2). Table 2 shows results of the primary endpoint. There was a significant difference in time to relapse of AD during the maintenance phase (*P* < 0.01) with a hazard ratio of 3.2, indicating that patients using the moisturizer reduced the risk of relapse to approximately one third of that on no treatment (Table 2). It could be estimated that only three patients were needed to be treated in order to prevent one relapse of eczema during a 6-month period (Table 2).

The difference in TEWL between the groups after three weeks of maintenance treatment did not reach statistical significance (*P* > 0.05; Fig. 3).

Discussion

The use of moisturizers not only reduces the need for corticosteroids¹⁸ and enhances clearance of eczema,^{31,32} but is also suggested to prolong the clinical improvement after therapy discontinuation.³³ To our knowledge, this is the first study in which the prevention-of-eczema strategy with a moisturizer has been compared with no treatment in the management of AD. We used a structured procedure and initiated the study by clearance of active lesions in the targeted body sites with a strong corticosteroid cream (BV 0.1%). By focusing on distinct body sites, we believed that we increased adherence to the moisturizer treatment and avoid recording relapses in body sites with less defined treatments. One possible limitation with the study design is that the obtained results may not be applicable to other body areas without further adjustments. The vulnerability to eczema may vary between body areas and patients, where those more prone to eczema may relapse earlier. However, it is presently unknown whether the treatment offers

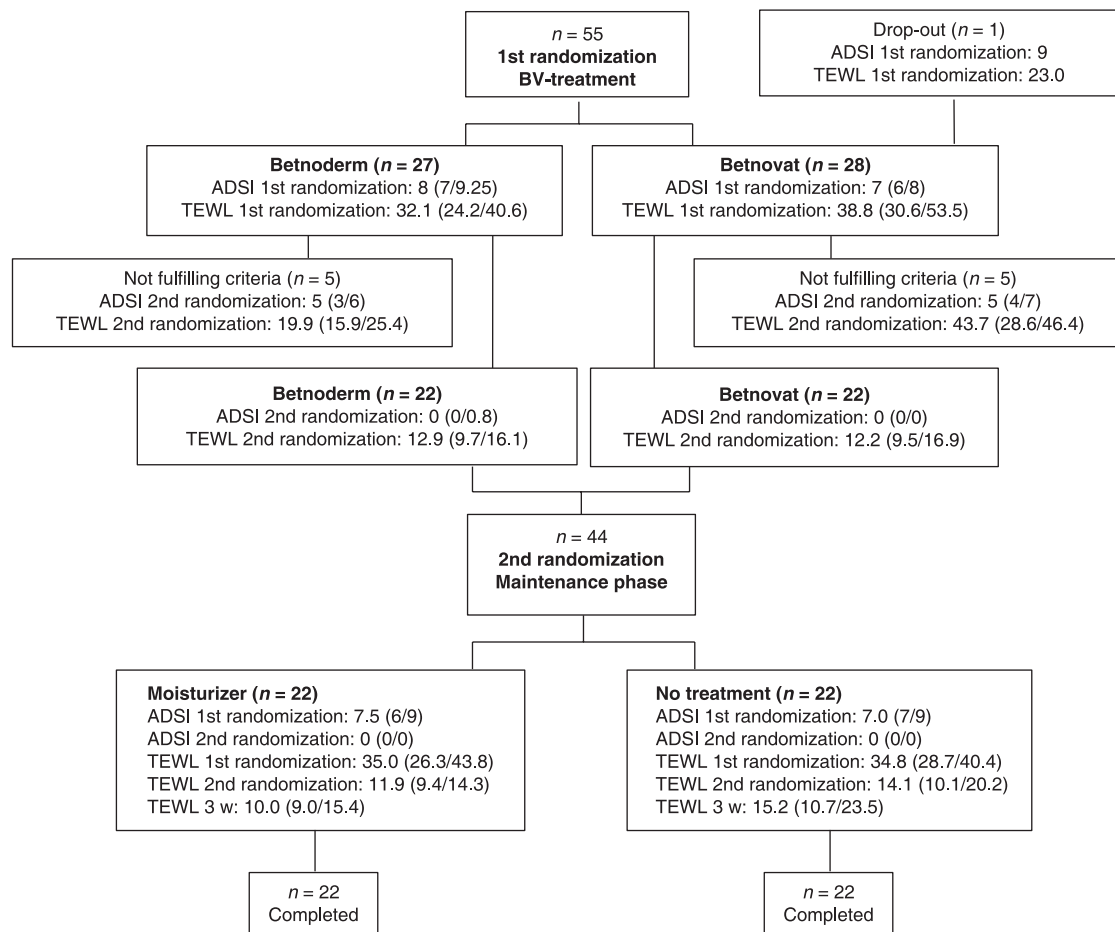


Figure 1 Flow of participants and the number of patients (*n*) in the different parts of the study. Median value of TEWL (g/m²/h) and ADSI score for the patients in the first and second randomization and after completion of the study. Numbers within parenthesis denote the lower (Q1) and upper quartile (Q3) value.

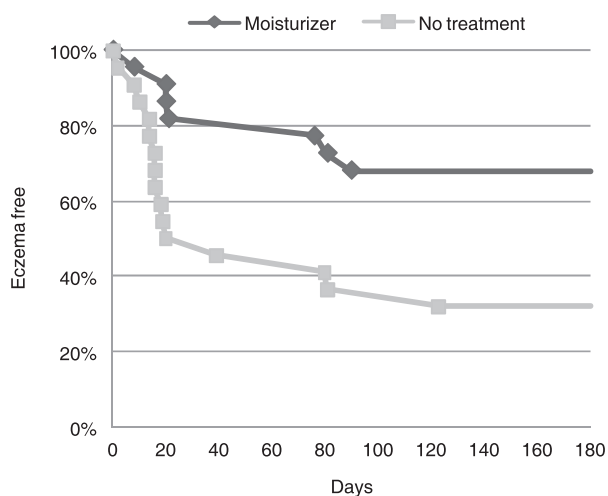


Figure 2 Kaplan-Meier plot of time to recurrence of eczema in the moisturizer and no treatment groups.

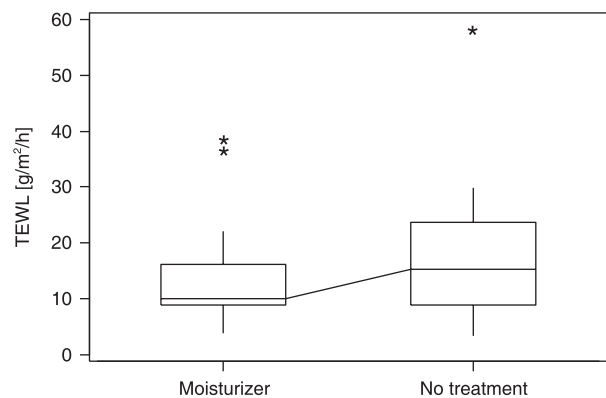


Figure 3 Skin barrier function measured as TEWL after 3 weeks in the maintenance period in the patients receiving treatment ($n_{\text{day 21}} = 20$) and those on no treatment ($n_{\text{day 21}} = 15$). The lower line of the box illustrates the first quartile (Q1) and the upper line the third quartile (Q3). The middle line in the box represents the median. The whiskers are the highest and lowest.

similar risk reduction for eczema relapse irrespectively of body site, or not.

The results showed that in the moisturiser group the majority of patients remained free from eczema at 180 days (i.e. the median time to relapse of eczema was longer than 180 days). In contrast, the median time to relapse in the untreated group was 30 days. The probability of not having a relapse during the 26-weeks period was 68% in the moisturizer group and 32% for those not using a moisturizer, which resulted in a 53% relative risk reduction and 36% absolute risk reduction during the 26-week period. For every three patients treated with the moisturizer for 6 months, one fewer eczema relapse on average should be expected.

The present findings could be compared with results from similar studies focusing on long-term control of atopic eczema using anti-inflammatory agents. Although these studies have slightly different designs, they give rough estimates on the efficacy of anti-inflammatory drugs and their corresponding vehicles to control eczema. Surprisingly, the outcome for the moisturizer treatment in the present study did not show pronounced differences to results from intermittent treatment with calcineurin inhibitors or corticosteroids on controlled atopic eczema.^{12–16} For example, only 45–60% of patients did not experience a flare during two 24-week studies of with early intervention or intermittent treatment with calcineurin inhibitors.^{12,14,15} The median time to first flare requiring more potent corticosteroids treatment was reported to be 142 days in one study¹² and > 190 days in another.³⁴

Furthermore, treatment with the vehicle in the cited studies did not give pronounced different results in comparison to the untreated site in the present study. For example, the probability of not having a relapse in patients treating their stabilized eczema with a corticosteroid vehicle for 16 weeks was reported to be 30% in one study¹⁰ and 66% in another study.¹⁶ In three other studies, only 19–22% of the patients remained free from relapses during a 24-week period^{12,14,15} to be compared with 32% in the untreated group in the present study. The median time to relapse in the vehicle groups was been reported to be 15, 36 and 67 days,^{12,13,34} whereas it was 30 days without treatment in the present study.

The delay in eczema relapse and the similarity in relapse rate between the moisturizer in the present study and the reported anti-inflammatory treatments suggest that barrier-strengthening therapy is a useful alternative in the long-term control of the eczema.^{4,17,24} The moisturizer in the present study has repeatedly been shown to improve barrier function in both normal¹⁹ and atopic skin,^{25,26} whereas in the present study, the decrease in TEWL did not reach statistical significance. One conceivable explanation might be the low number of patients remaining in the study at the time of measurement, which in combination with the parallel group comparison lowers the statistical power. Possible mechanisms behind barrier improvement are upregulation of pathways controlling *filaggrin* gene expression⁴ or barrier lipid synthesis. We have recently shown that in normal skin the expression of cyclin-dependent kinase inhibitor 1A is influenced by the

present moisturizer, whereas a barrier-deteriorating moisturizer induces differences in mRNA expression of involucrin, transglutaminase and enzymes responsible for barrier lipid synthesis, such as the gene involved in formation of cholesterol and the genes involved in the formation of ceramides.^{35,36}

Other possible avenues for therapeutic interventions are immediate effects on the intercellular lipid bilayers by replenishment of deficient lipids. For example, ceramide-dominant lipid mixtures have been shown to reduce disease severity as monotherapy and in combination with corticosteroid treatment in atopic dermatitis.^{37–40} However, the absorption of ceramides and the superiority of certain lipid mixtures to other lipids remain to be proven in randomized and controlled studies on humans, since no evidence of such effects appears to exist in humans.^{41,42}

The link between barrier function and eczema suggests that treatment with barrier-deteriorating moisturizers^{19,21,23,43,44} may actually reduce the time to relapse of AD compared to no treatment. Relapse of eczema was also found already within 10 days in the vast majority of patients in one of the eczema control studies,³⁴ despite the use of bland emollients (not containing ingredients such as lactic acid, urea, alpha-hydroxyacids) to control the eczema.³⁴ However, the authors also noted that some patients appeared to have derived benefit from treatment with certain emollients since no relapse was noted in them.³⁴ Hence, increasing evidence suggests clinical important differences on skin barrier function between creams which may question the general suitability of moisturizers for treatment and prevention of dry skin disorders.

In conclusion, the present clinical trial demonstrates that maintenance treatment with a barrier-improving urea moisturizer^{19,25,26} on corticosteroid-healed sites in AD patients reduces the risk of relapse of the eczema. The long-term control of AD with a moisturizer offers important possibilities for patients, as well as for the medical society to increase patients' quality of life. In addition, the study highlights the potential benefit with evidence-based treatment recommendations. Future studies should address the risk reduction in other body sites and with other type of moisturizers.

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