

CLINICAL REPORT

Comparison of Moisturizing Creams for the Prevention of Atopic Dermatitis Relapse: A Randomized Double-blind Controlled Multicentre Clinical Trial

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Atopic dermatitis (AD) affects adults and children and has a negative impact on quality of life. The present multicentre randomized double-blind controlled trial showed a barrier-improving cream (5% urea) to be superior to a reference cream in preventing eczema relapse in patients with AD (hazard ratio 0.634, $p=0.011$). The risk of eczema relapse was reduced by 37% (95% confidence interval (95% CI) 10–55%). Median time to relapse in the test cream group and in the reference cream group was 22 days and 15 days, respectively ($p=0.013$). At 6 months 26% of the patients in the test cream group were still eczema free, compared with 10% in the reference cream group. Thus, the barrier-improving cream significantly prolonged the eczema-free time compared with the reference cream and decreased the risk of eczema relapse. The test cream was well tolerated in patients with AD. Key words: atopic dermatitis; atopic eczema; emollients; moisturizer; prevention; urea.

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Atopic dermatitis (AD) is a common chronic inflammatory skin diseases affecting up to 10% of adults and 30% of children in the Western world (1). It is a multifactorial disease, which is influenced by inheritance as well as by the environment. AD is a relapsing and remitting disease with exacerbations. It has a considerable impact on the patient's quality of life (QoL) (2). Patients with AD have defects in skin barrier function, resulting in reduced water retention. The defected skin barrier also predisposes the skin to increased susceptibility to noxious substances, and may lead to allergies and asthma (3, 4).

In addition to the elimination of provoking factors, conventional therapy in the acute phase of AD is based on anti-inflammatory drugs, usually topical glucocorticoids or calcineurin inhibitors, combined with moisturiz-

er treatment (5). The use of moisturizers is emphasized by healthcare professionals as part of the treatment of AD (6–8). Moisturizer therapy is suggested to enhance the healing of eczemas (9, 10) and to prolong the clinical improvement after discontinuation of anti-inflammatory therapy (11), thereby reducing the need for additional treatment, including topical corticosteroids (12).

Selecting the most suitable moisturizer for treatment of AD has been a matter of trial-and-error, since the beneficial effects of most moisturizers on skin barrier function are not well documented. Some moisturizers have even been shown to worsen the skin barrier function on normal skin (13–15). The test cream used in this study is a medicinal moisturizer with 5% urea (Canoderm, ACO Hud Nordic, Sweden), which has been shown to improve skin barrier function, as measured by a reduced transepidermal water loss (TEWL) and skin susceptibility to surfactant-induced irritation, in AD as well as in normal skin (13, 16–19). The test cream has also been shown to delay time to eczema-relapse in patients with eczema, compared with no treatment (20, 21).

To our knowledge, no randomized controlled double-blind clinical studies have been done comparing the time to eczema-relapse with a barrier-strengthening moisturizer and a moisturizer without a measurable effect on skin barrier function in maintenance treatment. It was therefore important to evaluate this in order to facilitate an evidence-based choice of moisturizer. The primary objective of this study was to show that a barrier-strengthening moisturizer (test cream), is superior to a reference cream (without urea), in preventing eczema relapse in patients with AD.

PATIENTS AND METHODS

Study design

This multicentre study consisted of 2 phases, an open-label stabilization phase and a double-blind randomized, prospective and parallel group maintenance phase (visit 2/2b [randomization and start of maintenance phase], visit 3 [day 28 ± 5 days] and visit 4 [day 180 ± 14 days] or until relapse occurred). Patients were recruited at 15 dermatological clinics in Finland,

Norway and Sweden. All participants received oral and written information about the study and voluntarily signed an informed consent. The study was planned and carried out with the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association and good clinical practice. The protocol was approved by local ethics committees and by the Medical Products' Agencies in participating countries. The study was conducted during the period from September 2011 to September 2012.

Patients

Inclusion criteria were: subjects ≥ 18 years old, diagnosed with AD according to UK working party's criteria 1994 and with visible atopic eczema of the body surface area, corresponding to a total area of at least the size of the palm of one hand. Exclusion criteria were: eczema exclusively on the hands, any concomitant medications that might affect the study's outcome, known hypersensitivity or allergy to any of the study products, any serious current medical condition that could interfere with the evaluation of the study results, patients assessed by the investigator to have poor compliance, enrolled in any investigational study or using an investigational drug within 3 months prior to the screening visit. Patients who were pregnant, breastfeeding, or planning to become pregnant during the study time, were also excluded. Patients were randomized at visit 2/2b. Randomization to test cream and reference cream groups in 1:1, was performed according to a randomization list, with a block size of 4, and stratified for country with one randomization list for each country. The patients were provided with a randomization number. The randomization was prepared by an independent statistician using a validated SAS® program. All study personnel at the clinics and the sponsor staff remained blinded during the maintenance part of the study.

Interventions

At the screening visit (visit 1), the following assessments were performed: severity of AD (Rajka & Langeland; 22), evaluation of the eczemas (SCORing Atopic Dermatitis [SCORAD]) and QoL (EQ-5D). The study area eczemas were defined (SCORAD) and patients entered the stabilization phase during which the study areas were treated with once-daily topical mometasone furoate cream 0.1% (Elocon, Merck Sharp & Dohme B.V, Netherlands) on the trunk and extremities and/or hydrocortisone cream 1% (Hyderm® ACO Hud Nordic, Upplands Väsby, Sweden) on the face, groins and armpits. In addition, patients used a medicinal moisturizer containing 20% glycerol (Miniderm®, ACO Hud Nordic, Upplands Väsby, Sweden) on the study areas as well as on other dry areas as needed. At visit 2, evaluation of eczemas (SCORAD) and QoL (EQ-5D) was performed and patients were also evaluated by the Investigator's Global Assessment (IGA). Patients with cleared or almost cleared eczemas entered the maintenance phase. Patients with on-going eczema continued in the stabilization phase for an additional week before re-evaluation (visit 2b).

During the maintenance phase the test cream or the reference cream (ACO Hud Nordic AB, Upplands Väsby, Sweden) were applied at least twice daily on the study areas and on other dry areas until eczema relapsed (relapse visit) or until the end of the maintenance phase (visit 4), whichever came first. Relapse was defined as an episode that, from the patient's perspective, required escalation of treatment of the study areas. The patients were instructed to contact the investigator immediately if any study area relapsed or if any new eczematous area appeared. The relapse was confirmed by the investigator using IGA and SCORAD. At the relapse visit, QoL (EQ-5D) was also measured.

Patients without any relapse continued in the study until day 180 (visit 4) and were evaluated by IGA; SCORAD and EQ-5D.

Efficacy endpoints

The primary endpoint of the study was time between randomization and a subsequent event of relapse, measured as a hazard ratio. The hazard ratio is an expression of the hazard of events occurring in the reference cream group as ratio of the hazard of events occurring in the test cream group.

Secondary endpoints were time to relapse evaluated by Kaplan–Meier estimator, proportions of patients still eczema free after 3 and 6 months maintenance treatment, absolute and relative risk reduction, cream consumption of maintenance treatment and QoL.

During the maintenance phase, the study areas were evaluated by IGA and SCORAD at visit 2, visit 3, visit 4, and at the relapse visit. All patients were evaluated at visit 2, possibly visit 3 (depending on when the relapse occurred in time) and then either at the relapse visit or visit 4. Patient's QoL was assessed at visits 1–4 using the EQ-5D™ health questionnaire of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the visual analogue scale (VAS).

Reference and test cream

The reference cream used in this study was the placebo to the moisturizer Miniderm i.e. the reference cream was Miniderm without glycerol (ACO Hud Nordic, Upplands Väsby, Sweden). The reference cream has been studied clinically on atopic patients (23) and on normal healthy individuals showing no measurable effects on skin barrier function (24) and contains: white soft paraffin, hydrogenated canola oil, light liquid paraffin, glyceryl stearate, polyoxyethylene stearate, cetostearyl alcohol, hard paraffin, dimethicone, cholesterol, propyl- and methyl parahydroxybenzoate and purified water. The test cream is a medicinal cream, Canoderm® (ACO Hud Nordic, Upplands Väsby, Sweden), available in the Nordic countries, which is an oil-in-water emulsion containing 5% urea, fractionated coconut oil, polysorbate 60, hydrogenated canola oil, propylene glycol, carbomer, dimethicone, hard paraffin, glyceryl polymethacrylate, propyl- and methyl parahydroxybenzoate, sodium lactate, lactic acid, glyceryl stearate, polyoxyethylene stearate, cetostearyl alcohol and purified water.

Safety

Safety was assessed by recording adverse events (AE) at all visits. Any new eczema that appeared on the body ≥ 5 cm from study areas during the maintenance phase was documented as an AE. Relapse was defined as an episode that, from the patient's perspective, required escalation of treatment of the study areas. Any relapse was confirmed by the investigator by IGA and by SCORAD. The patients were instructed to contact the investigator immediately if any study area eczema relapsed or if any new eczema appeared on the body. The investigator estimated if it was a relapse of a study area eczema or if it was a new eczema. New eczemas were reported as AEs and the patient continued in the study until study area eczema relapse or 6 months, whichever came first.

Statistical methods

For the sample size determination the median time to relapse, based on a previous study (20), was estimated to be 3 months in patients treated with test cream and 1.8 months for patients treated with reference cream. This gives a hazard rate of 0.23

for test cream and 0.38 for reference cream, and a resulting hazard ratio of 1.65.

It was calculated that, for a fixed follow-up time of 6 months, a total of 125 events or 152 patients would provide 80% power to detect a hazard ratio of 1.65 at the 5% significant level (2-sided). All calculations were performed with software East® version 5.3. The event rate function for an exponential distribution is given by $S(t) = e^{-\lambda t}, \geq 0$, where λ is the hazard function, which does not change with time (t).

An interim analysis was to be performed if the recruitment rate was much slower than expected. Since the recruitment rate was as expected no interim analysis was performed in accordance with the clinical study protocol.

The primary statistical analysis compared the time to relapse between treatment and reference cream using a Cox proportional hazards model. The hazard ratio (test cream in combination with reference cream) was estimated together with its 95% 2-sided confidence interval. The time to relapse variable for the Cox model analysis was defined as the time from start of the maintenance phase (Day 1) to the time-point of relapse. The Cox regression of the primary analysis was stratified for country and employed the explanatory variables treatment, SCORAD evaluated at Visit 1 and historic severity of AD. This model thus accounted for censoring as well as explanatory variables.

The Kaplan–Meier estimation was used to estimate the distribution of time to relapse (25). The Kaplan–Meier estimation is a simpler model that does not require the assumption of proportional hazards; conversely, it does not adjust for explanatory variables apart from treatment.

The absolute risk reduction was calculated as the difference between the proportion of patients with eczema relapse treated with reference cream and the proportion of patients with eczema relapse treated with test cream. The relative risk was calculated as the ratio of the proportion of patients with eczema relapse treated with reference cream and the proportion of patients with eczema relapse treated with test cream. The relative risk reduction was calculated as the absolute risk reduction divided by the proportion of patients with eczema relapse treated with reference cream.

QoL was assessed using the EQ-5D™ questionnaire, the 5 dimensions were graded by the patient according to level of severity and using the VAS. In addition, the historic severity of AD was determined and recorded according to Rajka & Langeland (22).

A blind review of the data was performed prior to code breaking.

RESULTS

Patient disposition and demographics

A total of 198 patients were screened successfully, 172 patients were randomized and 87 received ≥ 1 dose of test cream and 85 received ≥ 1 dose of reference cream (Fig. 1). Baseline demographics, AD characteristics (years since diagnosis of AD, number of relapses during the last 12 months and severity of eczema) and medications were well balanced across the 2 treatment arms (Table I). In the test cream group 3 patients discontinued due to lost to follow-up and

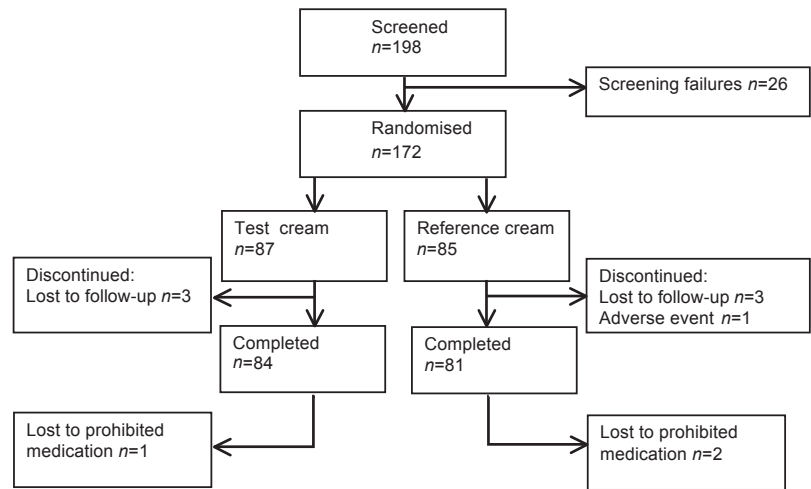


Fig. 1. Patient flow chart.

one patient used medication not allowed in the study. In the reference cream group 3 patients discontinued due to lost to follow-up, one patient discontinued due to an AE (folliculitis) and 2 patients used non-allowed medication (Fig. 1). In order to determine the historic severity of AD, the criteria set by Rajka & Langeland were used. The median score of severity when entering the study was 6.00 in both groups, and was classified as moderate according to Rajka & Langeland (22).

The full analysis set (FAS) was used as primary analysis set. Confirmatory analysis was conducted on the per protocol set (PPS). Patients not experiencing a relapse of eczema were clinically evaluated at 180 ± 14 days. All 172 patients who were diagnosed with AD and randomized for the maintenance phase were included in the FAS. Patients without major protocol violations were included in the PPS, in total 162 patients (83 test cream, 79 reference cream). Ten patients (4 test cream, 6 reference cream) were not included in the PPS. The safety set included 172 patients (87 test cream group, 85 reference cream group).

Table I. Patient demographics and other baseline characteristics, safety analysis set

Variable	Test cream (n=87)	Reference cream (n=85)	Total (n=172)
Age, years ^a	30 (18–66)	28 (18–82)	28 (18–82)
Sex: Female, n (%)	49 (56.3)	52 (61.2)	101 (58.7)
Race, n (%)			
Asian	1 (1.1)	1 (1.2)	2 (1.2)
Black	1 (1.1)		1 (0.6)
Other	2 (2.3)		2 (1.2)
Caucasian	83 (95.4)	84 (98.8)	167 (97.1)
Years since diagnosis of AD ^b	26 (0–64)	24 (0–62)	25 (0–64)
Relapses during previous 12 months ^a	5 (0–20)	4 (1–96)	4 (0–96)
Severity of eczema (Rajka & Langeland – score summation ^a)	6 (3–9)	6 (3–9)	6 (3–9)

^aMedian (min–max). AD: atopic dermatitis.

Primary efficacy endpoint

In FAS there was a clear effect of treatment (the null hypothesis of no difference was rejected) as the hazard ratio was significantly different from 1 (test cream 0.634, $p=0.0110$) (Table II). Similar results were seen in the PPS ($p=0.0250$) (Table II).

The risk of eczema relapse at any point in time was reduced when using the test cream compared with the reference cream. The risk was reduced by about 37% (95% CI) and 33% (95% CI) for the FAS and PPS populations, respectively. Supportive analysis using proportional hazard regression (FAS) agreed with the primary analysis (Table SI¹). Similar results were seen in the PPS (Table SI¹).

Secondary efficacy endpoints

Time to atopic eczema relapse was evaluated using the Kaplan–Meier estimator (Fig. 2). In FAS there was a statistically significant effect of treatment ($p=0.0129$). The test cream showed a statistically significantly prolonged estimated median time to relapse compared with the reference cream (22 days vs. 15 days, $p=0.0129$) (Table SII¹). In PPS, the median time to relapse was the same as in FAS ($p=0.0311$) (Table SII¹). At day 180, 26.4% of the patients using the test cream were still eczema-free, compared with 9.9% using the reference cream (Table III). Using the actuarial method at day 180, 23.9% and 9.9% of the patients in the test cream and the reference cream groups, respectively, were still eczema free (Table III). In the maintenance phase the absolute risk reduction of relapse when treated with the test cream compared with treatment with the reference cream was 13.7% at day 28 and 14.0% at day 180. The relative risk reduction was 18.3% at day 28 and 15.6% at day 180 (Table SIII¹). Similar results were seen in the PPS (Table SIII¹). Quality of life increased during the eczema-free periods (Table IV). Cream consumption was measured by weight and the median values for the total consumption were 347.0 g and 353.0 g for the test cream and the reference cream, respectively.

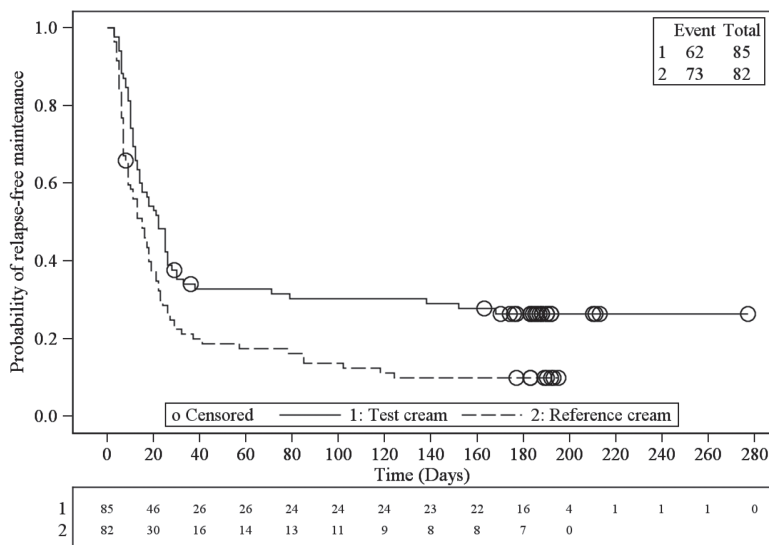


Fig. 2. Kaplan–Meier plot of time to recurrence of eczema in the test and reference cream treatment groups (full analysis set). The numbers of subjects at risk are shown below the horizontal axis.

Safety

The number of patients experiencing any AE was similar between the 2 groups (Table SIV¹). The majority of the 192 AEs recorded were of mild to moderate intensity and were judged by the investigator as unrelated to study treatment. In total, 7 eczemas were reported as AE. In the test cream group, 6 AEs (3 cases of pruritus, 1 eye discharge, 1 erythema and 1 burning sensation) were judged to be possibly related to the study treatment. In the reference group 5 AEs (1 case of eczema, 1 rosacea, 1 erythema, 1 pain and 1 folliculitis) were judged to be possibly related to the study treatment and 1 AE (pruritus) was judged to be probably related to study treatment. Three severe AEs were reported, but only one was judged by the investigator to be possibly related to the study treatment (test cream group, burning sensation in the neck). Only one serious AE (prostate infection) was reported in the study, this occurred in the reference cream group and was judged by the investigator as unrelated to the study treatment.

DISCUSSION

This randomized clinical study of patients with AD met its primary efficacy endpoint by demonstrating

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2051>

Table II. Proportional hazard regression (full analysis set (FAS), per protocol set (PPS))

Covariate	FAS			PPS		
	<i>p</i> -value	Hazard ratio	95% CI of hazard ratio	<i>p</i> -value	Hazard ratio	95% CI of hazard ratio
Test cream	0.0110	0.634	0.446, 0.901	0.0250	0.667	0.467, 0.950
Screening SCORing atopic dermatitis	0.0243	1.022	1.003, 1.041	0.0323	1.021	1.002, 1.040
Historic atopic dermatitis	0.5052	0.945	0.799, 1.117	0.4857	0.942	0.796, 1.114

95% CI: 95% confidence interval.

Table III. Eczema-free proportions of patients (full analysis set)

	Test cream	Reference cream
Day 28		
Eczema-free proportions (%) (actuarial)	38.8	25.2
Eczema-free proportions (%) (Kaplan–Meier)	37.6	24.9
Day 180		
Eczema-free proportions (%) (actuarial)	23.9	9.9
Eczema-free proportions (%) (Kaplan–Meier)	26.4	9.9

that the hazard ratio was significantly different from one, and that the risk of an eczema relapse was reduced by approximately 37% at any time-point when using the test cream compared with the reference cream. Almost 3 times more patients (26% vs. 10%) treated with the test cream completed the whole maintenance phase of 6 months without a single relapse. The data suggest that 1 out of 4 patients diagnosed with AD and treated by a dermatologist could manage their disease with this mild maintenance treatment for 6 months or even longer. These findings demonstrate that patients with AD could delay eczema relapse by the regular use of the urea-containing cream compared with a reference cream. The median time to relapse showed an almost 50% increase between the test cream and the reference cream (22 days vs. 15 days, respectively). A previous study on patients with controlled AD 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 (20). The differences in number of days to relapse between the 2 studies are probably due to differences in study features, type/location and severity of eczemas of the included patients and even seasonal timing of the studies. Nonetheless, both studies suggest that proper moisturizing-therapy prolongs the eczema-free periods and reduces the need for topical corticosteroids or calcineurin inhibitors.

It is also evident from the present study that moisturizers are different, not only from cosmetic perspectives, but also when it comes to functional properties; those with barrier-strengthening effects may be superior to those without barrier-strengthening qualities in main-

Table IV. Quality of Life EQ-5D™ visual analogue scale (VAS) and 5-item instrument (full analysis set)

	EQ-5D VAS		EQ-5D 5-item	
	Test cream Median	Reference cream Median	Test cream Mean ± SD	Reference cream Mean ± SD
Visit 1	80.0	78.0	0.849 ± 0.178	0.812 ± 0.194
Visit 2	90.0	89.0	0.945 ± 0.137	0.931 ± 0.135
Visit 3	87.5	87.0	0.960 ± 0.092	0.880 ± 0.214
Visit 4	90.0	95.0	0.951 ± 0.093	0.935 ± 0.136
Relapse visit	82.5	74.0	0.881 ± 0.154	0.851 ± 0.152

SD: standard deviation; EQ-5D VAS: EQ-5D™ visual analogue scale.

taining a healthy-appearing skin in eczema-patients. The active ingredient urea in the present test cream has been linked to barrier-strengthening properties in previous studies (26, 27), but notably not all urea-formulations improve skin barrier function (13). This is probably due to the excipients used, such as emulsifiers, lipids, pH-adjusters, chelators and preservatives, which also may affect the skin and the penetration of urea into the skin. Furthermore, the stability of urea also needs to be taken into account in order to prevent potential formation of ammonia in the cream.

There is a wide range of moisturizers on the market, but scientific evidence of their clinical benefit and the economic implications for healthcare systems in the treatment of AD are scarce (28). It is therefore important to gain clinical study data about the efficacy of different moisturizers in the treatment of AD. Results from such trials would help physicians and patients to choose moisturizer treatments that have proved clinically effective in AD. The effect on skin barrier and cream application has also been studied in children at risk for AD and dry skin (29–31).

In this study, effective anti-inflammatory treatment with topical corticosteroids before randomization was used to suppress the inflammation present in AD skin followed by a regular maintenance treatment with a moisturizer. This treatment protocol is in line with common clinical practise in many countries. To our knowledge this is the first study comparing a urea-containing moisturizer with a regular moisturizer containing no barrier-strengthening ingredients in this maintenance treatment strategy.

In conclusion, the present double-blind clinical study demonstrates that maintenance treatment with the barrier-strengthening urea-containing moisturizer was superior to a reference cream in delaying the time to relapse of eczema in AD patients. Treatment with the test cream was safe and well tolerated in the treatment of patients with AD.

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Conflicts of interest. U.Å., K.W. and P.S. are employees of ACO Hud Nordic AB. M.G. was an employee at ACO Hud Nordic AB at the time when the study was conducted. Å.S. participated as principal investigator, but did not receive any personal compensation. S.R. has acted as an expert and/or given lectures for ACO Hud Nordic AB, Dignity Sciences, and Astellas Pharma Europe. M.B. has acted as an expert and/or given lectures for

ACO Hud Nordic AB. M.L. has acted as a paid consultant to ACO Hud Nordic AB and has received funding for research carried out in this work."L.K., none declared. L.R., none declared. T.L., none declared.

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REFERENCES

- Bieber T. Atopic dermatitis. *N Engl J Med* 2008; 358: 1483–1494.
- Halvarsson K, Loden M. Increasing quality of life by improving the quality of skin in patients with atopic dermatitis. *Int J Cosmet Sci* 2007; 29: 69–83.
- Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol* 2010; 105: 99–106; quiz 107–109, 117.
- Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy* 2014; 69: 17–27.
- Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; 4: 1–191.
- Burr S. Emollients for managing dry skin conditions. *Prof Nurse* 1999; 15: 43–48.
- Lewis-Jones S, Mugglestone MA. Management of atopic eczema in children aged up to 12 years: summary of NICE guidance. *BMJ* 2007; 335: 1263–1264.
- Holden C, English J, Hoare C, Jordan A, Kownacki S, Turnbull R, et al. Advised best practice for the use of emollients in eczema and other dry skin conditions. *J Dermatolog Treat* 2002; 13: 103–106.
- Giordano-Labadie F, Cambazard F, Guillet G, Combemale P, Mengeaud V. Evaluation of a new moisturizer (Exomega milk) in children with atopic dermatitis. *J Dermatolog Treat* 2006; 17: 78–81.
- Draeos ZD. The effect of ceramide-containing skin care products on eczema resolution duration. *Cutis* 2008; 81: 87–91.
- Szczepanowska J, Reich A, Szepietowski JC. Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. *Pediatr Allergy Immunol* 2008; 19: 614–618.
- Lucky AW, Leach AD, Laskarzewski P, Wenck H. Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatr Dermatol* 1997; 14: 321–324.
- Buraczewska I, Berne B, Lindberg M, Torma H, Loden M. Changes in skin barrier function following long-term treatment with moisturizers, a randomized controlled trial. *Br J Dermatol* 2007; 156: 492–498.
- Held E, Sveinsdottir S, Agner T. Effect of long-term use of moisturizer on skin hydration, barrier function and susceptibility to irritants. *Acta Derm Venereol* 1999; 79: 49–51.
- Zachariae C, Held E, Johansen JD, Menne T, Agner T. Effect of a moisturizer on skin susceptibility to NiCl₂. *Acta Derm Venereol* 2003; 83: 93–97.
- Andersson A-C, Lindberg M, Lodén M. The effect of two urea-containing creams on dry, eczematous skin in atopic patients. I. Expert, patient and instrumental evaluation. *J Dermatolog Treat* 1999; 10: 165–169.
- Loden M, Andersson AC, Lindberg M. Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm). *Br J Dermatol* 1999; 140: 264–267.
- Lodén M, Mandahl P, Wessman C. The influence of urea treatment on skin susceptibility to surfactant-induced irritation: a placebo-controlled and randomized study. *Exogenous Dermatol* 2004; 3: 1–6.
- Loden M. Barrier recovery and influence of irritant stimuli in skin treated with a moisturizing cream. *Contact Dermatitis* 1997; 36: 256–260.
- Wiren K, Nohlgard C, Nyberg F, Holm L, Svensson M, Johannesson A, et al. Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial. *J Eur Acad Dermatol Venereol* 2009; 23: 1267–1272.
- Loden M, Wiren K, Smerud K, Meland N, Honnas H, Mork G, et al. Treatment with a barrier-strengthening moisturizer prevents relapse of hand-eczema. An open, randomized, prospective, parallel group study. *Acta Derm Venereol* 2010; 90: 602–606.
- Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol* 1989; Suppl. 144: 13–14.
- Loden M, Andersson AC, Anderson C, Bergbrant IM, Frodin T, Ohman H, et al. A double-blind study comparing the effect of glycerin and urea on dry, eczematous skin in atopic patients. *Acta Derm Venereol* 2002; 82: 45–47.
- Loden M, Wessman W. The influence of a cream containing 20% glycerin and its vehicle on skin barrier properties. *Int J Cosmet Sci* 2001; 23: 115–119.
- Kaplan E MP. Non-parametric estimation from incomplete observations. *J Am Stats Assoc* 1958; 53: 457–481.
- Grether-Beck S, Felsner I, Brenden H, Kohne Z, Majora M, Marini A, et al. Urea uptake enhances barrier function and antimicrobial defense in humans by regulating epidermal gene expression. *J Invest Dermatol* 2012; 132: 1561–1572.
- Loden M. Urea-containing moisturizers influence barrier properties of normal skin. *Arch Dermatol Res* 1996; 288: 103–107.
- Hjalte F, Asseburg C, Tennvall GR. Cost-effectiveness of a barrier-strengthening moisturizing cream as maintenance therapy vs. no treatment after an initial steroid course in patients with atopic dermatitis in Sweden – with model applications for Denmark, Norway and Finland. *J Eur Acad Dermatol Venereol* 2010; 24: 474–480.
- Schario M, Lunnemann L, Stroux A, Reissbauer A, Zuberbier T, Blume-Peytavi U, et al. Children with dry skin and atopic predisposition: daily use of emollients in a participant-blinded, randomized, prospective trial. *Skin Pharmacol Physiol* 2014; 27: 208.
- Simpson EL, Berry TM, Brown PA, Hanifin JM. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *J Am Acad Dermatol* 2010; 63: 587–593.
- Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014; 134: 818–823.