CLINICAL REPORT

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

Ulf ÅKERSTRÖM1, Sakari REITAMO2, Tor LANGELEND1, Mats BERG4, Lisbeth RUSTAD1, Laura KORHONEN6, Marie LODÉN7, Karin WIRÉN1, Mats GRÄNDE1, Petra SKARE1 and Åke SVENSSON8

1Department of Innovation, ACO Hud Nordic AB, Upplands Väsby, Sweden, 2Skin and Allergy Hospital, University of Helsinki, Helsinki, Finland, 3Hudlege Tor Langelands kontor, Oslo, Norway, 4Department of Dermatology, Mälar Hospital, Eskilstuna, Sweden, 5Department of Dermatology, Haukeland University Hospital, Bergen, Norway, 6Allergy Centre and Department of Dermatology, Tampere University Hospital, Tampere, Finland, 7Eviderm Institute AB, Solna, and 8Department of Dermatology, Skåne University Hospital, Malmö, Sweden

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.

Accepted Jan 15, 2015; Epub ahead of print Jan 16, 2015

Petra Skare, Manager Medicine, Department of Innovation, ACO Hud Nordic AB, Box 622, SE-194 26 Upplands Väsby, Sweden. E-mail: petra.skare@aconordic.com

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 moisturizer 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,
cortisone cream 1% (Hyderm® ACO Hud Nordic, Upplands B.V, Netherlands) on the trunk and extremities and/or hydro-

which the study areas were treated with once-daily topical mo-
tion of the eczemas (SCORing Atopic Dermatitis [SCORAD])

performed: severity of AD (Rajka & Langeland; 22), evalua-
tion 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.

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 in-
vestigational study or using an investigational drug within 3
months prior to the screening visit. Patients who were pregnant,
brastfeeding, 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 randomiza-
tion 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), evalua-
tion 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 mo-
metasone furoate cream 0.1% (Elocon, Merck Sharp & Dohme
B.V, Netherlands) on the trunk and extremities and/or hydro-
cortisone cream 1% (Hyderrm® ACO Hud Nordic, Upplands
Väoby, Sweden) on the face, groins and armpits. In addition,
patients used a medicinal moisturizer containing 20% glycerol
(Miniderm®, ACO Hud Nordic, Upplands Väoby, 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 Väoby, 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 eczematos area appeared.
The relapse was confirmed by the investigator using IGA and
SCORAD. At the relapse visit, QoL (EQ-5D) was also measu-
red. 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 randomi-
zaion 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
the 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 (de-
pending 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 Väoby, 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 pa-
raffin, 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
Väoby, Sweden), available in the Nordic countries, which is
an oil-in-water emulsion containing 5% urea, fractionated
coconut oil, polysorbate 60, hydrogenated canola oil, propy-
lene glycol, carboner, dimethicone, hard paraffin, glyceryl
polyethacrylate, 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 $S(t)=e^{-\lambda t}$, where $\lambda$ 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 reduction was calculated as the ratio of the proportion of patients with eczema relapse treated with test cream and 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 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**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test cream</th>
<th>Reference cream</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years&lt;sup&gt;6&lt;/sup&gt;</td>
<td>30 (18–66)</td>
<td>28 (18–82)</td>
<td>28 (18–82)</td>
</tr>
<tr>
<td>Sex: Female, n (%)</td>
<td>49 (56.3)</td>
<td>52 (61.2)</td>
<td>101 (58.7)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.1)</td>
<td>1 (1.2)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (1.1)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.3)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>83 (95.4)</td>
<td>84 (98.8)</td>
<td>167 (97.1)</td>
</tr>
<tr>
<td>Years since diagnosis of AD&lt;sup&gt;6&lt;/sup&gt;</td>
<td>26 (0–64)</td>
<td>24 (0–62)</td>
<td>50 (0–64)</td>
</tr>
<tr>
<td>Relapses during previous 12 months&lt;sup&gt;6&lt;/sup&gt;</td>
<td>5 (0–20)</td>
<td>4 (1–96)</td>
<td>4 (0–96)</td>
</tr>
<tr>
<td>Severity of eczema (Rajka &amp; Langeland – score summation)</td>
<td>6 (3–9)</td>
<td>6 (3–9)</td>
<td>6 (3–9)</td>
</tr>
</tbody>
</table>

<sup>6</sup>Median (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 SI\(^1\)). Similar results were seen in the PPS (Table SI\(^1\)).

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 SII\(^1\)). In PPS, the median time to relapse was the same as in FAS (\( p = 0.0311 \)) (Table SII\(^1\)). 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 SIII\(^1\)). Similar results were seen in the PPS (Table SIII\(^1\)). 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.

Safety

The number of patients experiencing any AE was similar between the 2 groups (Table SIV\(^1\)). 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. Three severe AEs were reported, but only one was judged by the investigator to be possibly related to the study treatment. 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

---

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

<table>
<thead>
<tr>
<th>Covariate</th>
<th>FAS</th>
<th>PPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( p )-value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Test cream</td>
<td>0.0110</td>
<td>0.634</td>
</tr>
<tr>
<td>Screening SCORing atopic dermatitis</td>
<td>0.0243</td>
<td>1.022</td>
</tr>
<tr>
<td>Historic atopic dermatitis</td>
<td>0.5052</td>
<td>0.945</td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval.

---

\(^1\)http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2051
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 III. Eczema-free proportions of patients (full analysis set)

<table>
<thead>
<tr>
<th>Day</th>
<th>Eczema-free proportions (%) (actuarial)</th>
<th>Test cream</th>
<th>Reference cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28</td>
<td>Eczema-free proportions (%) (actuarial)</td>
<td>38.8</td>
<td>25.2</td>
</tr>
<tr>
<td></td>
<td>Eczema-free proportions (%) (Kaplan–Meier)</td>
<td>37.6</td>
<td>24.9</td>
</tr>
<tr>
<td>Day 180</td>
<td>Eczema-free proportions (%) (actuarial)</td>
<td>23.9</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>Eczema-free proportions (%) (Kaplan–Meier)</td>
<td>26.4</td>
<td>9.9</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>EQ-5D VAS</th>
<th>EQ-5D 5-item</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test cream</td>
<td>Reference cream</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Visit 1</td>
<td>80.0</td>
<td>78.0</td>
</tr>
<tr>
<td>Visit 2</td>
<td>90.0</td>
<td>89.0</td>
</tr>
<tr>
<td>Visit 3</td>
<td>87.5</td>
<td>87.0</td>
</tr>
<tr>
<td>Visit 4</td>
<td>90.0</td>
<td>95.0</td>
</tr>
<tr>
<td>Relapse visit</td>
<td>82.5</td>
<td>74.0</td>
</tr>
</tbody>
</table>

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

ACKNOWLEDGMENTS

The authors would like to thank all the patients and investigators who participated in this study.

Funding sources. This study was sponsored by ACO Hud Nordic AB, an Omega Pharma Company and partly funded by the Knowledge Foundation, Sweden. The sponsor was responsible for the study design, co-ordination and collection of data provided by the investigators. The authors were responsible for data analysis, manuscript preparation and the decision to submit the manuscript for publication.

Conflicts of interest. U.Å., K.W. and P.S. are employees of ACO Hud Nordic AB. M.B. has acted as an expert and/or given lectures for ACO Hud Nordic AB, M.G. was an employee at ACO Hud Nordic AB at the time when the study was conducted. A.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...
REFERENCES