

ORIGINAL ARTICLE

Long-term emollient therapy improves xerosis in children with atopic dermatitis

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Abstract

Background Hydration with topical emollients forms the backbone of treatment for mild atopic dermatitis (AD), but few randomized controlled trials have assessed their efficacy in young children.**Objectives** Assess the efficacy and tolerability of long-term emollient therapy in the treatment of moderate to severe xerosis in young children with AD.**Methods** This was a phase III, multicentre, double-blind, randomized, vehicle-controlled trial. Children ($n = 251$) aged 2–6 years with AD-associated xerosis were randomized 1 : 1 to a 28-day treatment with an emollient combining glycerol and paraffin or its vehicle. Non-responders at the end of the double-blind period were treated open label with emollient until day 84. Responders stopped treatment until reassessment on day 56. Those who relapsed after stopping treatment were treated open label with emollient until day 84.**Results** During the double-blind period, xerosis score (XS) of the scoring atopic dermatitis (SCORAD) index, objective SCORAD and visual analogue score decreased and skin hydration increased more in the emollient group than in the vehicle group ($P < 0.001$ for all measures). More patients were responders with emollient than with vehicle (66.1% vs. 45.6%, $P < 0.001$). During the open-label period, stopping emollient treatment led to relapse but improvement returned if treatment was restarted with emollient. Regular use of the emollient also yielded improvement in children who did not initially respond. Adverse events were similar in the two groups, and no treatment-related severe adverse events were reported.**Conclusions** Long-term therapy with emollient is effective and well tolerated for the treatment of xerosis in children with atopic dermatitis.

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Conflicts of interest

F.B. received consulting fees and fees for participation in review activities from Pierre Fabre. M.S.A. and A.D. are employees of Pierre Fabre. G.T. received consulting fees from Pierre Fabre. H.R., A.K. and M.B. declare no conflicts of interest related to this article.

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with impaired epidermal barrier function, characterized by xerosis, relapsing eczematous lesions and intense pruritus.¹ AD appears within the first 5 years of life in

approximately 80% of the cases and affects up to 18% of children.² In infants, skin features include poorly demarcated scaly erythematous patches usually localized on the limbs and facial convexities, and in older children, symmetrical skin flexure involvement.

According to international guidelines, hydration with topical emollients forms the backbone of treatment for mild AD.^{3,4} However, only a few randomized controlled trials have assessed the efficacy of emollients for treating AD in young children,^{5–7} and none of these trials have examined xerosis as the main end-point. Moreover, to the best of our knowledge, no clinical trials on AD-associated xerosis have been carried out concerning mild form of AD, which account for the most frequent forms.

Here, we describe the results of a multicentre, randomized, vehicle-controlled phase III trial to assess the efficacy of long-term emollient therapy in the treatment of moderate to severe xerosis in children 2–6 years of age with AD. The emollient used was a mixture of glycerol and paraffin that has been previously shown to improve xerosis in children with ichthyosis.⁸

Materials and methods

Study design

This was an international phase III study in children suffering from AD (EudraCT number 2011-003295-37). The study included an initial 28-day double-blind, randomized, vehicle-controlled, parallel-group period and a 56-day open-label follow-up period. The primary objective, assessed in the randomized double-blind period, was to demonstrate the efficacy of a 28-day emollient therapy on xerosis. Secondary objectives included changes in objective scoring atopic dermatitis (SCORAD) and in pruritus during the double-blinded period, documenting the impact of the absence and the reintroduction of emollient treatment during the open-label period and documenting the clinical safety of the treatment. The study was performed at four centres in France, five in Estonia, five in Lithuania, nine in Poland and seven in Romania, and it was approved by all institutional ethics committees and by the competent authorities of all five countries. The study was carried out in accordance with the Declaration of Helsinki and with the International Committee for Harmonization Guidelines for Good Clinical Practice. Parents or legal guardians gave written informed consent for their child to be included in the trial.

Patient population

Paediatricians and dermatologists recruited children 2–6 years of age with AD according to the diagnostic criteria of the UK Working Party and with an objective SCORAD index <15.⁹ The children also had to have xerosis, including moderate or severe dryness on the anterior part of lower limbs as indicated by a SCORAD xerosis score (XS) ≥ 2 ^{10,11} associated with palmar hyperlinearity, scales on the lower limbs, or both. Children were excluded if they had acute AD with moderate to severe erythema and any excoriation, crust, oozing, or exudation; a recent treatment using systemic corticosteroids, antibiotics, antivirals, or hospitalization; a primary skin infection, ulcerated lesions, acne, or rosacea; dermatological disease other than AD that could

interfere with the assessment of xerosis; a history of allergy or intolerance to one of the components of the tested or associated products or to cosmetics; immune suppression; or a history of serious disease considered incompatible with the study.

Treatments

The study included a randomized, double-blind period, followed by an open-label period (Fig. 1a). During the double-blind period, patients were randomized 1 : 1 using a computer-generated and -validated list to be treated for 28 days with the study emollient (Glycerol 15%, liquid and soft paraffin 10%, glycerol monostearate, stearic acid, polydimethylcyclsiloxane, silicone oil, macrogol 600, trolamine, propyl parahydroxybenzoate and purified water), Dexeryl® (Pierre Fabre Medicament, Boulogne, France) or its vehicle (glycerol monostearate, stearic acid, polydimethylcyclsiloxane, silicone oil, macrogol 600, trolamine, propyl parahydroxybenzoate and purified water). The randomization list was generated by the Clinical Pharmacology Department using proprietary software and with parallel groups and a block size of four, and the list was validated by the Biometry Department. Treatments were provided in identical, sequentially numbered containers and were assigned to patients by investigators on the basis of the sequence number. Thus, patients, investigators and pharmacists were blinded to which treatment (emollient or vehicle) was supplied.

At the end of the double-blind period (day 28), patients considered non-responders (persisting lesions or XS ≥ 2) were treated open label with emollient until day 84. All other patients were considered responders and stopped treatment until reassessment on day 56. Those considered as having a relapse (XS ≥ 2) on day 56 were treated open label with emollient until day 84, whereas those who had not relapsed continued treatment free. Parents or legal guardians could request that their children continue treatment during the open-label period even though they were responders; however, these children were excluded from analysis of the open-label period.

Parents or guardians were instructed to apply 8 g of the test cream in the morning and evening as a thin layer to the child's whole body and face and to massage the cream into the skin until completely absorbed. In case of AD flares, the test treatment had to be applied in the morning and a moderately potent corticosteroid 0.1% desonide in the evening until complete resolution of inflammatory skin lesions. Application of 0.1% desonide was recorded in a diary during the double-blind period by the parents or legal guardians.

Assessments

Investigators received training on two occasions about the study design, treatment and performing the clinical assessments. On days 1, 7, 14, 21, 28, 56 and 84, they determined the XS, which was the dryness severity assessment of the SCORAD index, a validated assessment tool for AD (0 = *absent*; 1 = *mild*; 2 = *moderate*;

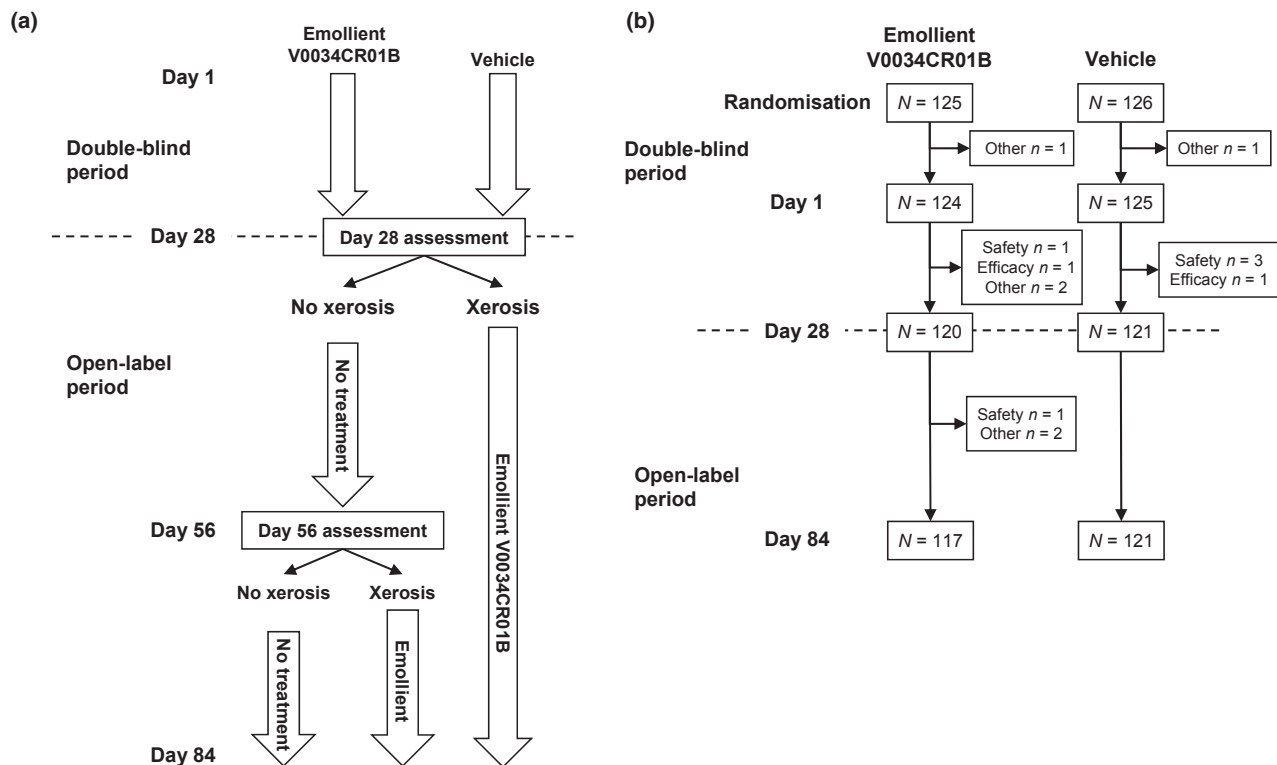


Figure 1 Study design and patient flow chart. (a) Study design. Patients were randomized 1 : 1 to be treated with the emollient or vehicle for 28 days. At the end of the double-blind period, patients considered responders (decrease in xerosis score (XS) and objective scoring atopic dermatitis (SCORAD) score from baseline) stopped treatment, but if they relapsed (persisting lesions or XS > 1) on day 56, they restarted treatment with the emollient until end of the study (day 84). Patients considered non-responders of the study were treated open label with the emollient until day 84. (b) Flow chart of the overall study population.

3 = severe).¹⁰ On days 1, 28, 56 and 84, investigators determined the objective SCORAD index¹¹; scored xerosis using a visual analogue scale (X-VAS) (linear 100 mm scale where 0 = 'No dry skin at all' and 100 = 'Extremely dry skin'); scored pruritus using a visual analogue scale (P-VAS); and measured the hydration index (HI) using a portable Corneometer® (Courage-Khazaka Electronic GmbH, Cologne, Germany).¹² Each HI measurement was made exactly on the same part of the anterior face of the forearm with the highest XS and without prior application of emollient during the 12 previous hours. A treatment response was defined as a decrease in XS score from 3 or 2 at baseline to 1 or 0.

Compliance

Tubes of used and unused products were returned to investigators and weighed on days 14, 28 and, if appropriate, on days 56 and 84. The average daily quantity of test product used during the double-blind period of the study was calculated. Children were considered to be in good compliance if they received between 6.4 and 19.2 g/day of cream (i.e. between 80% of the minimum [8 g] and 120% of the maximum [16 g]).

Safety

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were recorded by investigators up to day 84 and defined according to the International Committee for Harmonization Guidelines for Good Clinical Practice.

Statistical analysis

The primary efficacy criterion was the change in XS from baseline over 28 days. For each treatment group, 116 patients were required to achieve 90% power at a two-sided α of 0.05 to detect a difference of 0.3 in the change in XS between the emollient and vehicle groups assuming a standard deviation of 0.7 in the individual mean scores.

Statistical analyses for the double-blind portion of the study were performed for all randomized patients that received at least one application of the study treatment (intent-to-treat analysis) and using SAS version 9.3 (SAS Institute, Cary, NC, USA). To evaluate the global change in the XS over the double-blind period, a likelihood-based mixed-effects model for repeated measures was performed on data from baseline to days 7, 14, 21 and 28. The model included treatment group, centre and visit as

fixed factors, XS at baseline as a covariate and treatment group-by-visit and baseline-by-visit interactions. Robustness of results was assessed by repeating the analysis for the per-protocol population. The response to treatment at day 28 was compared between treatment groups using a Cochran–Mantel–Haenszel test stratified by centre. For the analysis of covariance and the response to treatment at day 28, the baseline observation carried forward principle was used for missing data imputation in case of dropout. The percentage of days of application of 0.1% desonide relative to the number of days between visits up to day 28 (or premature end of treatment) was compared between treatment groups using a Cochran–Mantel–Haenszel test stratified by centre with a modified ridit score. For the open-label portion of the study, descriptive statistics were calculated for all patients except those considered responders at the end of the double-blind period but who continued to receive treatment at the request of their parent or guardian.

Results

Patients

Between November 30, 2011 and May 24, 2012, a total of 251 children were included and randomized to be treated with the emollient or its vehicle (Fig. 1b). At enrolment, all patients had xerosis but were not in flare of AD (Table 1). Just over half of the children who received vehicle were boys (57.6%), whereas just over half of those who received the emollient were girls (55.6%). All other characteristics were similar between the two groups. In both groups, one patient withdrew before starting treatment and four who started treatment withdrew before the end of the double-blind portion (day 28). Another three withdrew during the open-label portion (day 24 to 84). None of AEs leading to withdrawal was considered treatment related. Finally, 21 patients in the emollient group and 17 in the vehicle group were responders but continued treatment after day 28 at the request of their parents or guardians and were therefore excluded from analysis of the open-label portion of the study.

Changes during the double-blind period (days 1–28)

During the double-blind period (days 1–28), mean XS decreased from baseline in both treatment groups, but the decrease for the intent-to-treat population was significantly greater with the emollient than with vehicle (mean adjusted change over 28 days from baseline $\pm$ standard error [SE] = -0.30 ± 0.061 ; $P < 0.001$) (Fig. 2a). Results were similar for the perprotocol population. Xerosis was significantly improved in patients treated with the emollient than in patients treated with vehicle at all individual time points (days 7, 14, 21 and 28) as assessed by XS (Fig. 2a) and X-VAS (Fig. 2b). Also, HI measured using a corneometer increased significantly more with the emollient than with the vehicle (Fig. 2c).

Table 1 Patient characteristics

Characteristic	Emollient N = 124	Vehicle N = 125
Sex, n (%)		
Male	55 (44.4)	72 (57.6)
Female	69 (55.6)	53 (42.4)
Age (years)		
Mean (SD)	4.04 (1.32)	4.05 (1.45)
Range	2.0–6.9	2.0–6.9
Body mass index (kg/m ²)		
Mean $\pm$ standard deviation	15.53 (1.83)	15.56 (1.94)
Range	11.1–20.6	10.2–23.5
SCORAD at baseline		
Mean (SD)	15.7 (4.3)	14.9 (4.4)
Range	7.8–27.4	7.0–29.8
Objective SCORAD at baseline		
Mean (SD)	11.7 (2.1)	11.2 (2.1)
Range	7.0–15.0	7.00–14.8
XS at baseline		
Mean (SD)	2.2 $\pm$ 0.4	2.1 $\pm$ 0.4
Range	2–3	2–3
X-VAS at baseline		
Mean (SD)	57.8 (16.7)	54.5 (17.2)
Range	21–96	17–94
HI at baseline		
Mean (SD)	29.1 (10.3)	29.4 (11.3)
Range	2.8–70.8	1.9–91.0
P-VAS at baseline		
Mean (SD)	2.8 (2.2)	2.5 (1.9)
Range	0.0–10.0	0.0–8.6
Family history of AD, n (%)	91 (73.4)	93 (74.4)
Months since first cutaneous lesions of AD		
Mean (SD)	36.4 (19.8)	38.5 (20.2)
Range	0–80	1–80
Other atopic symptoms, n (%)		
Asthma	13 (10.5)	8 (6.4)
Rhinitis	19 (15.3)	25 (20.0)
Other	42 (33.9)	39 (31.2)

Patient characteristics are given for all patients who received at least one daily dose of treatment.

AD, atopic dermatitis; HI, hydration index; SD, standard deviation; XS, xerosis score; X-VAS, xerosis visual analogue scale; P-VAS, pruritus visual analogue scale; SCORAD, scoring atopic dermatitis.

The objective SCORAD score decreased in both groups, although it decreased more with the emollient than with vehicle (least square mean adjusted change [95% CI] = -2.043 [-3.210 to -0.876], $P < 0.001$). At the end of the double-blind period (day 28), more patients treated with the emollient than with vehicle had both a decrease in XS and a lower objective SCORAD than assessed at baseline (66.1% [82/124] vs. 45.6% [57/125], $P < 0.001$). Finally, the percentage of days

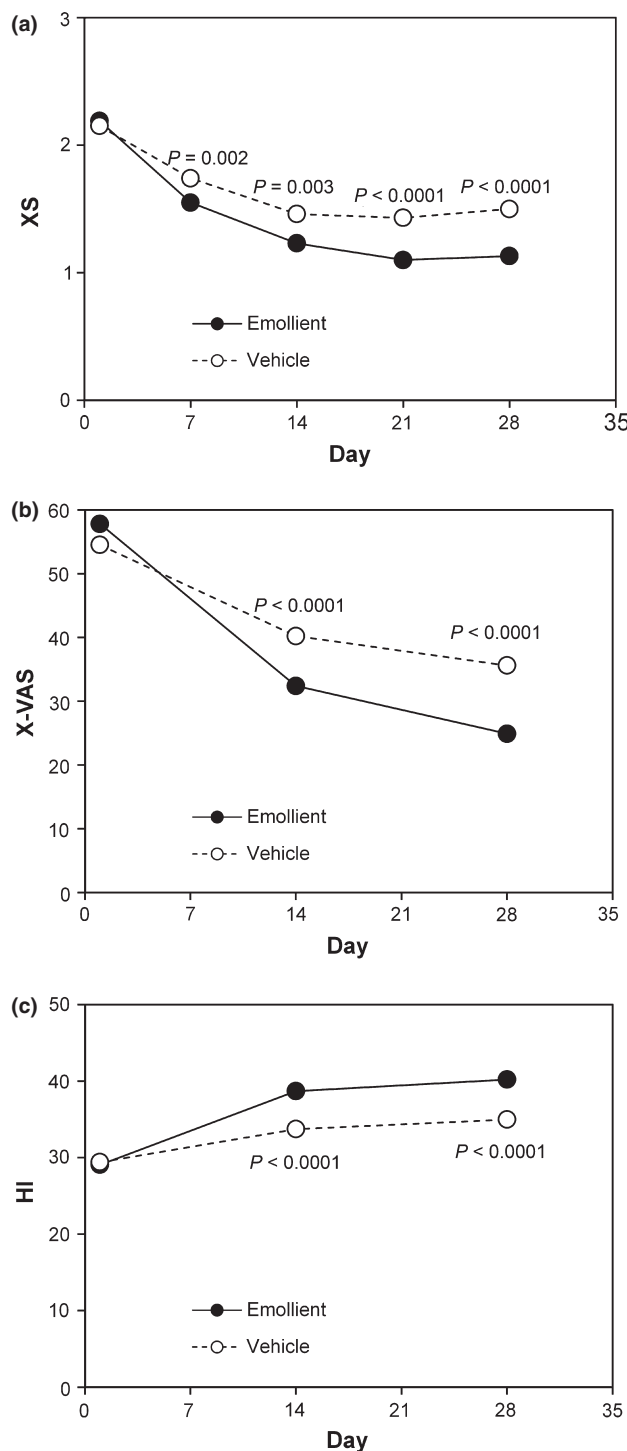


Figure 2 Changes in xerosis during the double-blind period (days 1–28) Shown are the mean xerosis score (XS) (a), mean xerosis visual analogue scale score, X-VAS (b) and mean hydration index, HI (c) in patients treated with the emollient ($n = 120$) or vehicle ($n = 121$) during the double-blind period.

of corticosteroid use was not significantly different between the two groups ($P = 0.67$).

Changes during the open-label period (days 29–84)

At the end of the double-blind period, some of the responders who stopped treatment had lesions or a XS >1 between days 28 and 56 so that mean XS, X-VAS and objective SCORAD increased and the mean HI decreased to values similar to those on day 0 (Fig. 3). Restarting treatment with the emollient on day 56 decreased mean XS, X-VAS and objective SCORAD and increased the mean HI so that they were approximately the same on day 84 as they had been on day 28. In a small subset of responders (10 initially treated with the emollient and three initially treated with vehicle), XS remained in the normal range despite stopping treatment.

Patients who were considered non-responders at the end of the double-blind period of the study (day 28; $n = 110$) were treated open label with the emollient starting on day 28 and until day 84. In these patients, the mean XS, X-VAS and objective SCORAD steadily decreased and the mean HI steadily increased with time (data not shown).

Compliance

During the double-blind portion of the study, all 249 children who received treatment were considered to be in good compliance (i.e. received 6.4–19.2 g/day of cream). Also, the mean quantity of test product used was similar for patients treated with the emollient (mean $\pm$ standard deviation, 13.3 ± 8.3 g/day) and vehicle (15.4 ± 8.1 g/day).

Safety

During the double-blind period, TEAEs were experienced by 34 patients (27.4%) treated with the emollient and 42 (33.6%) treated with the vehicle. TEAEs considered related to treatment were experienced by three patients (2.4%) in both treatment groups. All events were mild or moderate erythema, burning, or pruritus. No treatment-related discontinuations were reported. One SAE was reported in the vehicle group: one subject was hospitalized for nasopharyngitis considered not related to treatment.

Discussion

In young children with AD, treating xerosis improves quality of life¹³ and decreases the risk of developing percutaneous sensitization.¹⁴ Although few randomized controlled trials have assessed the efficacy of hydrating topical agents for AD, they are widely recommended by treatment guidelines.¹⁵

The randomized, controlled portion of this study showed that in young children with moderate to severe xerosis in AD, therapy with emollient improves xerosis over 28 days significantly more than its vehicle control. This occurred even though the children had palmar hyperlinearity and scales on the lower

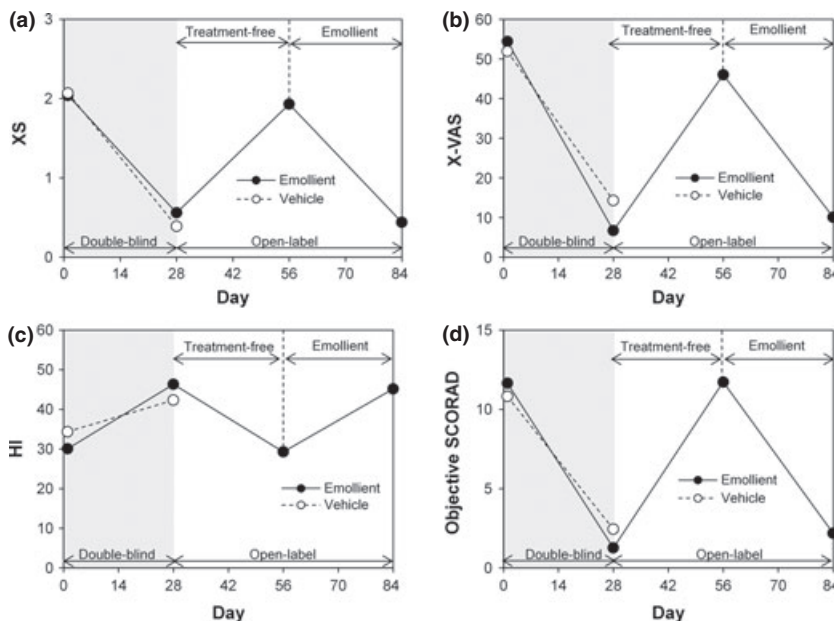


Figure 3 Changes in xerosis during the open-label period in patients considered responders at the end of the double-blind period treatment was stopped in patients who were responders at day 28. Those who remained responders at day 56 continued without treatment until day 84, and those who worsened at day 56 restarted treatment with the emollient and continued until day 84. Shown are the mean xerosis score (XS) (a), mean xerosis visual analogue scale score, X-VAS (b), mean hydration index, HI (c) and mean objective scoring atopic dermatitis (SCORAD) (d) in patients who worsened on day 56.

limbs, which are signs of constitutive disease that may be due to inherited filaggrin mutations.^{16,17} Significant differences in clinical effects could be detected within 1 week, and the differences increased progressively during the first month of treatment. Improved xerosis led to improved AD as demonstrated by a decrease in objective SCORAD. Stopping emollient treatment led to a relapse of xerosis but improvements returned if treatment was restarted. Also, improvements in xerosis were maintained when the emollient was continued for more than 28 days. Importantly, the study demonstrated that sustained treatment with the emollient is well tolerated by young children and that treatment compliance is excellent.

As previously reported by Breternitz *et al.*,⁵ this study showed positive effects of the vehicle on AD during the double-blind period of the study, with nearly half (45.6%) of patients treated with vehicle considered responders (vs. 66.1% for the emollient). This is not surprising because the vehicle was an emulsion of several components that can improve skin barrier function or hydration.¹⁸ Also, simply receiving regular care for AD may have contributed to improvements in xerosis. Despite these potential complications and despite the use of a subjective clinical score as a primary endpoint (XS), the emollient was significantly more effective than the vehicle at improving xerosis. This conclusion is further supported by the results from two other subjective assessments (X-VAS and objective SCORAD) and an objective measure (HI), all of which improved to normal values in patients treated with the emollient.

Because xerosis in AD usually worsens in the winter, especially in colder climates,² and may improve during warmer, sunnier months,^{19,20} patients were enrolled over a short period to reduce

the effect of season. Also, age was limited to 2–6 years and only patients with AD not in flare (objective SCORAD score <15) were included in this study to avoid treatments from interfering with the assessment of xerosis. Thus, the patients included represented the most common cases of AD.^{21–24}

In conclusion, the results of this study support the regular use of emollients as a first-line treatment to improve xerosis in young children with minor AD.

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References

- Boralevi F, Taieb A. Special aspects in pediatrics. In Bieber T, Leung DYM, eds. *Atopic Dermatitis*, 2nd edn. Informa Healthcare, New York, NY, 2009: 379–394.
- Levy RM, Gelfand JM, Yan AC. The epidemiology of atopic dermatitis. *Clin Dermatol* 2003; **21**: 109–115.
- Boralevi F. What additional measures should be recommended in atopic dermatitis in children? *Ann Dermatol Venereol* 2005; **132** Spec No 1: 1S79–1S85.
- Ring J, Alomar A, Bieber T *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012; **26**: 1045–1060.
- Breternitz M, Kowatzki D, Langenauer M *et al*. Placebo-controlled, double-blind, randomized, prospective study of a glycerol-based emollient on eczematous skin in atopic dermatitis: biophysical and clinical evaluation. *Skin Pharmacol Physiol* 2008; **21**: 39–45.
- Grimalt R, Mengeaud V, Cambazard F *et al*. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. *Dermatology* 2007; **214**: 61–67.
- Korting HC, Schollmann C, Cholcha W *et al*. Efficacy and tolerability of pale sulfonated shale oil cream 4% in the treatment of mild to moderate atopic eczema in children: a multicentre, randomized vehicle-controlled trial. *J Eur Acad Dermatol Venereol* 2010; **24**: 1176–1182.
- Blanchet-Bardon C, Tadini G, Machado Matos M *et al*. Association of glycerol and paraffin in the treatment of ichthyosis in children: an international, multicentric, randomized, controlled, double-blind study. *J Eur Acad Dermatol Venereol* 2012; **26**: 1014–1019.
- Williams HC, Burney PG, Hay RJ *et al*. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994; **131**: 383–396.
- European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology* 1993; **186**: 23–31.
- Oranje AP. Practical issues on interpretation of scoring atopic dermatitis: SCORAD Index, objective SCORAD, patient-oriented SCORAD and Three-Item Severity score. *Curr Probl Dermatol* 2011; **41**: 149–155.
- Clarys P, Clijsen R, Taeymans J, Barel AO. Hydration measurements of the stratum corneum: comparison between the capacitance method (digital version of the Corneometer CM 825[®]) and the impedance method (Skicon-200EX[®]). *Skin Res Technol* 2012; **18**: 316–323.
- Giordano-Labadie F, Cambazard F, Guillet G *et al*. Evaluation of a new moisturizer (Exomega milk) in children with atopic dermatitis. *J Dermatolog Treat* 2006; **17**: 78–81.
- Boralevi F, Hubiche T, Leaute-Labreze C *et al*. Epicutaneous aeroallergen sensitization in atopic dermatitis infants - determining the role of epidermal barrier impairment. *Allergy* 2008; **63**: 205–210.
- Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.
- Ezzedine K, Droitcourt C, Ged C *et al*. Usefulness of a global clinical ichthyosis vulgaris scoring system for predicting common FLG null mutations in an adult caucasian population. *Br J Dermatol* 2012; **167**: 1165–1169.
- Thyssen JP, Godoy-Gijon E, Elias PM. Ichthyosis vulgaris - the filaggrin mutation disease. *Br J Dermatol* 2013; **168**: 1155–1166.
- Mack Correa MC, Nebus J. Management of patients with atopic dermatitis: the role of emollient therapy. *Dermatol Res Pract* 2012; **2012**: 836931.
- Patrizi A, Savoia F, Giacomini F *et al*. The effect of summer holidays and sun exposure on atopic dermatitis. *G Ital Dermatol Venereol* 2009; **144**: 463–466.
- Byremo G, Rod G, Carlsen KH. Effect of climatic change in children with atopic eczema. *Allergy* 2006; **61**: 1403–1410.
- Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol* 1998; **139**: 73–76.
- Foley P, Zuo Y, Plunkett A *et al*. The frequency of common skin conditions in preschool-age children in Australia: atopic dermatitis. *Arch Dermatol* 2001; **137**: 293–300.
- Smidesang I, Saunes M, Storro O *et al*. Atopic dermatitis among 2-year olds; high prevalence, but predominantly mild disease—the PACT study Norway. *Pediatr Dermatol* 2008; **25**: 13–18.
- Ben-Gashir MA, Seed PT, Hay RJ. Predictors of atopic dermatitis severity over time. *J Am Acad Dermatol* 2004; **50**: 349–356.