

An Innovative Oat-Based Sterile Emollient Cream in the Maintenance Therapy of Childhood Atopic Dermatitis

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Abstract: Although emollients are recommended in the management of atopic dermatitis (AD), regimens for emollient maintenance therapy are awaiting validation. We conducted an international, multicenter, open-label trial to assess the effects of a 3-month maintenance treatment regimen with a sterile, preservative-free emollient cream containing oat plantlets in children (ages 6 mos–6 yrs) with moderate AD. After a 14-day run-in stabilization phase using a topical corticosteroid (TCS) treatment of medium potency, 108 children with a SCORing Atopic Dermatitis (SCORAD) index of 20 or less were included in the study. Emollient was applied twice daily for 3 months. Rescue TCS treatment was used only in cases of flare-ups. The SCORAD index, Patient-Oriented SCORAD (PO-SCORAD) index, number of flares, TCS use, and tolerance were assessed at months 1, 2, and 3 (M1, M2, M3). AD severity improved, with a highly significant decrease in the SCORAD and PO-SCORAD indexes at M2 and M3 ($p < 0.001$). Changes from baseline to M3 were $48.6 \pm 73.6\%$ for SCORAD and $29.6 \pm 125.3\%$ for PO-SCORAD. The number of flares and TCS use significantly decreased by M3 (both $p < 0.001$). Very good tolerance was recorded in 100% of children at M2 and M3. Notwithstanding the limitations inherent in open-label trials, twice daily application of the oat-based sterile emollient cream led to a significant improvement of clinical symptoms, evidenced by parallel changes in the SCORAD and PO-SCORAD indexes and fewer flare-ups. Clinical benefit and less TCS use were maintained at M3. Tolerance was very good.

Atopic dermatitis (AD) affects up to 20% of children in industrialized countries (1). It is an increasingly common chronic and relapsing inflam-

matory skin disease, probably initiated by abnormal skin barrier structure and function (2). The pathophysiology of AD is complex and includes defects of

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the innate and adaptive immune systems, as well as epidermal barrier dysfunction. A diminution of epidermal filaggrin content, abnormal intercellular lipid composition, and excess proteolytic activity result in a deficiency in the epidermal barrier function (2).

In the absence of a cure for AD, controlling symptoms and acute flares and, in particular, breaking the itch-scratch cycle is the primary therapeutic approach. Another therapeutic goal is repair of the skin barrier. Skin hydration can be preserved and the integrity of the skin barrier restored by the application of emollients, which international consensus reports and guidelines strongly recommended as first-line agents (3–5). Topical corticosteroids (TCSs) are the mainstay of treatment for exacerbations (3). Although baseline emollient skin care with early antiinflammatory intervention is the best approach for stabilizing AD and preventing acute flares (3,4), maintenance therapy regimens require validation.

In 2007 a randomized controlled study (6) showed less TCS use in infants with moderate to severe AD treated using an emollient containing oat plantlet extracts.

In this study we tested a new protein- and preservative-free emollient containing oat plantlets. The formula is preservative free, because use of a patented packaging system allows product sterility to be preserved throughout its use, without risk of bacterial contamination. Oat plantlets are the nondietary aerial parts of the plant, rich in flavonoids and avenacosides. This extract, displaying antiinflammatory and immunomodulatory activities *in vitro* (7), is protein free to reduce any risk of allergic reactions. The other active ingredients (*Oenothera biennis* oil, niacinamide, 10-hydroxydecenoic acid), which make up the emollient and the carrier excipient (paraffinum liquidum and glycerine), have been shown to improve epidermal barrier function (8,9).

AD severity is usually assessed using the SCORing Atopic Dermatitis (SCORAD) index, a validated clinical assessment tool (10–12). The emergence of patient-oriented medicine led to the development of the Patient-Oriented SCORAD (PO-SCORAD) index. This self-assessment tool allows patients to evaluate the course of AD using subjective and objective criteria derived mainly from the SCORAD index (13).

In line with our previous study (6), the aim of the present study was to assess the efficacy and safety of a 3-month maintenance treatment with a new sterile, preservative-free emollient cream containing oat plantlet extracts (7) in children (ages 6 mos–6 yrs) with stabilized AD. Evaluation criteria were SCO-

RAD and PO-SCORAD changes, number and duration of flares, TCS use, and tolerance.

PATIENTS AND METHODS

This international, multicenter (13 centers in France, Italy, Romania, and Georgia), open-label trial was conducted according to Good Clinical Practices (CPMP/ICH/135/95) and the Declaration of Helsinki. National ethics committees approved the protocol and the study was registered at the French Agency for the Safety of Health Products.

To limit seasonal fluctuation of AD (14), our study was performed over a short period of time, during winter. Girls and boys ages 6 months to 6 years with moderate AD according to the criteria of the UK Working Party (15) and a SCORAD index score of 20 to 40 at selection for the run-in period (D–14) and 20 or less at inclusion (D1) were recruited from outpatient consultations. Before selection, parents or guardians gave written consent for their child's participation in the study.

The test product (Exomega D.E.F.I Emollient cream, A-DERMA, Pierre Fabre Dermo Cosmétique, Toulouse, France) was composed of water, mineral oil, polyethylene glycol 12 (PEG-12), glycerin, cyclopentasiloxane, glyceryl stearate, PEG-100 stearate, *Oenothera biennis* oil, myreth-3 myristate, cyclohexasiloxane, polyacrylamide, niacinamide, 10-hydroxydecenoic acid, *Avena sativa* leaf and stem extract (oat plantlet extract), butylated hydroxytoluene, C13-14 isoparaffin, disodium ethylenediaminetetraacetic acid, laureth-7, sodium acetate, and tocopherol.

The study consisted of a 3-month maintenance treatment after a 2-week run-in stabilization phase. During the run-in period, all subjects were treated with a medium-potency TCS (fluticasone propionate 0.05% cream) until their SCORAD index was 20 or less. Fluticasone propionate 0.05% cream is a corticosteroid (CS) of proven efficacy (16), registered in all the countries involved in the study. Subjects with a SCORAD index of 20 or less were included in the maintenance treatment study. Emollient cream was applied twice daily (morning and evening) over the whole body and face. In patients with flare-ups, the test product was applied once daily (in the morning) and a rescue treatment of fluticasone propionate 0.05% cream was applied to inflammatory lesions once daily (in the evening) until complete resolution of inflammatory signs.

Dermatologic examinations and SCORAD calculations were conducted at each visit: at D–14 (during the run-in preliminary phase), D1 (inclusion), and

months 1, 2, and 3 (M1, M2, M3). During the 3-month maintenance therapy trial, investigators assessed global treatment efficacy and parents or guardians used a diary to record study product use, potential TCS use, number of days with flare-ups, and self-assessed global efficacy. Parents were instructed how to use the PO-SCORAD and to recognize a flare-up. Evaluation criteria were

- AD severity assessed using the SCORAD index at each visit, PO-SCORAD weekly and at each visit, and in the case of flare-ups, at the beginning and end of the flare-up
- Number of flares per month assessed from the diary
- Global efficacy of the study product assessed by the investigator and parents at M1, M2, and M3 using a 4-point scale ranging from 0 (not efficient) to 3 (very efficient)
- TCS use in children, defined as the amount of fluticasone propionate 0.05% cream used at the end of M3 estimated by weighing the returned products and the number of days of application per month assessed from the subject's diary
- Amount of study product used, estimated by weighing the returned product tubes at the end of the study

The occurrence of adverse events (AEs) since the last visit was determined at each visit. The investigator assessed local tolerance at M1, M2, and M3 using a 4-point grading scale ranging from 1 (very good) to 4 (poor).

Adherence was assessed using the diaries and the case report form.

Statistical methods

Statistical analysis was performed using SAS software, version 9.2 (SAS Institute, Cary, NC). Quantitative variables were described using sample size, mean, standard deviation (SD), median, and range and qualitative variables were described using percentage and frequency. Time effect was analyzed using analysis of covariance with or without repeated measures for parametric variables using center as a cofactor or Wilcoxon rank test or analysis of variance for nonparametric variables with a non-Gaussian distribution. The significance level was 0.05.

RESULTS

In total, 108 children (0.5–5.2 yrs, 60 boys) were included in the study (Table 1). Fourteen were excluded because of major protocol deviations.

TABLE 1. Demographic and Clinical Parameters of the Study Population

Characteristic	Value
Demographic	
Age at selection, mean $\pm$ SD	2.8 $\pm$ 1.7
Male, %	55.6
Female, %	44.4
Atopic dermatitis history	
Age at diagnosis, mean $\pm$ SD	1.4 $\pm$ 1.2
Previous flare-up in medical history, %	84.3
Number of flare-ups in the 6 months preceding selection, mean $\pm$ SD	2.4 $\pm$ 2.3
Duration of previous flare-up, days, mean $\pm$ SD	13.9 $\pm$ 18.1
Topical corticosteroid use per subject during 14-day run-in phase, g, mean $\pm$ SD	10.2 $\pm$ 0.2
Clinical parameters, mean $\pm$ SD	
SCORAD at selection	29.6 $\pm$ 6.2
SCORAD at inclusion	9.3 $\pm$ 4.8
PO-SCORAD at selection	29.2 $\pm$ 8.5
PO-SCORAD at inclusion	6.5 $\pm$ 4.8

SD, standard deviation; SCORAD, SCORing Atopic Dermatitis index; PO-SCORAD, Patient-Oriented SCORAD index.

AD severity assessed using the SCORAD and PO-SCORAD indexes decreased significantly after 1, 2, and 3 months of treatment (Fig. 1), reaching 3.0 ± 4.8 (percentage change from inclusion $48.6 \pm 73.6\%$) for SCORAD and 2.2 ± 4.5 ($29.6 \pm 125.3\%$) for PO-SCORAD at M3.

The number of flare-ups per subject per month decreased from 0.76 at M1 to 0.46 at M2 ($p < 0.001$) and was maintained at M3 (0.42, $p < 0.001$ vs M1) (Fig. 2). The mean duration of flare-ups was 2.2 days at M3, whereas it had been 13.9 days during the 6 months preceding recruitment for the run-in period (Table 1).

The proportion of investigators and parents giving an assessment score of “very efficient” increased from M1 to M2 ($p = 0.02$ for the investigator and $p = 0.003$ for parents) and from M1 to M3 ($p < 0.001$ for both; Fig. 3). Investigators and parents alike observed highly significant improvement in global efficacy (M3 vs M1, $p < 0.001$).

The mean amount of TCS used between D1 and the end of maintenance treatment (M3) was 0.16 ± 0.18 g/day in the full analysis set population. The TCS amount and number of applications decreased significantly from M1 to M2 ($p = 0.006$ and $p < 0.001$, respectively) and M3 (both $p < 0.001$) (Fig. 4). A total of 13.5 g per patient was used on average during the 3-month treatment (vs 10.2 ± 0.2 g used in 14 days during the run-in phase), approximately 4.5-fold less than during the 2-week run-in phase. In addition, 19% of patients did not use TCS rescue treatment during the 3-month study and 26% did not use TCS rescue treatment during the first 2 months (Table 2).

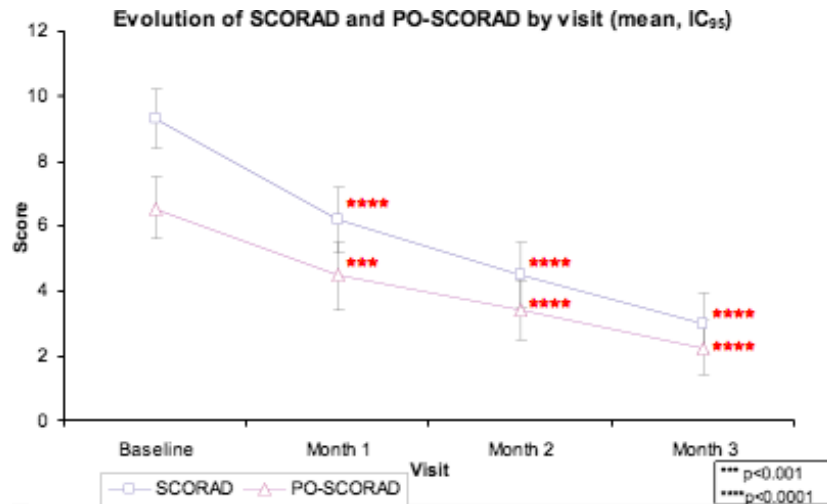


Figure 1. Changes in the SCORAD and PO-SCORAD indexes versus month 1 using analysis of covariance.

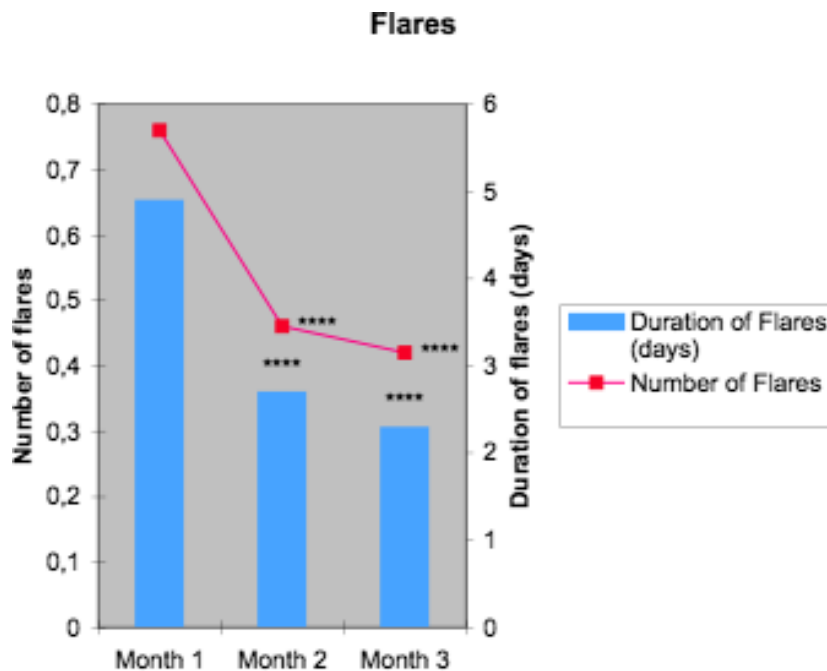


Figure 2. Changes in the mean number and mean duration of flares. Comparisons versus month 1 using the Wilcoxon rank sum test for the number of flares and parametric analysis of covariance with repeated measures for the duration of flares. **** $p < 0.0001$.

Investigators recorded tolerance as very good in 100% of the children at M2 and M3 and very good for all but one subject at M1. This patient experienced a burning sensation of the skin immediately after application, and although this reaction was mild, it led to withdrawal of the subject from the study.

Compliance

Study compliance was very good, with patients' diaries indicating that the study product was applied

over 85.9 ± 8.6 days. The total amount of study emollient used was 231.8 ± 79.2 g at M1, 234.1 ± 76.4 g at M2, and 233.1 ± 69.6 g at M3 (approximately one 200-mL tube per month).

DISCUSSION

This study showed that 3 months of emollient maintenance therapy led to a significant improvement in AD clinical symptoms measured using the SCORAD and PO-SCORAD indexes and a reduction in the

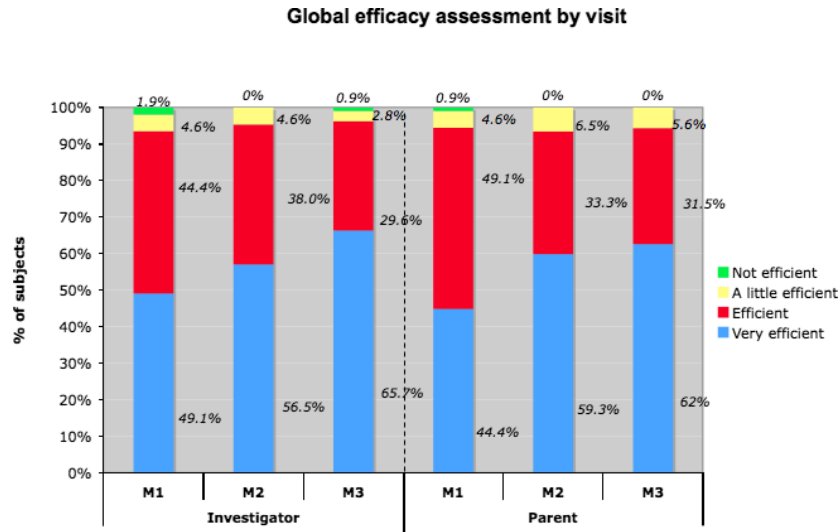


Figure 3. Global efficacy assessed by the investigators and parents by visit at month 1 (M1), month 2 (M2) and month 3 (M3).

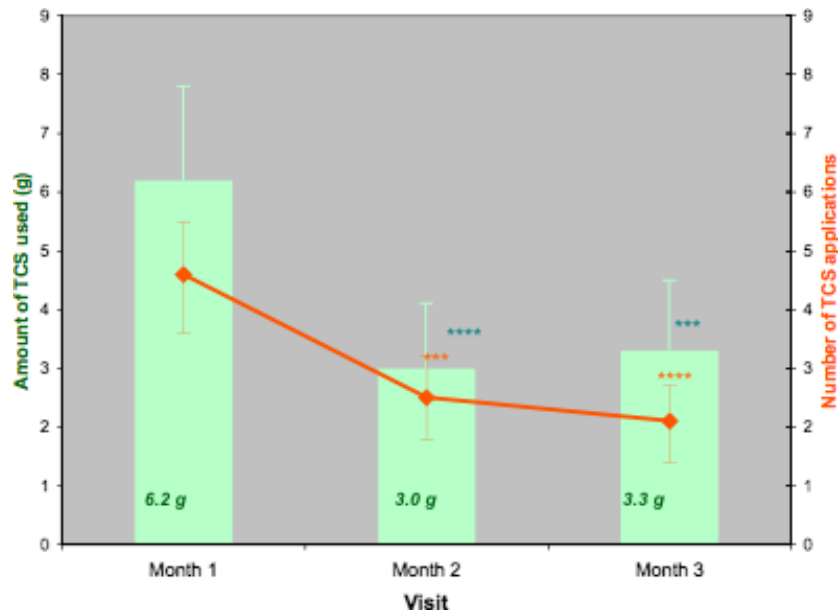


Figure 4. Changes in topical corticosteroid (TCS) use in grams and number of TCS applications between visits (mean, 95% confidence interval). Comparisons versus month 1 using analysis of covariance. *** $p < 0.001$, **** $p < 0.0001$.

number of flare-ups in children with mild to moderate AD. In parallel, the amount of medium-potency TCS used significantly decreased by M2 and was maintained at M3.

Most patients with AD are treated with topical drugs such as CSs and calcineurin inhibitors, but there are safety concerns over the long-term use of these topical agents (17,18). Emollients are recommended as the standard of care and as steroid-sparing agents in AD management (3,4). Their steroid-sparing action may be related to the fact that they reduce skin dryness and improve and restore skin barrier func-

tion, thus decreasing the penetration of allergens and the inflammation they trigger (6,19–21), but few studies have investigated the use of emollients in sparing long-term CS use (22,23). Although our study was not designed to investigate CS sparing, our results are consistent with those of our previous study (6) demonstrating less TCS use with 6 weeks of oat plantlet extract emollient treatment than in a control emollient-free group. The present open-label study extended the emollient treatment to 3 months; although more relapses would have been expected over this 3-month period, AD stabilization occurred.

TABLE 2. *Subjects Who did not Use Any TCS During Each Month and During the Entire Study (n = 108)*

Absence of TCS rescue treatment use during	% of subjects
Month 1	31
Month 2	52
Month 3	58
Months 1 and 2	26
Months 1, 2, 3	19

The number of flare-ups per subject per month decreased and flare-ups were much shorter than those occurring before study recruitment. These flare-ups could be managed with small amounts of TCS (Fig. 4), indicating that emollients can be used to lessen CS use.

Limitations of the study

One limitation of this study is its open design. As such, we did not account for the spontaneous evolution of the disease over the 3-month study period. Furthermore, patient and investigator biases could occur, because both were aware of the treatment, and because international guidelines recommend the use of emollient treatment (3), including a nontreated group in a 3-month study would be unethical. Although some previous studies have included a group of patients not receiving emollient treatment (6,19,24–27), these studies were performed over a shorter period—up to 56 days (25). A study on a prescription (medical device) emollient included a placebo, but the study was conducted for 35 days and focused on short-term outcomes (28). Recently a long-term emollient therapy study included a vehicle control, but the placebo-controlled phase lasted only 28 days and the study was evaluating xerosis rather than TCS use (29). Finally, few studies have been performed with emollients given over the long term (≥ 3 months) and, to our knowledge, none was placebo controlled. The quality of life study by Gelmetti et al (30) was conducted for 3 months but was open label. Placebos are difficult to design and develop in cosmetic studies. Even controls for TCS consisting of its vehicle could be misinterpreted as an emollient. Humectants can be removed from a formula (31), but the remaining formula can still play a moisturizing role (act as an emollient).

Another limitation could be the use of TCS as rescue treatment. TCS could have played a synergistic role in the efficacy observed, but considering the small amount of TCS used, it is likely that the emollient highly contributed to the smaller number of flares and to the use of less TCS (6). In addition, 19% of the

patients did not use TCS rescue treatment during the 3-month study and 26% did not use it during the first 2 months (Table 2), whereas the literature shows that, after acute treatment with TCS, flare-ups occur on average after 6–8 weeks of maintenance treatment (32).

Our study has several strengths. First, our results are robust because all subjects were included during a single season and over a short period of time to limit seasonal fluctuation (14). Second, to our knowledge, no other study has followed CS use with a maintenance design and used the PO-SCORAD index (13) to evaluate emollient efficacy. Furthermore, this first study examining changes in the SCORAD and PO-SCORAD indexes over a long-term period revealed parallel changes in these two values, indicating that evaluation of AD severity is consistent between physicians and patients. Quantification of the amount of emollient used showed that a substantial but not overwhelmingly large amount of the study product (230 g/mo: one tube per month with twice-daily application) allowed stabilization of AD. In comparison, international guidelines recommend the use of up to 150–200 g/wk (up to 800 g/mo) for young children, which seems difficult to manage in practice (in particular, the application of large amounts of emollient can cause difficulties in dressing just after application). The efficacy observed in our study with the use of far smaller amounts of cream is of interest because “the cost of high-quality (low in contact allergens) emollient therapies often restricts their use because...the quantities required are usually high” (3).

With only one AE in 108 subjects, the acceptability and tolerance of the emollient was very good. This good level of tolerance could be related to the new dispensing and closure system, which includes a valve at the end of the tube, allowing the formula to remain sterile while being preservative free. This system may reduce the risk of bacterial superinfection and potential allergic reactions, especially in children, who have greater transcutaneous absorption than adults and for whom hypoallergenic and nontoxic emollient therapies are strongly advised (33). Altogether, this formula was shown to improve skin hydration and restore skin barrier, and its anti-inflammatory effect may be useful as adjunctive or maintenance therapy and may help to limit the use of TCS.

In conclusion, this study of a sterile, protein-free, oat-based emollient strengthens the case for the role of emollients in the maintenance therapy of childhood AD. Twice-daily application of small amounts of the emollient cream studied led to significant improvement

in clinical symptoms, evidenced by parallel changes in the SCORAD and PO-SCORAD indexes, fewer flares, and a significant decrease in TCS use after 2 months of treatment. The clinical benefits and TCS reduction were maintained at 3 months. Controlled studies are necessary to confirm the efficacy of such maintenance treatment regimens in AD and its potential CS-sparing effect.

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CONFLICT OF INTEREST

Valerie Mengeaud, Chloe Phulpin, Adeline Bacquey, Anne-Marie Schmitt are employees of Pierre Fabre. Franck Boralevi and Alain Taieb received grants from Pierre Fabre for conducting this study.

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