

The Steroid-Sparing Effect of an Emollient Therapy in Infants with Atopic Dermatitis: A Randomized Controlled Study

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Key Words

Atopic dermatitis · Corticosteroids · Emollients · Avena

Abstract

Background: No study has clearly demonstrated the steroid-sparing effect of emollients in the treatment of atopic dermatitis (AD). **Aim:** Evaluating the effect of an emollient containing oat extracts on the amount of topical corticosteroids used in infants with moderate to severe AD. **Study Design:** During 6 weeks, 173 infants under 12 months old treated for inflammatory lesions by moderate- and/or high-potency topical corticosteroids randomly received the emollient or not (control group). **Methods:** Evaluation of corticosteroid consumption by weighing the tubes, disease severity

by the Scoring Atopic Dermatitis Index (SCORAD), and infants' and parents' quality of life by Infant's Dermatitis Quality of Life Index and Dermatitis Family Impact scores at D0, D21 and D42. **Results:** Compared to the control group, the amount of moderate- and high-potency corticosteroids used in 6 weeks decreased by 7.5% (not significant) and 42% ($p < 0.05$), respectively, in the emollient group. The SCORAD index, and infants' and parents' quality of life significantly improved ($p < 0.0001$) in both groups. **Conclusion:** The emollient treatment significantly reduced the high-potency topical corticosteroid consumption in infants with AD.

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease of genetic origin [1], which occurs in 10–20% of children in industrialized countries [2, 3]. It is mainly due to the development of an inflammatory immune response in the skin, along with abnormalities in cutaneous permeability barrier function characterized by a significant increase in basal transepidermal water loss [4, 5] and dysfunctions of the stratum corneum lipid metabolism [6–8]. This higher epidermal barrier permeability favours the penetration of environmental irritants and allergens that trigger cutaneous inflammatory mechanisms [9].

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By limiting water loss and restoring the lipid composition of the stratum corneum [5, 10, 11], emollients improve the barrier function and xerosis, leading to the reduction of itching, pruritus and risks of infection [10–13]. Besides, some of them can display anti-inflammatory properties [5, 14]. Consequently, emollients are considered as first-line agents in the management of AD, highly recommended by the international consensus reports and guidelines [15–18]. They are also advised as adjuvant to topical anti-inflammatory treatments such as corticosteroids and calcineurin inhibitors, as they are thought to have steroid-sparing properties [15, 16]. However, the use of emollients as steroid-sparing agents has never been clearly demonstrated, since their effect on topical corticosteroid consumption has been only indirectly evaluated [19, 20].

Therefore, the aim of this study was to perform a standardized, quantitative and objective evaluation of the steroid-sparing effect of a 6-week emollient treatment, compared to a control emollient-free group, in a large population of infants suffering from AD and treated for the inflammatory lesions by topical corticosteroids.

Patients and Methods

This randomized, controlled, clinical phase III study was conducted by 41 French dermatologists, from January 2004 to the end of July 2004. It was carried out in respect of the ethical principles stated in the Declaration of Helsinki, and the study protocol was approved by the independent ethics committee of Saint-Etienne, France. According to the French law, both parents of the infants signed an informed consent form.

Patient Population

Inclusion Criteria. Male and female infants less than 12 months old, with moderate to severe AD assessed by a Scoring Atopic Dermatitis Index (SCORAD) [21] between 20 and 70 were eligible for enrolment.

Exclusion Criteria. Infants with a SCORAD index below 20 or over 70 or having used emollients or topical corticosteroids within the week prior to inclusion were excluded from the study, as well as infants with a history of allergy to a constituent of the study product or with any medical problem able to interfere with AD evaluation.

Treatments

Emollient. The tested product was an emollient emulsion (Exomega® lotion, Laboratoires Pierre Fabre) mainly containing water, petrolatum, shea butter, evening primrose oil, glycerin, paraffin oil, niacinamide, butylene glycol, benzoic acid, carbomer and also specific active Rhealba® oat extracts that had previously demonstrated potential beneficial effects on skin inflammation [14]. This emollient was packed in unidentifiable 400-ml bottles.

Topical Corticosteroids. The topical corticosteroids used for the treatment of inflammatory lesions in both groups were of high [micronized desonide 0.1% cream (Locatop®, Laboratoires P. Fabre)] and/or moderate potency [desonide 0.1% cream (Locapred®, Laboratoires P. Fabre)], according to the investigators' regular practice.

Study Design

The included infants were randomly allocated to an 'emollient group' receiving the tested product or to a 'control group' receiving no emollient. At inclusion (D0), the investigators delivered the emollient to the infants according to a randomization list on the basis of their order of inclusion and provided both groups with the topical corticosteroids for the treatment of eczematous inflammatory areas.

The parents of the emollient group were instructed to apply the emollient in sufficient amount on the dry, non-inflammatory areas of the skin, over the whole body, twice a day (e.g. after morning cleansing and before bed in the evening) during the 6 weeks of the study. At D21, they received a new bottle of emollient according to their randomization number.

The parents had to record any modification in the frequency or mode of application of the emollient and to report this information to the investigator at each post-baseline visit, i.e. D21 and D42.

Any other emollient product was strictly forbidden during the study in both groups.

Evaluation Criteria

Primary Outcome. To evaluate the steroid-sparing effect of the emollient, the amount of topical corticosteroids given at D0 was recorded, then a standardized measure of the corticosteroid consumption was performed after 3 and 6 weeks (D21 and D42). With this aim, the parents returned the tubes of corticosteroids (used or not) at each visit, and the remaining amount was weighed and expressed in grams of product. Furthermore, the frequency of application was recorded by the parents and reported to the investigator.

Secondary Outcomes. The severity of AD was assessed by the measurement of the SCORAD index at D0, D21 and D42. Before the beginning of the study, the investigators participated in a training session on the measurement of the SCORAD index.

The effect of the disease on parents' and infants' quality of life was evaluated by 2 validated 10-item questionnaires provided at each visit, completed at home by the parents and sent back to the investigator.

Infants' and parents' quality of life was assessed using the French versions of the Infant's Dermatitis Quality of Life Index (IDQoL) [22] and the Dermatitis Family Impact (DFI) [23] questionnaires, specifically designed for the patients affected by AD. The IDQoL and DFI scores ranged from 0 (no quality of life impairment) to 30 (highest quality of life impairment).

Tolerance and Safety

Global tolerance was evaluated at each post-baseline visit in all the subjects treated with the emollient, using a 4-point scale from 1 (no sign of intolerance) to 4 (intolerance signs leading to treatment discontinuation). In case of an adverse event, its duration, severity and consequences were reported to the investigator and registered. Severe adverse events were reported within the 2 days following the notification by the investigator.

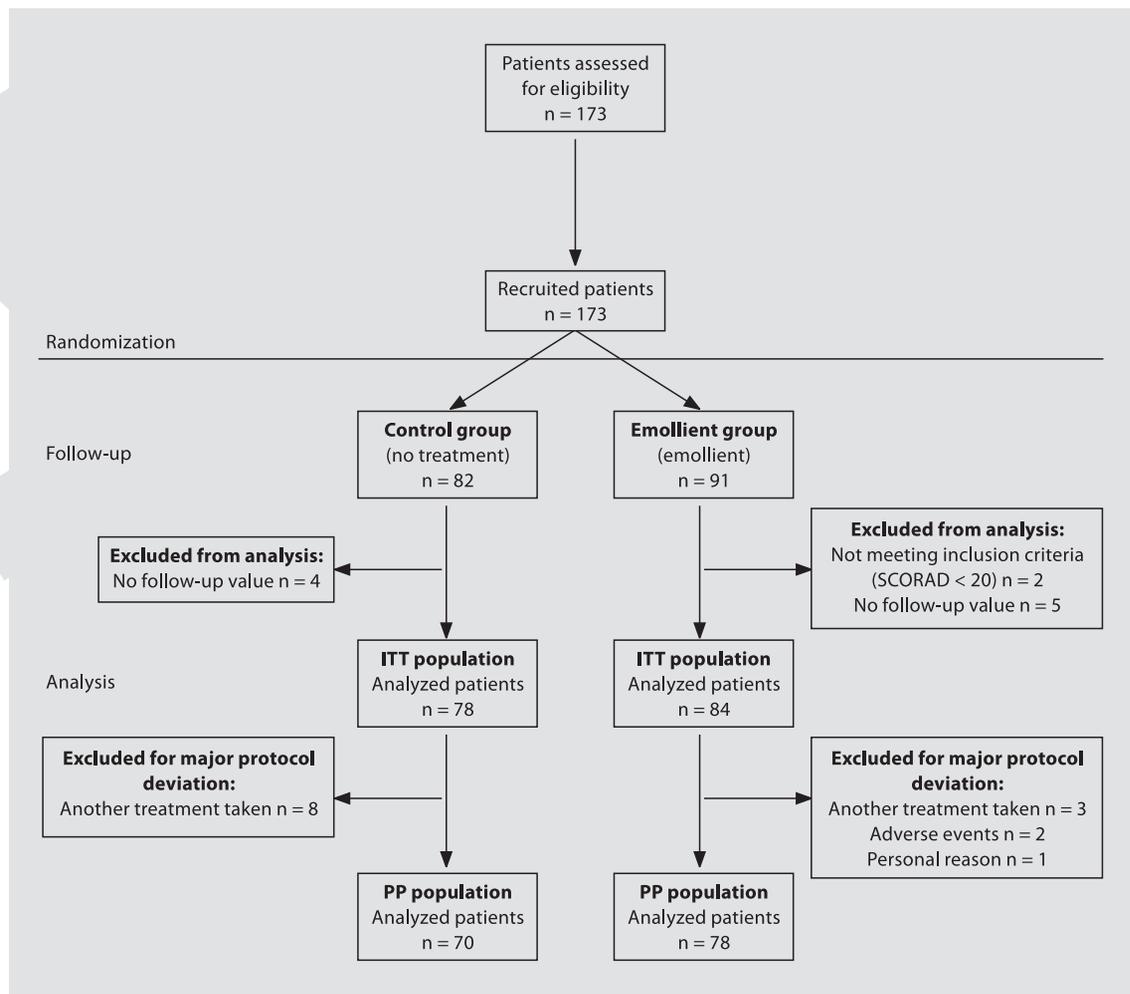


Fig. 1. Participants flowchart.

Statistical Methods

The sample size estimation was based on the data of topical corticosteroid consumption resulting from a previous study evaluating an emollient. Considering that the number of subjects using no corticosteroids over the first 3 weeks of the study was 25% in the emollient group and 10% in the control group, 97 subjects per group were required to detect a 15% mean difference of corticosteroid spare between both groups, with an α -risk of 0.05 and a β -risk of 0.2. Taking into account the low risk of patients' withdrawing and loss to follow-up due to the short study duration, it was planned to include a total of 210 patients.

The statistical analysis was performed on SAS® software, version 8.2.

All quantitative criteria were calculated and expressed by sample size, mean, standard error (SE), median and range values, and qualitative criteria by percentage of the sample size and frequency.

For quantitative criteria, within- and between-group analyses were performed using paired Student or Wilcoxon tests. For qual-

itative criteria, within-group analyses were performed using the Mac Nemar test and between-group analyses using χ^2 or Fischer exact tests for a sample size <5 and the Wilcoxon test for >4 classes.

All statistical tests were 2-sided and performed using a significance level of 0.05.

Results

Participant Flow

The intention-to-treat population (ITT) consisted of 162 infants and the per-protocol population (PP) of 148 infants, as 14 of them had a major protocol deviation (fig. 1). Since similar results were obtained for the PP population, the results are given for the ITT population.

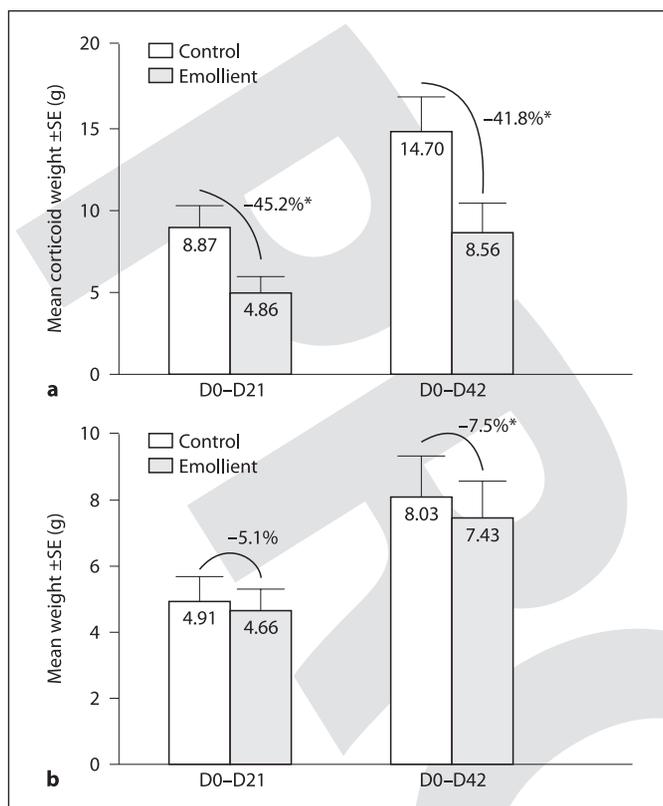


Fig. 2. Consumption of high- (a) and moderate-potency (b) corticosteroids in the 2 study groups, from D0 to D21 and from D0 to D42. * $p < 0.05$.

Table 1. Demographic data and clinical characteristics at baseline

Characteristics	Emollient group (n = 84)	Control group (n = 78)	p value
Gender			
Male	50 (53.76)	43 (46.24)	0.5719
Female	34 (49.28)	35 (50.72)	
Age, months			
Mean \pm SE	6.07 \pm 0.28	5.83 \pm 0.32	0.5754
Min.–max.	1 – 12	1 – 12	
Height, cm			
Mean \pm SE	66.67 \pm 0.59	65.25 \pm 0.64	0.1033
Min.–max.	53 – 78	52 – 78	
Weight, kg			
Mean \pm SE	7.55 \pm 0.15	7.25 \pm 0.18	0.1977
Min.–max.	4.20 – 11.00	4.30 – 11.70	
SCORAD index			
Mean \pm SE	35.63 \pm 1.25	35.96 \pm 1.16	0.9181

Min. = Minimum; max. = maximum. Figures in parentheses represent percentage. p value by between-group comparison.

Demographic Data and Other Baseline Characteristics

At inclusion, no difference between the groups was observed for demographic data and for the severity of AD as measured by the SCORAD index (table 1), as well as for the number of moderate- and high-potency corticosteroid tubes provided to the infants ($p = 0.614$ and 0.263 , respectively).

Primary Outcome

The consumption of high-potency corticosteroids (fig. 2a) was significantly lower in the emollient group compared to the control group from D0 to D21 [8.87 ± 1.37 g vs. 4.86 ± 0.97 g (-45.2%), $p = 0.019$] and from D0 to D42 [14.7 ± 2.08 g vs. 8.56 ± 1.74 g (-41.8%), $p = 0.025$].

The consumption of moderate-potency topical corticosteroids from D0 to D21 and D42 in the 2 study groups is shown in figure 2b. From D0 to D21 and from D0 to D42, the emollient group consumed slightly less moderate-potency topical corticosteroid than the control group (4.66 ± 0.65 g vs. 4.91 ± 0.75 g and 7.43 ± 1.13 g vs. 8.03 ± 1.23 g, respectively), but this difference of consumption was not significant either at D21 (-5.1% , $p = 0.8043$) or D42 (-7.5% , $p = 0.722$).

Secondary Outcomes

AD Severity Assessment. The AD severity highly significantly decreased with time in both groups ($p < 0.0001$), with a drop of the SCORAD index of 54–55% after 6 weeks (fig. 3a). However, the inter-group analysis did not show any significant difference between the emollient-treated and control subjects, either after 3 ($p = 0.883$) or 6 weeks ($p = 0.918$).

The 6 clinical symptoms evaluated for the measurement of the SCORAD index (i.e. oozing/crusts, erythema, excoriations, lichenifications, edema/papulations and dryness) were analyzed in detail. All were significantly improved during the trial, but none was significantly different between the groups, except dryness. For this latter symptom, the clinical severity was significantly reduced in the emollient group at D21 and D42 compared to D0 ($p = 0.0001$). By contrast, in the control group, the decrease in dryness clinical score was only significant at D42 ($p < 0.001$). The between-group comparison showed a significant difference in dryness severity at D21 ($p = 0.015$). A significantly lower percentage of infants had a moderate or severe dryness in the emollient group compared to the control group at D21 (33 vs. 61.5%, $p = 0.007$) but not at D42 (20.25 vs. 36.36%, not significant; fig. 3b).

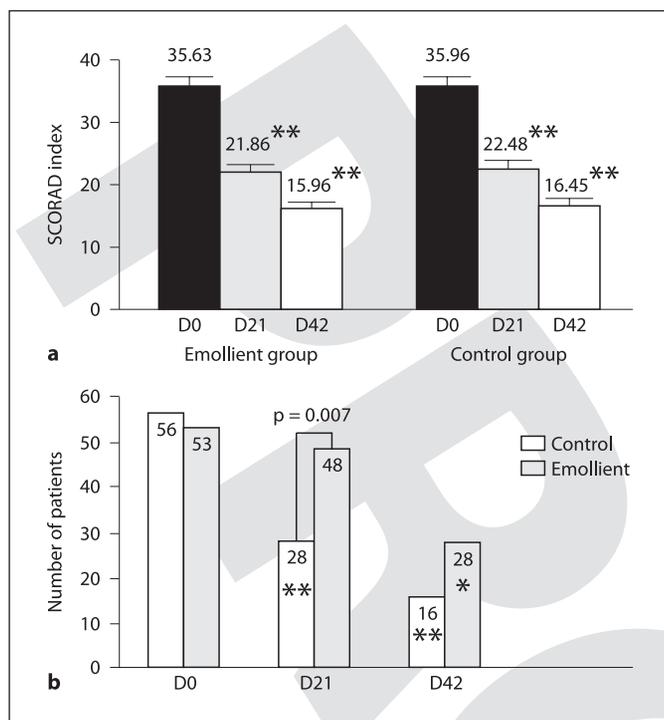


Fig. 3. Evolution of the SCORAD index (a) and of the numbers of infants with moderate or severe dryness (b), from D0 to D42 in the emollient and control groups. * $p > 0.0005$, ** $p > 0.0001$: analysis at D21 and D42 versus D0.

Parents' and Infant's Quality of Life Assessment. Parents' and infant's quality of life was assessed by the analysis of the IDQoL and DFI questionnaires, which was performed on the subjects having available scores at D0 and D42, i.e. 103 patients for the IDQoL analysis and 102 for the DFI analysis (ITT population). Though the IDQoL and DFI scores were statistically comparable in both groups at inclusion ($p = 0.131$), they were higher in the control than in the emollient group (7.2 ± 4.56 vs. 6.32 ± 5.44 and 6.42 ± 5.32 vs. 5.30 ± 5.23 , respectively).

Intra-group analyses revealed the same highly significant improvement of the quality of life of both parents and infants in the emollient and control groups, with a decrease from D0 to D42 of 43 and 48%, respectively, for the IDQoL score and 56 and 45% for the DFI score ($p < 0.0001$). However, between-group analyses did not show any significant difference (IDQoL: $p = 0.131$ and DFI: $p = 0.208$), except for the sleep item of the DFI score, which was better at D42 in the emollient group than in the control group (0.26 ± 0.48 vs. 0.53 ± 0.77 , $p = 0.006$).

Safety

According to the investigators' evaluation, a good and very good tolerance was recorded in 89% of the infants at D21, reaching 94% at D42.

Concerning the adverse events possibly treatment-related, 3 were reported as mild and 3 as moderate. Only 2 were severe (insomnia and pruritus, allergic reaction) and led to a treatment discontinuation. All the adverse events spontaneously resolved without sequel.

Discussion

This randomized controlled study quantitatively and objectively demonstrated the effect of a 6-week emollient adjuvant therapy on the reduction of the consumption of topical corticosteroids, in infants suffering from moderate to severe AD. The amount of highly potent topical corticosteroids used over the 6-week treatment markedly decreased ($>42\%$) in the emollient group compared to the control group, along with a dramatic improvement of clinical symptoms of AD. Indeed, the corticosteroid/emollient therapy lowered the SCORAD index by $>55\%$ at D42 to reach a SCORAD of about 15, which corresponds to mild AD [17].

Though emollients are recommended as standard of care and steroid-sparing agents in the treatment of AD [15–18], few studies have been carried out to properly demonstrate the effects of emollients on topical corticosteroid consumption. Only 2 studies evaluated the significance of emollients in the corticosteroid spare [19, 20], but they did not quantify the corticosteroid consumption by a standardized method. The study of Lucky et al. [19] was a bilateral trial, performed in a small sample of children of various ages. The other study performed in Pakistan [20], was carried out with the same design, but the population of children was larger, and the disease severity was defined according to the SCORAD index in the inclusion criteria. Both studies were not double-blind and compared a twice-a-day corticosteroid application on one side to a once-a-day corticosteroid and emollient application on the other side in the morning and in the evening, respectively. However, the fact that the 2 regimens have the same efficacy does not demonstrate any sparing effect of emollients. Indeed, there is no evidence that a more frequent application of a corticosteroid enhances its efficacy [17, 24, 25], and limited data regarding optimal frequency and quantity of application of the topical corticosteroid therapy are available [15, 17, 24, 25]. Two other studies that did not have as primary endpoint

criterion the evaluation of corticosteroid consumption indirectly described a steroid-sparing effect of the emollients [26, 27]. Cork et al. [26] demonstrated that specific education and counselling induced an 89% reduction of AD severity due to an 800% increase in emollient utilization without any concomitant increase in the use of topical corticosteroids. Hanifin et al. [27] compared the efficacy of a twice-a-day corticosteroid treatment along with a thrice-a-day emollient application versus a twice-a-day corticosteroid treatment alone. They demonstrated a gain of efficacy with a significant difference between groups for the evaluated criteria (erythema, dryness, pruritus, global clinical score) but did not quantify the corticosteroid consumption.

Compared to these trials, our study was performed on a large population of 173 patients of homogenous age range (1–12 months). The severity of AD was an inclusion criterion and was evaluated by the SCORAD index, the most frequently used validated tool in dermatology trials [28]. Furthermore, the topical corticosteroid consumption was objectively evaluated by weighing the amount of used product after each 3-week treatment period. Although the amount of topical corticosteroids used by the patients in both groups was in the range of usual recommendations [17], we were able to demonstrate that infants of the emollient group used significantly fewer corticosteroids to achieve a similar SCORAD index improvement. Thus, the use of such an adjunctive treatment in AD management is likely to minimize the risk of corticosteroid adverse effects and to improve the parents' confidence in the efficacy of the treatment.

The sparing effect of emollient on corticosteroid consumption observed in this study could be explained by the fact that by improving the skin barrier function, it would limit the penetration of environmental irritants and allergens that trigger cutaneous inflammatory mechanisms [9]. Besides, this emollient contains specific active oat extracts that could display potential anti-inflammatory properties in skin inflammatory disorders such as AD¹ [14].

Another way of providing a corticosteroid spare could be to use wet-wrap dressing in combination with emollient as adjunctive treatment in the management of AD,

as it has been demonstrated that this combination was able to significantly reduce disease severity in patients with AD compared to a topical corticosteroid treatment alone [29].

It is commonly accepted that AD profoundly affects not only the infants' and childrens' life but also that of their parents and other family members, often by generating sleep disturbance and threatening social life, as has been observed in other studies [23, 30–32]. Hence, this study evaluated infants' and families' quality of life using the IDQoL and DFI validated questionnaires, specific for AD. It showed a real improvement of infants' and parents' quality of life along with the decrease of AD severity over the 6-week treatment, confirming the close relationship between quality of life and severity of the disease demonstrated in previous studies [31–33].

Finally, as our main objective was to objectively demonstrate for the first time the direct steroid-sparing effect of the addition of an emollient in the treatment of AD, this comparative clinical study was not performed in a blinded manner. Indeed, it would necessitate the use of the vehicle of the tested emollient as control, which has by itself moisturizing properties.

In conclusion, this clinical trial showed that an emollient containing oat extracts is a highly efficient steroid-sparing agent when used as adjunctive treatment in AD management. Further studies are now needed to confirm these results and to compare the steroid-sparing effect of differently formulated emollients in double-blind randomized studies.

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