Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention

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Background: Atopic dermatitis (atopic eczema) is a chronic inflammatory skin disease that has reached epidemic proportions in children worldwide and is increasing in prevalence. Because of the significant socioeconomic effect of atopic dermatitis and its effect on the quality of life of children and families, there have been decades of research focused on disease prevention, with limited success. Recent advances in cutaneous biology suggest skin barrier defects might be key initiators of atopic dermatitis and possibly allergic sensitization.
Objective: Our objective was to test whether skin barrier enhancement from birth represents a feasible strategy for reducing the incidence of atopic dermatitis in high-risk neonates.
Methods: We performed a randomized controlled trial in the United States and United Kingdom of 124 neonates at high risk for atopic dermatitis. Parents in the intervention arm were instructed to apply full-body emollient therapy at least once per day starting within 3 weeks of birth. Parents in the control arm were asked to use no emollients. The primary feasibility outcome was the percentage of families willing to be randomized. The primary clinical outcome was the cumulative incidence of atopic dermatitis at 6 months, as assessed by a trained investigator.
Results: Forty-two percent of eligible families agreed to be randomized into the trial. All participating families in the intervention arm found the intervention acceptable.
A statistically significant protective effect was found with the use of daily emollient on the cumulative incidence of atopic dermatitis with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; $P = .017$). There were no emollient-related adverse events and no differences in adverse events between groups.
Conclusion: The results of this trial demonstrate that emollient therapy from birth represents a feasible, safe, and effective approach for atopic dermatitis prevention. If confirmed in larger trials, emollient therapy from birth would be a simple and low-cost intervention that could reduce the global burden of allergic diseases. (J Allergy Clin Immunol 2014;134:818-23.)

Key words: *Atopic dermatitis, eczema, skin barrier, prevention, emollients*

Atopic dermatitis (atopic eczema) is a chronic inflammatory skin disease that has reached epidemic proportions in children worldwide and is increasing in prevalence.[1,2] Children with atopic dermatitis experience intractable itch along with inflamed, cracked, and often infected skin lesions. The onset of atopic dermatitis in childhood often heralds the development of subsequent allergic disorders, such as food allergy, asthma, and allergic rhinitis (the atopic march), as well as neurodevelopmental disorders.[3,4] Development of an effective prevention strategy for atopic dermatitis and associated allergic disease would represent a major public health breakthrough.

Atopic dermatitis has been historically classified as an allergic disease, given its association with IgE-mediated diseases, such as food allergy. Prevention trials to date have primarily focused on allergen avoidance. Unfortunately, the results of these studies have been largely disappointing or inconsistent, and no single accepted prevention strategy has emerged.[5]

Recent advances in cutaneous biology suggest epidermal defects might be a key initiator of atopic dermatitis and possibly allergic sensitization.[6-8] Skin barrier dysfunction is now recognized as central to the initiation and progression of atopic dermatitis. These new findings create an opportunity for the development of novel prevention strategies focusing on the skin barrier. We hypothesize that enhancement of a defective skin barrier early in life might prevent or delay the onset of atopic dermatitis.

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Emollients provide a safe and effective method of skin barrier enhancement because they provide the skin with a source of exogenous lipids, improving its barrier properties.[9-11] The results of a previous case-control study and open-label trial suggest the use of bland emollients from birth might protect against the onset of skin inflammation in neonates.[12,13] The objective for this study was to test the hypothesis that emollient therapy from birth represents a safe, feasible, and efficacious approach to the prevention of atopic dermatitis (Fig 1).

METHODS

Study design

This was a multicenter, multinational, 2-arm parallel-group, assessor-blind, randomized (1:1) controlled pilot trial of 6 months' duration. The intervention started within 3 weeks of birth.

Participants

Infants at high risk of eczema, which was defined as having a parent or full sibling who has (or had) physician-diagnosed atopic dermatitis, asthma, or allergic rhinitis, were included. The strongest and most established risk factor for atopic dermatitis is a family history of atopic disease.[14,15] Thus to qualify for this study, neonates had to have had 1 first-degree relative with a history of allergic rhinitis, asthma, or atopic dermatitis. Between 25% and 40% of children with a family history of atopic disease have atopic dermatitis in the first year of life, with some reports putting the risk at greater than 60%.[16] Infants needed to be in overall good health, and the mother needed to be at least 16 years of age at delivery and capable of providing informed consent. If mothers had taken *Lactobacillus rhamnosus* supplements during pregnancy, their infants were excluded. Infants were excluded if they were born before 37 weeks' gestation or if they had a major congenital anomaly, hydrops fetalis, an immunodeficiency syndrome, a severe genetic skin disorder, or a serious skin condition that would make the use of emollients inadvisable.

Intervention

Parents in the intervention group were offered a choice of 3 emollients of different viscosities (an oil, a cream/gel, or an ointment) that had been selected based on previous data regarding their safety, tolerability, or barrier-protective qualities.[17-22] In the United Kingdom emollient choices were sunflower seed oil (William Hodgson and Co, Congleton, United Kingdom), Doublebase Gel (Dermal Laboratories, Hitchin, United Kingdom), and liquid paraffin 50% in white soft paraffin. In the United States parents were offered the same sunflower seed oil as used in the United Kingdom, Cetaphil Cream (Galderma Laboratories, Fort Worth, Tex), or Aquaphor Healing Ointment (Beiersdorf, Chester, Ohio). We used sunflower seed oil with a high ratio of linoleic/oleic acid to optimize the positive skin barrier effects.[23] None of the emollients offered contain sodium lauryl sulfate because this emulsifier has been shown to adversely affect the skin barrier.[24] Parents were asked to apply the emollient to the baby's entire body surface, with the exception of the scalp, starting as soon as possible after birth (within a maximum of 3 weeks) and continuing until the infant was 6 months of age.

Both the intervention and control groups were given an infant skin care advice booklet, which reflected current guidelines.[25] Parents are advised (1) to avoid soap and bubble bath; (2) use a mild, fragrance-free synthetic cleanser designed specifically for babies; (3) avoid bath oils and additives; (4) use a mild, fragrance-free shampoo designed specifically for babies and avoid washing the suds over the baby's body; and (5) avoid using baby wipes, where possible.

Outcomes

The primary purpose of this trial was to determine the feasibility of this approach for atopic dermatitis prevention in preparation for larger trials. Thus the primary outcome for this pilot study was the proportion of eligible families who were willing to be randomized.

Secondary outcomes were as follows:

- proportion of families eligible for the trial;
- proportion of families accepting the initial invitation to participate;
- percentage of early withdrawals;
- proportion of families who found the intervention acceptable;
- reported adherence with intervention;
- amount of contamination in the control group;
- age of onset of eczema and proportion of transient cases;
- incidence of emollient-related adverse events;
- success of blinding of the assessor to allocation status; and
- cumulative incidence of eczema at 6 months, as determined by an investigator.

Filaggrin mutation testing was performed in the McLean laboratory (Dundee, United Kingdom), evaluating the 4 loss-of-function mutations (R501X, 2282del4, S3247X, and R2447X) that are most prevalent in populations of white European ancestry by using TaqMan allelic discrimination (Thermo Fisher Scientific, Waltham, Mass), as described previously.[26]

Recruitment and setting

Recruitment took place in the United Kingdom and the United States between May 2010 and May 2011. In the United Kingdom research nurses were based in 3 acute National Health Service hospital trusts (Nottingham University Hospitals, Derby Hospitals, and United Lincolnshire Hospitals) and 1 general practice surgery (the Surgery@Wheatbridge, Chesterfield). In the United States the study recruited in 1 hospital, Oregon Health & Science University Hospital and Clinics (Portland, Oregon).

Visit schedule and randomization

Participation in the trial was for 6 months' duration. Methods of identifying suitable families differed between the United Kingdom and the United States. In the United Kingdom families were usually identified and screened during pregnancy by means of advertisement. After the family had made contact with the study team and initial eligibility checks had been carried out by the coordinating center, the research nurse carried out the screening and consent visit, usually at the family home. The baseline visit, including randomization, then took place within 3 weeks of delivery, usually as a home visit. In the United States families were identified by study coordinators visiting the postnatal wards each day and approaching parents about the study directly. After giving parents time to consider the study, the study coordinators returned to the family to obtain written consent and randomize the subjects.

Infants were randomized at a 1:1 ratio using random block sizes to either the intervention or control group with a central, Web-based, computer-generated, Internet randomization service provided by the Nottingham Clinical Trials Unit. The allocation list was held by the Nottingham Clinical Trials Unit and concealed from trial investigators and other trial staff. Allocation was only released to the research nurse by telephone once eligible participants' details were irrevocably entered into the online database by the coordinating center staff. Randomization was stratified by the recruiting research nurse. In the case of multiple births, the firstborn was the index child.

The research nurse contacted parents by telephone at 10 days and 6 weeks, with a face-to-face visit at 12 weeks (usually at home in the United Kingdom and as a clinic visit in the United States). This was then followed by a further telephone call at 18 weeks, and the final contact was a clinic visit at 24 weeks for an assessment by the dermatologist or dermatology specialist nurse, who conducted a blinded assessment of the skin. In addition to these scheduled contact points, parents were encouraged to contact the research nurse if they had any concerns about the child's skin. If parents reported symptoms of eczema, then an unscheduled visit to the hospital to see the dermatologist was arranged so that the presence of eczema could be confirmed.

Blinding

It was not possible to blind parents in a trial of daily emollient application. An independent outcome assessor who was blinded to treatment allocation performed the skin examinations and diagnosis of eczema. This was usually a general practitioner, dermatologist, or dermatology nurse specialist. The statistician was blinded to treatment group until the analysis was complete.