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A Pilot Study of Emollient Therapy for the Primary Prevention of Atopic Dermatitis

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Abstract

Background—Prevention strategies in atopic dermatitis (AD) using allergen avoidance have not been consistently effective. New research reveals the importance of the skin barrier in the development of AD and possibly food allergy and asthma. Correcting skin barrier defects from birth may prevent AD onset or moderate disease severity.

Objective—We sought to determine the feasibility of skin barrier protection as a novel AD prevention strategy.

Methods—We enrolled 22 neonates at high risk for developing AD in a feasibility pilot study using emollient therapy from birth.

Results—No intervention-related adverse events occurred in our cohort followed up for a mean time of 547 days. Of the 20 subjects who remained in the study, 3 (15.0%) developed AD, suggesting a protective effect when compared with historical controls. Skin barrier measurements remained within ranges seen in normal-appearing skin.

Limitations—No conclusions regarding efficacy can be made without a control group.

Conclusions—Skin barrier repair from birth represents a novel and feasible approach to AD prevention. Further studies are warranted to determine the efficacy of this approach.

Keywords

atopic dermatitis; emollient therapy; prevention therapy; skin barrier defects; skin barrier protection; stratum corneum

The increasing prevalence, patient morbidity, health care costs, and potential toxicities of current therapies make the development of disease prevention strategies in atopic dermatitis (AD) an important goal. The development of new AD prevention strategies was one of the 6 “urgent calls” for research in a systematic review of AD therapy published in 2000 from the United Kingdom (1). Despite decades of research, primarily focusing on allergen avoidance, no accepted strategies exist for AD prevention (1). Most recently, probiotic supplementation and extensively hydrolyzed infant formulas have shown some promise but have produced inconsistent results (2–9). Over the past several years, new insights into the pathogenesis of AD have emerged indicating that skin barrier dysfunction plays a prominent role in AD development (10–16). Although advances have been made in understanding the genetic and biochemical basis for skin barrier defects seen in AD, there have been no primary prevention strategies that target the skin barrier.

There are several lines of evidence to suggest that skin barrier protection from birth may prevent or modify the development of AD. First, a small case-control study found that the use of petrolatum early in life may be protective against AD development (17). Second, a small study by Kikuchi and et al. (18) identified a trend toward increased transepidermal water loss (TEWL) and skin hydration in subjects before the development of AD. Third, the use of emollients in premature infants protects against developing skin inflammation (19–24). Fourth, emollients are effective at preventing flares in established AD (25,26).

Despite the prominent role emollients play in AD therapy according to several published guidelines (27–29), there are no prospective studies examining neonatal emollient use in the primary prevention of AD. This strategy could be a cost-effective, easy, and safe intervention to prevent or delay the onset of AD. Finding an approach to even delay the onset of AD or decrease its severity could have a large public health benefit.

Our hypothesis is that skin barrier protection from birth using bland emollients is a safe and feasible strategy for AD prevention that warrants further study. We report the results of a pilot study in high-risk neonates testing this hypothesis.

METHODS

Study Design

Institutional review board approval was obtained for this study, which was performed using Good Clinical Practice Guidelines as published by the Food and Drug Administration (30). This study was registered at clinicaltrials.gov (NCT00806221). We performed an open-label prospective study of emollient use in high-risk neonates starting between days 1 and 7 of life. Infants were examined at scheduled visits at Months 1, 6, 12, and 24. Telephone visits were performed at months 3 and 18 to assess for side effects, rashes, and compliance. Parents were also instructed to come to clinic for evaluation outside of scheduled study visits if any rash had developed in the infant.

Population

Pregnant mothers were recruited from prenatal and dermatology clinics at Oregon Health & Science University in Portland, OR, from November 2006 to November 2008. We aimed to enroll pregnant mothers continuously until we achieved a cohort of infants with a mean follow-up time of at least 1 year.

We enrolled only families considered to be at high risk of having a child with AD. A high-risk family in our study was defined as one parent or related sibling who currently or previously met criteria for AD according to the definitions used in the International Study of Allergies and Asthma in Children (ISAAC) (31). In addition, one parent or sibling must have had either allergic rhinoconjunctivitis or asthma as defined by the criteria used in the ISAAC studies. Previous studies reveal that similarly defined high-risk infants have a 30% to 50% chance of developing AD by age 2 years (1).

Other inclusion criteria included routine pregnancies not generally regarded as high risk and mothers must have been between the ages of 15 and 35 years at delivery. Exclusion criteria included pre-term birth as defined as birth defined as birth before 37 weeks' gestation, a major congenital anomaly, hydrops fetalis, any infection at birth, significant dermatitis at birth not including seborrheic dermatitis ("cradle cap"), any immunodeficiency disorder, any genetic skin disorder excluding ichthyosis vulgaris, and any other major medical problems that the investigator deemed may increase the risk of adverse events with the intervention.

Intervention

The goal of the intervention was to maintain an intact skin barrier in patients at risk for developing AD. Emollients, either creams or ointments, improve barrier function by supplying the stratum corneum with water and lipids; however, the exact mechanisms in which emollients exert their effects are unknown (32). Ghadially et al. (33) showed that petrolatum lipids can replace stratum corneum bilayers and accelerate barrier recovery in human volunteers. Newer barrier repair creams have been developed, although there are scant data in human beings showing improved skin barrier function when compared with more traditional petrolatum-based emollients (33).

Our emollient intervention was Cetaphil cream (Galderma Laboratories, Fort Worth, TX), an oil-in-water, petrolatum-based cream used widely in the United States to treat dry skin and often recommended for the management of AD. Two studies have shown that Cetaphil cream improves skin barrier function (34,35). Parents were instructed to apply the emollient once daily or more often to all body surfaces excluding the diaper area and the scalp. Caregivers were encouraged to use the emollient immediately (within 3 minutes) after bathing.

Parents were also instructed to minimize soap exposure during bathing as recommended by the American Academy of Pediatrics and to use a fragrance-free mild cleanser designed for infants (36). No other moisturizers were allowed except plain petrolatum to any areas that continue to be xerotic despite twice-daily Cetaphil use. Sunscreen use was allowed, but parents were generally instructed to use physical protective measures. No limits on bathing or other bathing advice was provided.

Outcomes

The primary outcome was the incidence of skin-related adverse events and serious adverse events during the study. Secondary endpoints included the cumulative incidence of AD at study end, mean age of onset of AD, and compliance with the intervention.

There are no standardized or validated definitions for defining an incident case of AD that enable an accurate measurement of time of disease onset. Currently used standardized criteria for diagnosing AD, such as the Hanifin-Rajka criteria, do not accurately specify time frames that allow for precise measurement of the time of onset of AD. In this study, we derived the definition of an incident case of AD using the primary features of the Hanifin-Rajka criteria and included a specified time element (37). An incident case of AD was recorded only when all of the following were met: 1) the presence of eczema in typical locations, 2) pruritus, and 3) eczema that lasted for at least 2 weeks.

Skin barrier function was assessed by measuring TEWL using a Tewameter TM 210 (Courage & Khazaka, Cologne, Germany). TEWL is a measure of the permeability barrier of the stratum corneum, and is the most commonly used objective measure of stratum corneum barrier function in AD studies. Stratum corneum hydration was assessed by measuring the skin electrical capacitance using a corneometer CM 820 (Courage & Kazaka). Measurements of TEWL and capacitance were made in duplicate and averaged. Measurements were taken from the back of the forearm of the infant after 15 minutes of inactivity in the room. Measurements were made following published guidelines maintaining correct room humidity and temperature ranges (38). Parents were asked to not apply the emollient on the morning of the measurements. If a parent mistakenly applied the emollient the morning of the measurements, these measurements were not used in the skin measurement analyses, thus some values were missing from analyses and are reflected in the graphs.

RESULTS

In all, 27 pregnant mothers were screened and 22 enrolled. Of the 22 total enrolled, two were lost to follow-up or withdrew consent (Figure 1). The racial composition of the subjects was as follows: 16 non-Hispanic Caucasian, 2 Hispanic Caucasian, 2 Asian, and 2 African American. Subjects enrolled were from highly atopic families with the majority of parents having a history of AD. Thirteen mothers and 6 fathers had a history of AD. Fourteen subjects had at least one sibling with AD. To date, 13 subjects have been followed up beyond 1 year and 7 have completed 2 years of follow-up. Figure 2 displays individual subject data and outcomes.

There were no adverse events thought to be related to the intervention such as contact dermatitis or skin yeast or bacterial infection during the course of this study. The mean follow-up time was 547 days with a range of 90 to 773 days (Table 1). Overall parental-reported compliance was excellent with parents reporting an average of 85% compliance at the last measured visit for the entire cohort. Excluding subjects who were lost to follow-up, 3 of 20 subjects (15.0%) developed AD by the time of manuscript submission. If we conservatively assume all dropouts developed AD (intent-to-treat analysis), then 5 (3 meeting criteria, 2 lost to follow-up) of 22 subjects developed AD during the course of the study (22.7%) (Table II). The mean age of onset of AD for the 3 subjects was 11.0 months.

TEWL and capacitance measurements remained within the range of what would be expected from infants with normal-appearing skin (39) (Figure 3). Population sizes vary at each time point as a result of subjects incorrectly using emollient within 8 hours of examination or because subjects have yet to reach a designated time point. We could not detect any significant TEWL or capacitance differences at any time point in the 3 subjects who developed AD compared with the subjects without AD (data not shown). Should subtle barrier dysfunction precede AD development, more sensitive measures of barrier function or larger subject numbers would likely be needed to detect it.

DISCUSSION

Emollient therapy from birth represents a novel AD prevention strategy and our pilot data suggest it is a safe and feasible approach that warrants further investigation currently underway. There were no adverse events in more than 1 year of follow-up and compliance with the intervention was excellent. Skin barrier measurements yielded values that were comparable to those of normal-appearing skin (39). Infants enrolled in our study were part of a very high-risk cohort. A review of prevention studies of similar high-risk cohorts revealed that the risk of developing AD by 2 years of age varies between 30% and 50% (1). Only 3 of our 20 subjects (15.0%) developed AD with an average follow-up of 547 days, suggesting a protective effect. Controlled studies are, of course, needed to establish the efficacy of this approach with longer follow-up times. Any prevention strategy that even delays the onset or reduces the severity of this common disease would have a large public health impact. Improving barrier function early in life may have the added benefit of reducing transcutaneous sensitization thought to be important in the development of IgE-mediated diseases such as food allergy and allergic asthma (40).

AD prevention strategies have been based upon the notion that early life allergen exposures initiate childhood AD. Maternal dietary antigens can cross the placenta and have been found in breast milk (41,42). Because the majority of AD develops before the age of 2 years (43), interventions must begin in utero or in early infancy. Previous allergy-based AD prevention strategies have included maternal dietary manipulation, dietary manipulation of the infant, environmental allergen avoidance, and probiotic supplementation. Despite decades of

research, no one allergy-based strategy has been proven consistently effective for the prevention of AD (1,44,45).

Although used widely for flare prevention (secondary prevention), emollients have not been previously studied as a primary prevention strategy for AD. In a case-control study by Macharia et al. (17) published in 1991, there was a suggestion that the use of topical petrolatum in infancy protected against AD development. Since that report, there have been no studies examining what effect emollients may have on AD development, yet studies in premature infants provide proof of principle that emollients may be utilized to prevent or delay the onset of skin inflammation. Several studies have shown a reduction in the incidence of “dermatitis” or improved skin condition in premature neonates treated with emollients (19–21,46,47). Caution is warranted as a Cochrane review in 2004 (48) and a case-control study in 2000 (49) both concluded that ointment therapy may increase the rates of infection in premature neonates. Since these two reports, there have been 3 more published reports that sunflower seed oil or Aquaphor (Biersdorf, Germany) lead to improved mortality rates and no increased rates of infection (21,46,47). The data from our pilot study demonstrate the preliminary safety of this approach in infants at-risk for AD.

A major outstanding question pertains to what type of emollient is best suited for this approach. Studies in both healthy and diseased skin have shown that most oil-in-water emollients improve skin barrier function (32,50). Some emollient formulations, however, may have detrimental effects on the skin barrier. Held et al. (51) showed a slight increase in irritant responses in normal-appearing skin after treatment with an oil-in-water emollient, but no negative effect on TEWL was seen. Buraczewska et al. (52) showed that pretreatment of normal-appearing skin with an emollient containing canola oil and urea worsened the skin barrier function after challenge with a skin irritant. Water itself has also been shown to be a skin irritant making emollients high in water content (e.g., lotions) less appealing (53,54). Other factors that may affect the effectiveness of an emollient include cost, viscosity, and parental acceptance that may depend on both climate and cultural factors. Because AD is a global concern, the ideal emollient would be widely acceptable, widely available, affordable, safe, and effective.

Several other questions, in addition to emollient choice, arise when planning future studies. For example, whom should we target for this therapy? Should we target only high-risk neonates or all neonates? Should we target only those families with a known filaggrin mutation? Williams (45) points out that targeting high-risk groups for AD prevention strategies would greatly limit the impact of the prevention program.

Although skin barrier protection from birth is a novel approach with many outstanding questions, we view these areas of uncertainty as opportunities. Decades of allergen avoidance measures have not yielded concrete strategies for AD prevention. New insights into the importance of the skin barrier in AD development lend support to shifting the AD prevention paradigm toward skin barrier strategies. Combined approaches utilizing skin barrier protection and allergen avoidance may ultimately yield the best results.

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Figure 1.
Subject enrollment and follow-up diagram.

Figure 2.
Individual subject data with length of follow-up and outcomes. *AD*, Atopic dermatitis.

Figure 3. Transepidermal water loss (TEWL) and capacitance measurements during study from back of arm. Asterisks and dots indicate outliers.

Table 1

Follow-up time of cohort (n=22).

Measure	Time
Mean	547 days
Median	628 days
Range	90–773 days
Average age of AD onset (n=3)	11.0 months

Table 2

Main clinical outcomes from study.

Outcome	Result
Adverse events	None
AD in total cohort (ITT analysis) (n=22)	5 (22.7%)
Definite AD in entire cohort excluding drop-outs (n=20)	3 (15.0%)