A Supplement to
Skin & Allergy News®

Managing Atopic Dermatitis in Children:
The Role of Newer Nonsteroidal Topical Treatments

POSTER REVIEW
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Atopic dermatitis (AD), also commonly referred to as eczema, is a chronic, typically pruritic condition with an eruption that appears on the flexural surfaces of the body. The diagnosis of AD is made on the basis of the clinical criteria presented in a seminal paper published in 1980 by Hanifin and Rajka[1] and summarized in the table below.

Prompt, effective treatment and long-term monitoring for and management of acute flares of the disease are essential for a number of reasons. These include relieving patient discomfort and preventing skin infections secondary to excoriation, as well as mitigating the myriad psychosocial and economic burdens on patients, their families, and society.[2] In addition, early and effective treatment of AD also may reduce the subsequent manifestations of atopy as children become older.[3–8] (Long-term, prospective studies are under way to explore this and other issues relating to the "atopic march.")

The standard pharmacologic management options for AD are well known to clinicians who treat pediatric patients and include topical corticosteroids, narrow-band ultraviolet B phototherapy, and topical immunomodulators (ie, the calcineurin inhibitors). These therapies are briefly reviewed on page 4.

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In addition to the management options for AD are the medical devices that have been introduced—three nonsteroidal topical skin barrier creams, Atopiclair™, MimyX™, and, most recently, Eletone™. As a class, these devices are extremely safe because they contain no active drug. Therefore, there are no restrictions on age, duration of use, site of use, or use during pregnancy. See page 4 for an overview of this class of devices.

Highlights of the study specific to Eletone efficacy and safety are on pages 2 and 3.

Treatment Options

Topical corticosteroids have been, remain, and will likely continue to be the mainstay of therapy for controlling acute flares of AD. No other medication currently available can be considered a replacement for appropriately prescribed topical corticosteroids.

Nevertheless, clinicians and parents are understandably concerned about the side effects that are associated with the use of these agents. Among the concerns with long-term use of topical corticosteroids—particularly the high-potency formulations—are adverse effects on bone growth, hypothalamic-pituitary-

continued on page 4

CLINICAL FEATURES OF ATOPIC DERMATITIS

MAJOR FEATURES

- Pruritus
- Facial and extensor involvement in infants and children
- Typical morphology
- Chronic or relapsing dermatitis
- Personal or family history

MINOR FEATURES

- Xerosis
- Cutaneous infections
- Nonspecific dermatitis of the hands or feet
- Ichthyosis, palmar hyperlinearity, keratosis pilaris
- Pityriasis alba
- Nipple eczema
- Dermatographism
- Anterior subcapsular cataracts
- Elevated serum IgE levels

IgE = immunoglobulin E.
Modified from: Hanifin and Rajka.[1]

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An Evaluation of the Safety and Efficacy of a Nonsteroidal Cream in the Management of Mild to Moderate Atopic Dermatitis in Pediatric Subjects

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Basic science research on the etiology and natural history of atopic dermatitis has resulted in new understanding about the role of the skin barrier in this condition.

The search for alternative, safer treatments has led to a more extensive understanding of the importance of the skin barrier in all inflammatory dermatologic diseases, including atopic dermatitis.

To briefly review, the stratum corneum consists of two main structural elements: corneocytes and lipid lamellae that form the "cementing" matrix. (Elias[13] has used the analogy of a brick wall, with the corneocytes as bricks and the lipid lamellae as the mortar.) Dysfunction of this epidermal barrier is common in patients with atopic dermatitis as well as other inflammatory skin diseases. The clinical signs of barrier abnormality are xerosis, inflammation, and irritation; laboratory experiments involving measures of transepidermal water loss (TEWL) have demonstrated that increased TEWL is typical in patients with atopic dermatitis, even in areas of skin that appear to be not involved.[14]

Loss-of-function mutations in the filaggrin gene have been identified relatively recently, and a genetically determined deficiency in this important basic stratum corneum protein has been found in individuals with atopic dermatitis. In turn, a deficiency in filaggrin is known to result in epidermal barrier dysfunction.[15]

Restoration of the epidermal barrier in patients with atopic dermatitis reduces irritation and inflammation, decreases penetration of irritants, and improves pruritus and associated scratching. Thus, the number of flares are reduced, so patients' exposure to topical corticosteroids also can be reduced.

Eletone Cream is a new nonsteroidal prescription product that was investigated in a multicentered study comparing it to a midpotent topical corticosteroid in a pediatric population with atopic dermatitis. Eletone Cream was brought to market after the study showed that the Eletone group had marked improvements in the signs and symptoms of their disease. A subsequent analysis of the data from the Eletone population in that study was done and is summarized in the following pages.

TABLE 1. BASELINE CHARACTERISTICS INTENT-TO-TREAT POPULATION

Characteristic	(n=133)
Age (years)	
Overall Mean	6.80
STD	5.13
Range	0.3 – 17.6
Gender	
Male	74 (56%)
Female	59 (44%)
Race*	
White	82 (62%)
Black/African American	43 (32%)
Asian	7 (5%)
American Indian or Alaska Native	2 (2%)
PGA Score	
Mild (Score=2)	51 (38%)
Moderate (Score=3)	82 (62%)
Pruritus	
None	0 (0%)
Mild	42 (32%)
Moderate	69 (52%)
Severe	22 (17%)

*Percentages may sum to greater than 100% if subjects reported more than one race category.

Patient Demographics and Baseline Characteristics

Two hundred sixty (260) male and female pediatric patients (range, 3 months–18 years) with mild to moderate atopic dermatitis were enrolled in a 4-week, US, multicenter, prospective, randomized, vehicle-controlled study undertaken to evaluate a new, midpotency topical corticosteroid formulation in a lipid-enhanced, nonsteroidal cream base.

At the end of the study, 134 patients who had received vehicle only had achieved impressive improvements over baseline in atopic dermatitis signs and symptoms, particularly pruritus.

Because of this observation, an analysis was performed on a subset of data from 133 patients in the vehicle-only group. The results reported here are for the 133 patients in the intent-to-treat (ITT) population; one subject was excluded from the ITT analysis because of ineligibility at the baseline visit. The purpose of the analysis was to evaluate the safety and efficacy of twice-daily application of the nonsteroidal cream.

TABLE 2. PHYSICIAN'S GLOBAL ASSESSMENT SCORE: SUBJECTS CLEAR OR ALMOST CLEAR

Study Day	Number of subjects (n=133)
Day 8	20 (15%)
Day 22	43 (32%)
Day 29	51 (39%)

Clinical Assessments

Clinical assessments were performed for overall disease condition, individual signs and symptoms, and body surface area (BSA) involvement on days 1, 8, 22, and 29. Overall disease severity was scored using a five-point Physician's Global Assessment (PGA) scale, ranging from 0 (clear) to 4 (severe). Individual signs and symptoms (erythema, induration/papulation, lichenification, and excoriation) were rated as 0 (none) to 3 (severe) for each patient's overall body and for body regions

TABLE 3. CHANGE IN PRURITUS SCORES*

Change†	Number of subjects (n=133)
–3	0 (0%)
–2	2 (2%)
–1	7 (5%)
0	52 (39%)
+1	45 (34%)
+2	25 (19%)
+3	2 (2%)

*Last observation carried forward was used to impute missing data prior to analysis.

†Worsening change is expressed as a negative number (–), improvement as a positive (+).

(head/neck, upper limbs, trunk, and lower limbs). The severity of oozing/crusting were rated for the overall body, using that same scale.

The percentage of BSA involvement was assessed by body region (head/neck, upper limbs, trunk, and lower limbs), and an overall BSA percentage was computed using the weighted, body region, and percentage scores. Intensity of pruritus for the previous 24-hour period was rated by the subjects (or, where applicable, by the parent or guardian), using a four-point scale (ranging from 0, none, to 3, severe). The demographics and baseline characteristics of the ITT study group are summarized in **Table 1**.

Safety Evaluation

Safety was assessed by monitoring and reporting adverse events that occurred during the study. The occurrence of telangiectasia, skin atrophy, and striae were reported as either absent or present at each evaluation.

Results

According to the PGA scores, efficacy of the nonsteroidal cream was observed at the first assessment, on day 8, and continued through the end of the study, according to PGA on day 29. At the evaluation on day 8, 20 patients (15%) were assessed as clear or almost clear; by day 29, this number increased to 51 (38%) (**Table 2**).

Seventy-two patients (54%) had some degree of improvement in pruritus: 52 patients (34%) had a 1-grade improvement; 25 patients (19%) had a 2-grade improvement; and 2 patients (2%) had a 3-grade improvement. Fifty-two patients (39%) said they had no change. Nine patients had either a grade-1 or grade-2 worsening of itching—n=7 (5%) and n=2 (2%), respectively. These results are summarized in **Table 3**.

Average BSA involvement at baseline was 22.6%. This decreased to 14% by day 29—a reduction of 43.6%.

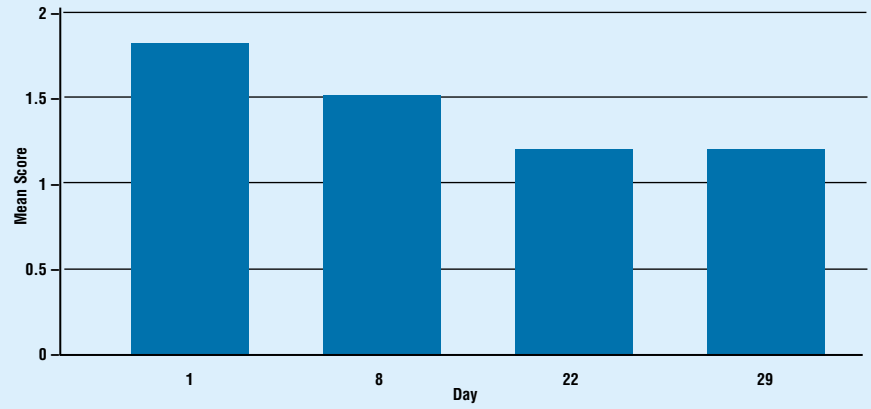
The mean pruritus scores are shown in **Figure 1.** The mean scores of erythema, induration/papulation, lichenification, excoriation, oozing/crusting, and scaling all progressively improved from day 8 through day 29 (**Figure 2**).

Adverse Events

The safety evaluation showed no severe adverse events; the cream had a safety profile similar to or better than that of products commonly used in the management of atopic dermatitis. All adverse events that were reported were considered mild or moderate in severity and the majority were considered to be unrelated to the nonsteroidal cream.

Specifically, 28 (21%) patients reported a total of 42 adverse events; 32 (76%) were mild and 10 (24%) were moderate. Moderate events were application-site dermatitis, pyrexia, application-site erythema, bacterial infection, folliculitis, sinus congestion, in-growing nail, and accident. Two cases of mild telangiectasia were reported; one was considered probably related to the study medication and the other was judged possibly related. Also possibly related to the study medication were one case of moderate application-site dermatitis and one case of application-site erythema. All other adverse events were either unassessable or were considered unrelated to the study medication.

FIGURE 1. MEAN PRURITUS SCORE



Summary by Dr Kircik

This study, involving 133 patients, had a large "n" value. The use of Eletone Cream resulted in impressive improvements in the disease parameters measured, specifically pruritus and BSA.

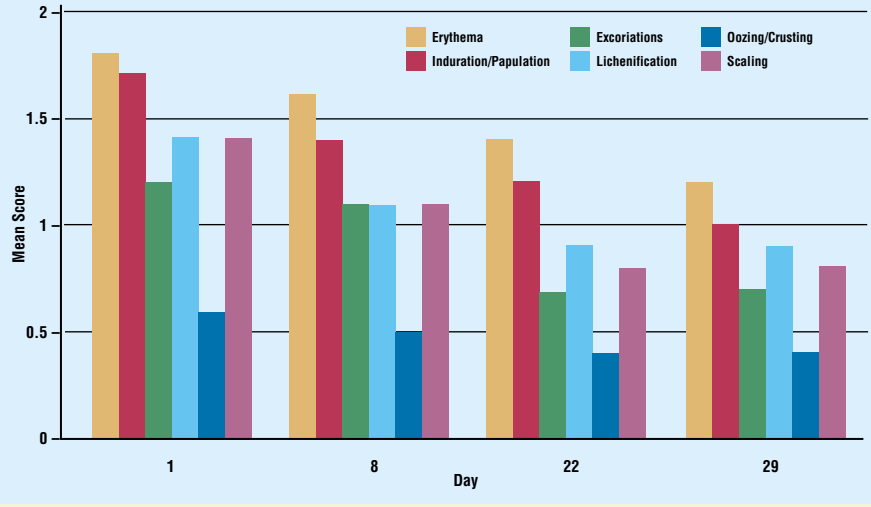
Use of this lipid-enriched cream product is thought to yield the results described above because of its barrier repair qualities. The unique vehicle, created by Hydrolipid™ technology, provides the advantages of an ointment but the feel, convenience, and texture of a cream that patients find more acceptable and, thus, are more likely to use as directed.

The findings in this study suggest that this nonsteroidal skin barrier cream is suitable as an adjunct to prescription drug therapy with topical agents such as corticosteroids, calcineurin inhibitors, and oral antihistamines. In addition, the results suggest that the cream may be appropriate in monotherapy during periods of remission and/or situations where other topical prescription products are not considered appropriate to reduce the flare.

Source:

Abramovits W, Alvarez-Connelly E, Breneman D, et al. A double-blind, randomized, vehicle-controlled trial to determine the efficacy and safety of hydrocortisone butyrate 0.1% lipocream in the treatment of mild to moderate atopic dermatitis in pediatric subjects. Poster presented at: 25th Anniversary Fall Clinical Dermatology Conference; October 6–9, 2006; Las Vegas, Nev.

FIGURE 2. CHANGES IN ATOPIC DERMATITIS SYMPTOMS, DAY 8 – DAY 29



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adrenal axis suppression, and striae, telangiectasias, and atrophy of the skin.

Until recently, none of these agents was approved by the US Food and Drug Administration (FDA) for use in young children.Today, fluticasone propionate cream and desonide gel and foam are approved for up to 4 weeks of use in children who are at least 3 months of age; alclometasone dipropionate cream and ointment, prednicarbate emollient cream, and fluticasone propionate lotion are approved for children down to 1 year of age; and mometasone furoate monohydrate cream is approved for children who are at least 2 years of age.[9]

When the affected body surface areas are extensive, a commonly used treatment is narrow-band ultraviolet B phototherapy, which often proves effective in bringing a flare under control.[10]

In 2000, the topical immunomodulators pimecrolimus and tacrolimus—the first in the class of topical calcineurin inhibitors (TCIs)—were introduced and were quickly accepted by parents and widely used by primary care clinicians as well as by pediatricians and dermatologists due to the fact that they were nonsteroidal drugs.

According to currently approved labeling, TCIs are indicated as second-line therapy for patients who do not respond to traditional treatment—that is, topical corticosteroids—or when those treatments are not medically advisable. In addition, the package inserts specify a minimum age limit of 2 years for these drugs.[11,12] When it is a clinician's judgment that TCI therapy is appropriate for a patient younger than 2 years of age, such use is off label, and prior authorization from third-party payers may be required.

For flares of AD that are both severe and extensive, oral therapy with corticosteroids, immunosuppressants such as methotrexate, mycophenolate mofetil, or cyclosporine may be indicated. However, because of the risk for serious side effects, particularly with long-term use of such drugs, these agents are reserved for the most serious cases of atopic dermatitis.

Nonsteroidal Agents for Skin Barrier Repair

Three 510(k) medical device creams have become available over the past several years that are cleared by the FDA for the treatment of atopic dermatitis. This medical device designation means that there is no active drug in the formulation. These products—Atopiclair, Eletone, and MimyX—are also known as barrier creams because they hydrate the skin, help restore damaged stratum corneum, and improve the integrity of the epidermal barrier. Another product, EpiCeram® cream, also is FDA-approved for the treatment of atopic dermatitis but currently is not marketed.

Atopiclair contains 2% glycyrrhetinic acid in a hydrolipid base. Atopiclair contains a nut oil and should be used with caution in patients with a known allergy to nuts or nut oil. However, the nut oil in Atopiclair is shea butter, derived from the nut of a North African tree (*Butyropermum parkii*). The shea nut is not a legume, and Atopiclair contains no peanut oil or peanut extracts.

MimyX contains ingredients that mimic natural lipids and squalane, which are components of the stratum corneum. The main ingredient in MimyX is *N*-palmitoylethanol amine (more commonly referred to as PEA); PEA is a naturally occurring essential fatty acid with anti-inflammatory properties that usually is deficient in patients with atopic dermatitis.

Eletone is unique among the barrier creams because it contains 70% oil dispersed in 30% water yet maintains the consistency and feel of a cream. (Most creams contain 30% oil in 70% water; most ointments contain 30% water dispersed in 70% oil). This is possible through the use of Hydrolipid™ "reverse emulsion" technology. As a result of this proportion of lipids and water, Eletone provides the advantages of ointments (occlusion and maximal barrier protection) without the disadvantages: many patients object to the cosmetic appearance and feel of "greasiness" and fail to comply with regimens involving ointments.

In prescribing any of these products, clinicians should be aware of coverage issues. Since these products are available only by prescription, patients assume the treatment will be covered by their prescription plans. However, many pharmacy benefits managers have determined that because these are devices and not drugs, they are, by definition, not covered.

Conclusion

A number of inflammatory dermatologic conditions adversely affect the dermal barrier; among the most common is atopic dermatitis. The nonsteroidal barrier creams discussed here are welcome additions to the roster of treatments that may be useful as adjuncts to topical corticosteroid therapy during acute flares and as long-term maintenance during periods of disease remission. Their safety profile is excellent: there is no pregnancy category, and there are no age, application-site, or duration of treatment restrictions on their use.

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