Prednicarbate Emollient Cream 0.1% in Pediatric Patients With Atopic Dermatitis

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Atopic dermatitis, common among infants and children, is an intensely pruritic, chronic, inflammatory dermatosis that is traditionally treated with emollients for dry skin and topical corticosteroids for inflamed areas. A multicenter, 3-week, open-label study evaluated prednicarbate emollient cream 0.1%, a nonhalogenated midpotency corticosteroid, in 55 patients aged 4 months to 12 years who were diagnosed with atopic dermatitis. No suppression of the hypothalamic-pituitary-adrenal (HPA) axis was evidenced by serum cortisol levels obtained before and after intravenous injection of 250 mg of cosyntropin on days 1 and 22, and biochemical tests detected no other systemic effects. Adverse events were few and within the expected range. Prednicarbate resulted in improvements based on global evaluations and sign/symptom scores. In conclusion, this study found prednicarbate emollient cream 0.1% to be safe and effective for the treatment of atopic dermatitis in pediatric patients for up to 3 weeks.

Atopic dermatitis, an intensely pruritic, chronic, inflammatory dermatosis, is common in infants and children. The estimated incidence is 10% to 15% of children younger than 18 years.[1] This condition frequently accompanies or precedes allergic respiratory disease.[2] All races[3] and both sexes can be affected, although females are more likely to exhibit the condition than males (female-male ratio, 1.5:1).[4] Generally, the diagnosis is based on history, physical examination, and clinical diagnostic criteria; no laboratory test is available to establish a definitive diagnosis. Sites of involvement vary according to the age of the patient, with the following common involvement: the face in young infants; the extensor surfaces of the arms and legs in toddlers younger than 1 year; and the flexural aspects of the antecubital and popliteal fossae, face, and neck in older children and adolescents.[1]

Traditional treatment mainstays for chronic atopic dermatitis include emollients for areas of dry skin and topical corticosteroids for inflamed areas.[2,5] Topical corticosteroids are used widely in the pediatric group, and there have been relatively few reports of severe adverse events. Because young children have a greater body surface-to-volume ratio, however, the potential suppression of the hypothalamic-pituitary-adrenal (HPA) axis by topical corticosteroids is always a concern and has been reported to occur even with corticosteroids considered to be midpotent.[6-8] Halogenation of corticosteroids markedly enhances anti-inflammatory effects but also may increase the potential for systemic effects of corticosteroids. Prednicarbate emollient cream 0.1% is a relatively new midpotent corticosteroid approved for use in pediatric patients. Prednicarbate is the first corticosteroid of its potency class that is a nonhalogenated prednisolone derivative. This present study was designed to evaluate the local and systemic safety of this corticosteroid for the treatment of atopic dermatitis in young children. Efficacy of treatment was assessed secondarily.

Methods

Study Design—This was a multicenter, open-label study of prednicarbate emollient cream 0.1%. After written informed consent was obtained, patients were enrolled from 7 centers. Study visits were scheduled at 1-week intervals (days 1 [baseline], 8, 15, and 22) during a 21-day treatment period.

Patients—Patients were eligible for the study if they were between the ages of 2 months and 12 years, had atopic dermatitis that involved at least 20% of

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Table 1.

Demographic Characteristics

Variable	N=59
Sex, %	
Male/female	37/63
Race, %	
White	63
Black	27
Asian	2
Hispanic	5
Other	3
Age	
Mean, mo	61.4
Median, mo	53
Range, mo	4–143
<2 years old, %	17
≥2 years old, %	83
Overall disease status, %	
Mild	1
Moderate	58
Severe	41
Total body surface affected, %	
Mean	46.7
Median	44
Range	21–97
Baseline key sign/symptom, mean scores*	
Pruritus	2.63
Fresh excoriations	2.21
Erythema	2.08
Induration/papulation	1.98

*Scores: 0=none; 1=mild; 2=moderate; 3=severe.

their body surface, were in good general health, and had a normal response to cosyntropin stimulation testing. The diagnosis of atopic dermatitis had to include 2 of the following features: pruritus, typical morphology and distribution of signs and symptoms, and personal or family history of atopy. Eligible patients had a history of chronic or chronically relapsing eczema of at least one month, with a current flare of the disease that had been stable or slowly worsening for more than one week. The total rating for the treatment target area had to be 7 out of a possible 12, based on the scoring of 4 variables: erythema, induration/papulation, fresh excoriations, and pruritus. Each variable used a rating scale of 1 to 3 (1=mild, 2=moderate, 3=severe, with no variable missing or scored as 0).

Patients excluded from the study included those children with concomitant chronic illnesses; abnormal physical or laboratory findings; evidence of active infection or atrophy in the target areas; and requirements for continued use of alternative treatments during the study, such as antihistamines. Children whose previous treatments suggested potential suppression of the HPA axis (eg, prolonged or frequent use of systemic corticosteroids), or who had serum cortisol responses to cosyntropin testing at baseline (suggesting HPA-axis suppression), also were excluded.

Treatment—On days 1 through 21, prednicarbate emollient cream 0.1% was applied twice daily to the same specified areas (a target area for study evaluation and other areas specified at baseline). The diaper areas could be treated if they were documented to have atopic dermatitis and not infectious or other forms of dermatitis. The scalp was not included as a study area. Petrolatum and Eucerin® creams were used on nonstudy areas during the study. Therapy was to be continued even if the areas cleared of signs and symptoms before the end of the treatment period. Occlusive dressings, as well as ultraviolet light and grenz-ray therapy, were not to be used, and excessive sunlight was to be avoided.

Evaluations

Systemic Effects—The systemic effect of treatment on suppression of the HPA axis was determined by comparing the differences between serum cortisol levels before and 30 and 60 minutes after intravenous injection with 250 μg of cosyntropin on days 1 and 22. Other potential systemic effects were evaluated by comparing blood chemistry, blood hematology, and urine data collected on days 1 and 22 (or at an early discontinuation visit). Laboratory assays were performed by SmithKline Beecham Clinical Laboratories, Van Nuys, California. If the

Table 2.

Serum Cortisol Levels (μg/dL) Before and After Cosyntropin Stimulation

			30-Minute Poststimulation			60-Minute Poststimulation			Maximum Poststimulation		
	N	Basal Mean (SD)	N	Mean (SD)	Mean Change	N	Mean (SD)	Mean Change	N	Mean (SD)	Mean Change
Day 1	59	13.4 (5.4)	58	25.2 (4.5)	11.8	57	28.3 (4.8)	14.9	59	28.3 (4.6)	14.9
Day 22	53	13.1 (5.4)	55	25.2 (3.8)	12.1*	55	27.4 (5.4)	14.3*	55	28.1 (4.1)	15.0*

*Mean change based on N=53.

basal (prestimulation) serum cortisol levels were >20 μg/dL, a 6 μg/dL increase would be considered a normal response to cosyntropin stimulation, whereas if the basal cortisol level was <20 μg/dL, a poststimulation level >20 μg/dL would be considered a normal response. Any patients with an abnormal cosyntropin stimulation test suggesting HPA-axis suppression on day 22 were reevaluated 2 weeks later and followed biweekly until values normalized (as discussed below for only one patient).

Safety—At each visit, adverse experiences were noted, and examinations were done for signs of skin atrophy in the target area. Vital signs were recorded at baseline (day 1) and at the end of treatment.

Efficacy—At each visit, global evaluations were made of change from baseline in the disease status of all treated areas, using the following scale: 0=cleared, 100% clearance of disease; 1=excellent improvement, 75% to <100% clearance of disease; 2=moderate improvement, 50% to <75% clearance of disease; 3=slight improvement, <50% clearance of disease; 4=no change, no detectable improvement from baseline; and 5=exacerbation, flare. Also, total key and other nonkey disease sign/symptom scores were determined at each visit. Key disease signs and symptoms rated included erythema, fresh excoriations, induration/papulation, and pruritus in the target area. Nonkey signs included weeping, erosions, scaling, dryness, crusting, and lichenification in the target area. The following rating scale was used: 0=none (absent); 1=slight (mild or minimal); 2=moderate (average or easily discernable); and 3=severe (extensive or markedly evident). Half values were used when necessary. The cosmetic acceptability of the test preparations was evaluated by the parent or guardian of each patient on day 22, using the following scale: 0=excellent; 1=good; 2=fair; and 3=poor.

Statistical Analyses—Mean values for serum cortisol levels and mean changes from baseline at 30 and 60 minutes, as well as the maximal value of serum cortisol post–cosyntropin stimulation, were calculated for days 1, 22, and endpoint. The data were analyzed for all patients, as well as for patients stratified by gender, age (<30 months vs ≥30 months), and race (Caucasian vs non-Caucasian). Paired *t* tests and analyses of variance determined the significance of differences between mean basal values and mean changes from basal values at 30 and 60 minutes poststimulation and at maximum response on days 1 and 22. Descriptive statistics were used to summarize the results of patients' assessments of signs and symptoms and global evaluations.

A planned sample size of 50 was chosen, based on a calculated 92% probability of detecting one or more cases of adrenal suppression, if the suppression rate is 0.05.[9]

Results

Patient Characteristics—Of the 60 patients enrolled in the study, 59 were treated with prednicarbate emollient cream 0.1%. The required baseline blood specimens were not obtained from one enrolled patient who was therefore not treated. Demographic characteristics of the 59 treated patients are presented in Table 1. At baseline, patients had had their disease for 2 to 132 months, a significant portion of their lives. On average, 46.7% of the total body surface was affected. The duration of the current episode of atopic dermatitis ranged from 1 to 52 weeks and was exacerbating for 36 patients and stable for 23. Fifty-six of the 59 (95%) treated patients had a personal or family history of atopy.

Dose and Duration of Treatment—Two patients missed more than 2 applications of study medication

Table 3.

Most Common Adverse Events*

Sign or Symptom	No. of Patients Affected (N=59)
Upper respiratory tract infection	6
Infection	5
Accidental injury	3
Asthma	3
Fever	3
Lymphadenopathy	3
Otitis media	3
Skin disorder	3
Tooth disorder	3
Cough increase	2
Flu syndrome	2
Pruritus	2
Rhinitis	2

*Adverse events reported by >3% of patients.

between visits. In addition, one patient had an anomalous response to cosyntropin stimulation on day 22 (the basal value was greater than normal, suggesting that perhaps the specimens were incorrectly labeled), and repeat cosyntropin testing was performed on day 41 to evaluate HPA-axis function. Nonetheless, the data for all 3 patients were included in all analyses. Four patients were dropped from the study because they did not meet the baseline criteria for normal response to cosyntropin stimulation. A few patients treated new lesions during the course of the study, resulting in a slight increase of the percentage of area treated. Increases ranged from 0.5% to 3% of additional body area treated in 10 patients and were 7% and 12% in 2 patients.

Serum Cortisol Levels—HPA-axis function was considered to be normal and unaffected by use of the test material. There were no differences in serum cortisol levels between days 1 and 22 for basal mean values or mean changes from basal values at 30-minute, 60-minute, or the greater (maximal value) of the 2 poststimulation cortisol levels (Table 2). Similar results (data not shown) were found when analyses were stratified by gender, age, and race. The one patient who required repeat testing demonstrated normal responses to cosyntropin on day 41, indicating no HPA-axis suppression, despite prolonged use of prednicarbate.

Safety—Twenty-eight (47.5%) patients experienced one or more adverse events, all of mild or moderate severity, and none were drug related. The adverse events that were experienced by at least 2 patients (3%) are presented in Table 3. No adverse event resulted in discontinuation from treatment. No clinically noteworthy treatment-related abnormal laboratory results were recorded. Seven patients (12%) were observed to have signs of atrophy in the target area (only telangiectasia, thinness, and/or shininess).

Efficacy—Treatment with prednicarbate emollient cream 0.1% resulted in good-to-excellent improvement in all treated areas at all return visits and at endpoint. Mean global scores reflected improvement over the study period (1.9 on day 8, 1.5 on day 15, and 1.1 on day 22). The percentage of patients with scores indicating ≥75% clearance of disease increased from 33% on day 8 to 78% on day 22 (Figure 1). All patients showed some improvement, and no patients showed exacerbation at any return visit. Total key sign/symptom scores improved dramatically during the first week and continued to improve through the end of the study (85% on day 22)(Figure 2). Fresh excoriations and pruritus showed the greatest improvement (approximately 90% by day 22), and erythema showed a 76% improvement on day 22 (Figure 3). The total score for non–key disease signs (weeping, erosions, scaling, dryness, crusting, and lichenification) showed rapid improvement during the first week of treatment, and more gradual improvement thereafter (76% on day 22)(Figure 4).

The cosmetic acceptability score at endpoint was 0.29 (close to a score of 0=excellent). Seventy-one percent of the parents/guardians rated acceptability as excellent; the remainder rated it as good (1). There were no ratings of fair or poor (2 or 3, respectively).

Comment

The management of chronic atopic dermatitis in pediatric patients is challenging and often includes the use of topical corticosteroids for inflamed areas.[2] These drugs are ranked according to potency in 7 classes, ranging from group I, the most potent, to group VII, the least potent.[2] Drugs in the mid-strength (groups IV and V) and mild (groups VI and VII) categories are used most frequently in pediatric

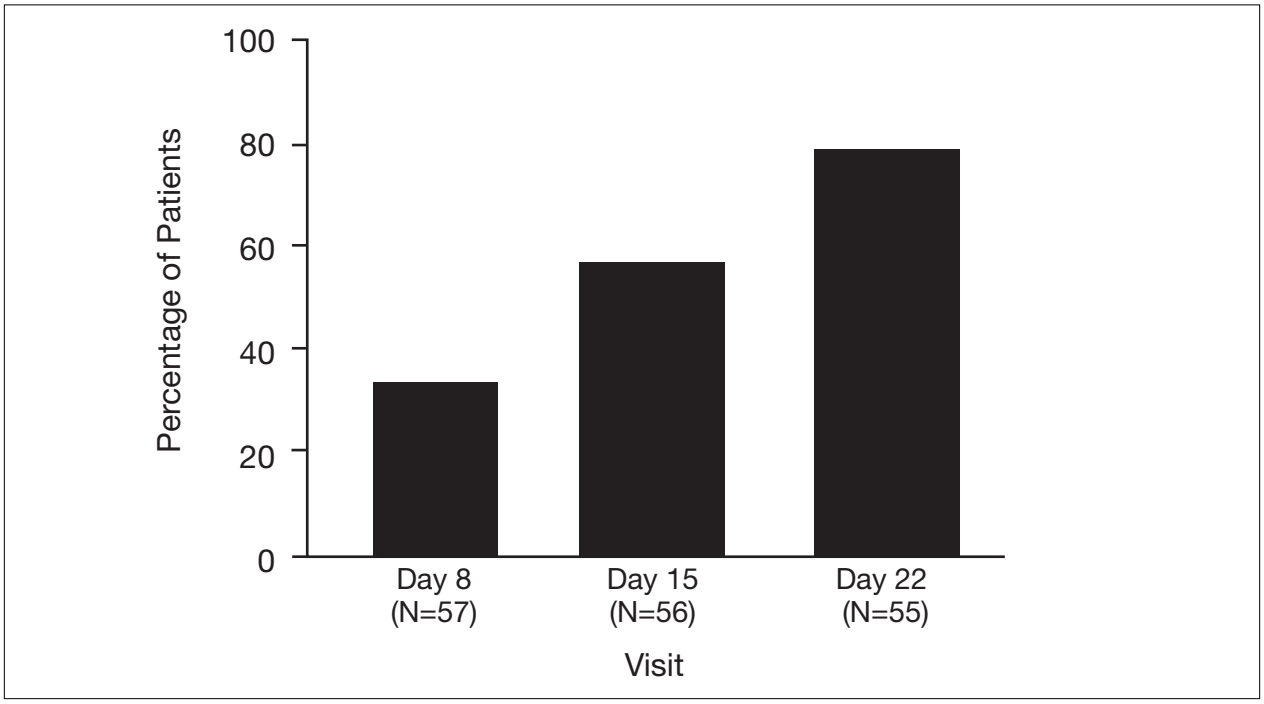

Figure 1. Percentage of patients with complete or excellent improvement based on global evaluations (scores of 0 or 1).

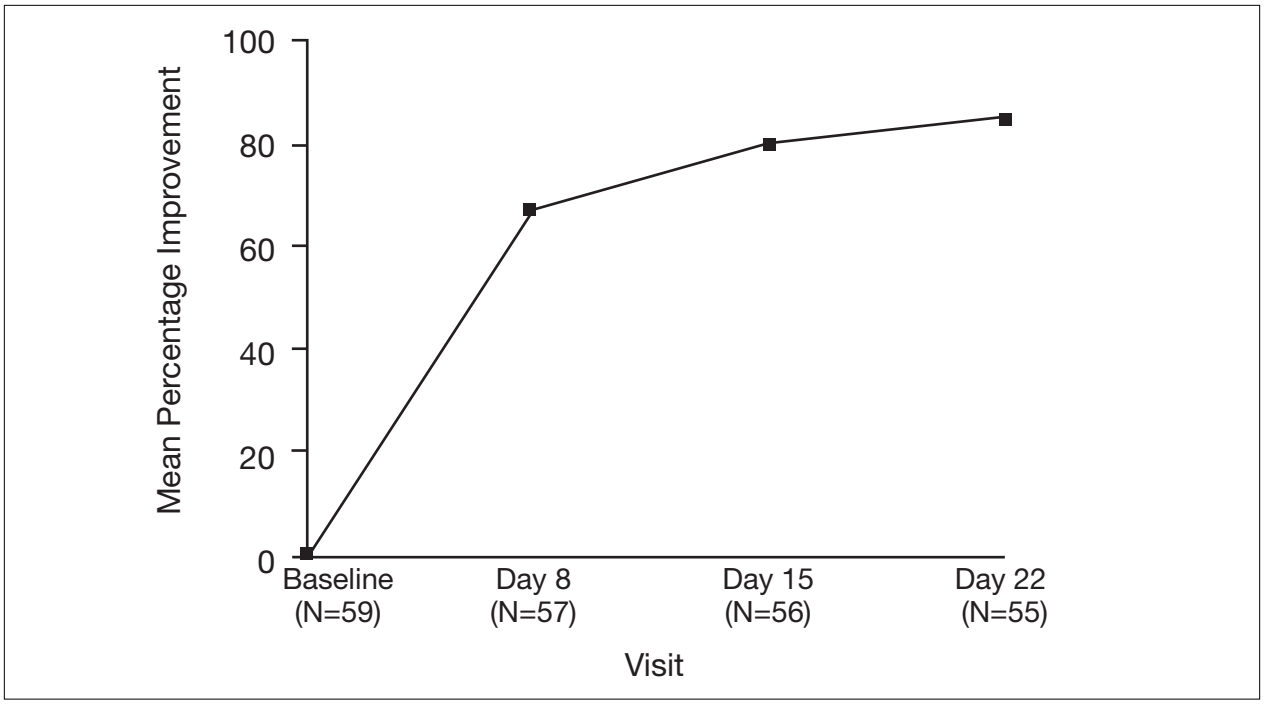

Figure 2. Mean percentage improvement of total key sign/symptom scores.

populations, and, when applied over short periods on limited areas of the skin without occlusion, usually are very effective and cause few side effects.[10] Because long-term use may be required to treat children with atopic dermatitis, however, concern remains about potential systemic side effects, including HPA-axis suppression.[1]

The reasons for concern about HPA-axis suppression range from the possibility of Cushing's syndrome,[11] growth retardation,[12] and lenticular cataracts,[13] to biochemical changes detected only by biochemical studies.[6-8] Newer and more sensitive tests, such as the corticotropin-releasing hormone (CRH) stimulation test[14] and a low-dose (0.5–1.0 g)

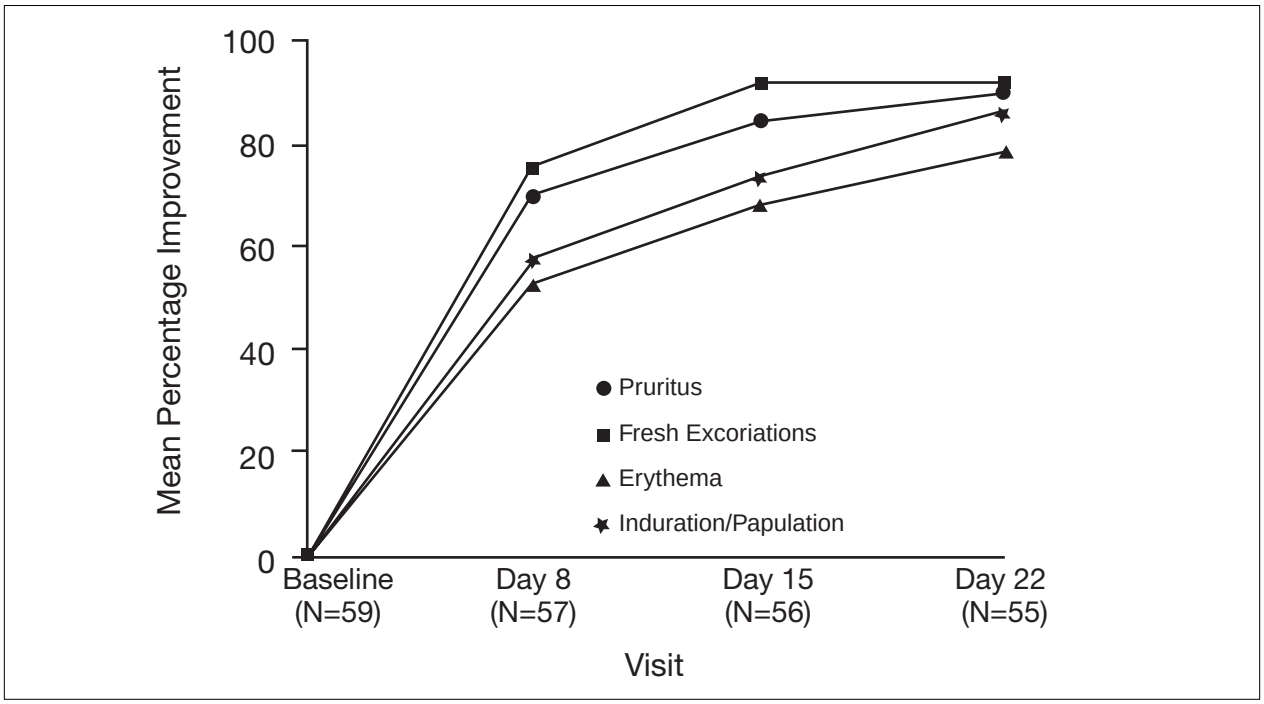

Figure 3. Mean percentage improvement of individual key signs and symptoms.

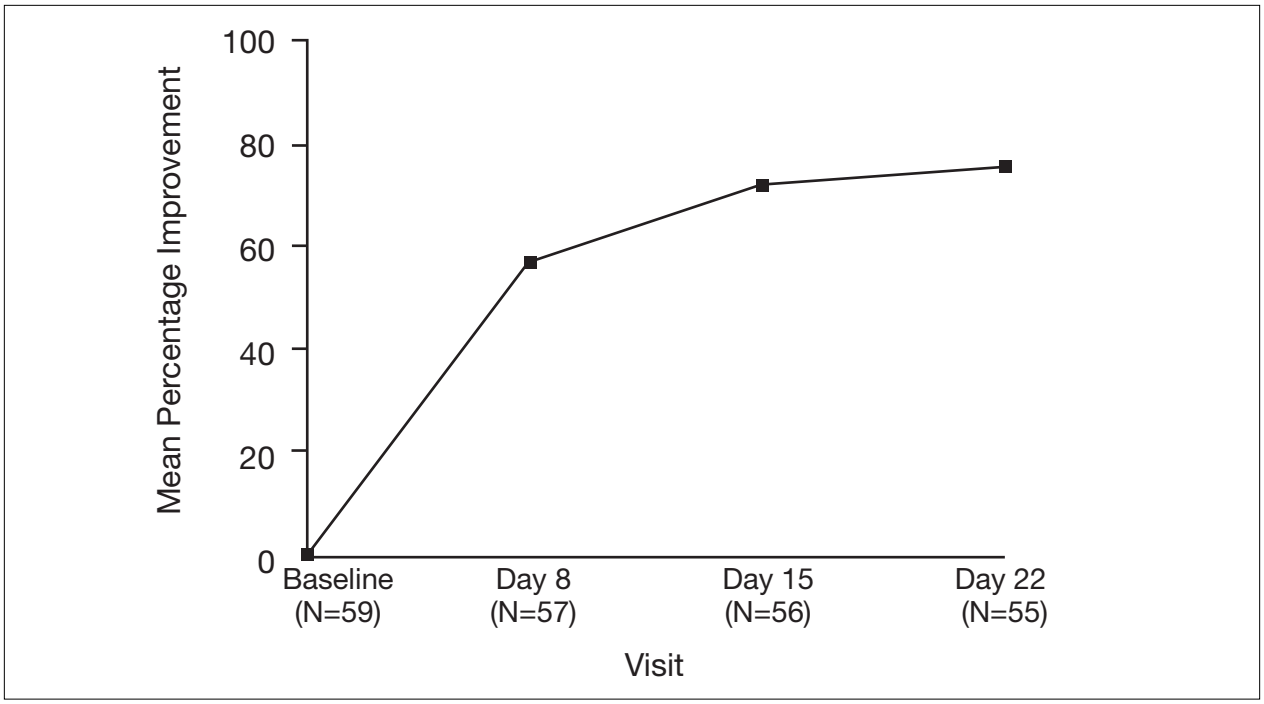

Figure 4. Mean percentage improvement of total non–key disease signs.

corticotropin test,[15] have been used to evaluate the HPA axis. The CRH stimulation test has demonstrated subtle suppression of the HPA axis following prolonged use of corticosteroids.[16] A low-dose (0.5 g) corticotropin test revealed mild adrenal insufficiency in patients with asthma on long-term therapy with inhaled corticosteroids; adrenal suppression was not detected by the standard high-dose (250 μg) test in these patients.[17] There are, however, no good normative data for CRH and low-dose corticotropin testing of the HPA axis in young infants. The standard high-dose (250 μg) corticotropin test used in this study showed no suppression of the HPA axis following prednicarbate treatment. Mean basal, 30-minute, and

60-minute serum cortisol levels and peak serum cortisol response to cosyntropin were not different on day 22 when compared with studies conducted on day 1.

The present study demonstrates that prednicarbate emollient cream 0.1%, a new midpotency (group V) corticosteroid, is both safe and effective in children aged 4 months to 12 years. The severity of disease in the population studied and the greater body surface-to-volume ratio in pediatric patients should have maximized the availability of the drug in the systemic circulation and, therefore, the chances of eliciting systemic effects. Nonetheless, over a 3-week period, cosyntropin-stimulation testing revealed no HPA-axis effects. Laboratory tests detected no other systemic effects, and adverse events were few and within the expected range. The relationship of the signs of atrophy noted in 7 patients (12%) during the current study to the study drug is unclear. Because most patients had used topical corticosteroids on the target lesions before the study, preexisting signs of atrophy may have been masked by signs of disease at baseline.

Efficacy evaluations found that treatment with prednicarbate emollient cream 0.1% resulted in improvements in global evaluations, in total key sign/symptom scores, and in scores concerning nonkey disease signs. The cosmetic acceptability of the medication was rated by all parents/guardians as either excellent (71%) or good.

These promising results should be validated in randomized, double-blind trials of the use of prednicarbate emollient cream 0.1% among pediatric patients. In addition, because most children with this condition suffer repeated exacerbations, the potential effects of multiple usages of the medication over time should be evaluated.

In conclusion, this research has found prednicarbate emollient cream 0.1%—a new, medium strength corticosteroid—to be safe and effective for the treatment of atopic dermatitis in pediatric patients, for up to 3 weeks. Theses results indicate that prednicarbate emollient cream 0.1% is an additional option for physicians in the treatment of this chronic and often debilitating disease.

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