Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug

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Background: Pimecrolimus cream 1% (Elidel, SDZ ASM 981), a nonsteroid selective inhibitor of inflammatory cytokines, is effective in the treatment of atopic dermatitis (AD). In this study we compared early intervention with pimecrolimus cream with treatment with a vehicle control.

Objective: The purpose of this investigation was to assess whether early treatment in infants of AD signs/symptoms with pimecrolimus could influence long-term outcome by preventing disease flares.

Methods: In this 1-year, double-blind controlled study, 251 infants aged 3 to 23 months with AD were randomized 4:1 to a pimecrolimus-based regimen (n = 204) or a conventional treatment regimen (n = 47). Both groups used emollients for dry skin. Early AD signs and symptoms were treated either with pimecrolimus cream to prevent flares or, in the control group, with vehicle. Vehicle was used to maintain blinding conditions. In the event of flares, moderately potent corticosteroid was permitted in both groups. The primary efficacy end point was the incidence of flares at 6 months.

Results: Pimecrolimus significantly reduced the incidence of flares compared with control treatment ($P < .001$), with 67.6% versus 30.4% of patients completing 6 months with no flare and 56.9% versus 28.3% completing 12 months with no flare. Overall corticosteroid use was substantially lower in the pimecrolimus group: 63.7% versus 34.8% of patients did not use corticosteroids at all during the study. Pimecrolimus was also more effective than control treatment in the long-term control of pruritus and the signs of AD. There were no clinically significant differences in incidence of adverse events between the 2 treatment groups.

Conclusions: Treatment with pimecrolimus of early signs and symptoms significantly modified the disease course in infants by reducing the incidence of flares and improving overall control of AD. Pimecrolimus was safe and well tolerated. (J Allergy Clin Immunol 2002;110:277-84.)

Key words: *Pimecrolimus, Elidel, SDZ ASM 981, atopic dermatitis, eczema, long-term management*

Atopic dermatitis (AD) is a common inflammatory skin disease, with an especially high prevalence in children and infants.[1,2] The prevalence of AD has been increasing over the past several decades. Among individuals born before 1960, 1.4% to 3.0% have had one or more episodes of AD compared with 8.9% to 20.4% of those born after 1970.[3] In developed countries approximately 10% to 15% of children younger than 5 years of age have AD,[3] of whom 48% to 75% present with signs and symptoms within the first 6 months of life.[4,5] Thus AD has become a disease of public importance, especially with regard to its effect on the pediatric population.

The current conventional treatment strategy for AD is emollients for dry skin and reactive use of topical corticosteroids for disease flares.[6,7] However, topical corticosteroids must be used with care because long-term use can cause skin atrophy and suppression of the hypothalamic-pituitary-adrenal axis.[8–13]

Pimecrolimus cream 1% (Elidel, SDZ ASM 981) was developed specifically for the treatment of inflammatory skin diseases.[14] At clinically relevant concentrations, pimecrolimus selectively inhibits activation of T cells and mast cells, suppressing inflammatory cytokines and other mediators of the allergic inflammatory reaction.[15,16] Pimecrolimus does not have the atrophogenic potential of topical corticosteroids, and there should be

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Abbreviations used
AD: Atopic dermatitis
EASI: Eczema Area and Severity Index
IGA: Investigators' Global Assessment

no restriction regarding treatment duration on the basis of safety considerations.[17]

In this study we investigated whether the early treatment of the signs and symptoms of AD with pimecrolimus would influence long-term outcome by preventing progression to disease flares in infants.

METHODS

Study conduct

This study was conducted at 41 centers in 8 countries (Belgium, Canada, France, Germany, New Zealand, South Africa, Spain, and the United Kingdom). The institutional review board at each center approved the protocol, and written informed consent was obtained from the legal guardians of all study participants.

Study population

In total, 251 infants aged 3 to 23 months with a clinical diagnosis of AD according to the criteria of Seymour et al[18] were randomized to treatment. For the main inclusion and exclusion criteria, refer to Table I.

Study design

This was a randomized, double-blind, parallel-group, multicenter study. Patients were randomized 4:1, respectively, to receive either a pimecrolimus cream–based treatment regimen or a conventional control treatment regimen for up to 12 months to facilitate recruitment.

The study treatment scheme is shown in Fig 1. For long-term management of AD, parents and caregivers were to apply study medication (ie, pimecrolimus cream or vehicle) to affected areas twice daily to treat at the first signs (ie, erythema) or symptoms (ie, pruritus) of AD to prevent the progression to flare. Study medication was to be used on affected areas twice daily until complete clearance of signs and symptoms. In addition to study medication, emollients and moderately potent topical corticosteroids were mandated. Emollients were used in both groups to treat dry skin. Moderately potent topical corticosteroids were allowed in both groups for flares not controlled by study medication (ie, at least severe erythema and severe infiltration-papulation; Investigators' Global Assessment[19] [IGA] score of ≥4, the IGA being a static [ie, no reference to the baseline state] 6-point measure of disease severity based on overall assessment of skin lesions) and were to be administered until clearance or until the maximum treatment duration allowed by the local country label was reached. Treatment with corticosteroid was followed by a week of treatment with study medication for residual disease. In each participating country, one specific topical corticosteroid was selected for use. The corticosteroids used were 0.02% difluprednate cream, 0.1% hydrocortisone butyrate cream, 0.05% clobetasone butyrate cream, 0.02% triamcinolone acetonide cream, and 0.2% hydrocortisone valerate cream.

The control group received a conventional treatment: regular skin care with emollients and short-term treatment of flares with moderately potent topical corticosteroids. Vehicle instead of pimecrolimus was used in the control group to maintain blinding conditions. Patients whose AD flares were not controlled by the topical corticosteroid could leave the study.

Blinding

The study blinding was preserved by using study medication (ie, pimecrolimus cream or corresponding vehicle) of identical appearance and odor. The results of the 6-month part of this study were reported to the US Food and Drug Administration as an update to a New Drug Application submission, but personnel unblinded for this report had no further contact with study centers or with data-handling personnel. The blinding conditions were strictly maintained for all site-monitoring and data-management personnel at all times.

Primary and secondary outcome measures

The primary efficacy end point was the incidence of flares of AD at 6 months (described in detail in the "Statistical analysis" section). The incidence of flares was chosen as the primary efficacy end point because of its robustness, simplicity, and clinical relevance. A flare of AD was defined in cases in which, at a scheduled or unscheduled visit, the IGA score was assessed as 4 or 5 (ie, at least severe erythema and severe infiltration-papulation). For the purpose of the analysis and to ensure that each flare was a clearly separate event, the definition of a flare also required that corticosteroid therapy had to begin within 3 days of such a visit and be preceded by at least 7 days without corticosteroid use.

In addition, a series of secondary outcome measures were assessed, including IGA score, Eczema Area and Severity Index (EASI),[20] and caregivers' assessments of pruritus and the level of overall disease control. Pruritus was assessed by the primary caregiver for the 24 hours before each study visit by using a scale ranging from 0 (none) to 3 (severe), and caregivers were asked to assess the level of control over the 7 days before each visit according to a 4-point scale, ranging from 0 (complete control), through 1 (good control), 2 (limited control), and 3 (uncontrolled dermatitis). The IGA score, pruritus severity assessment, and the caregiver assessment results were dichotomized for analysis into treatment success (score of 0 or 1) and treatment failure (all other scores).

All adverse events occurring during the study were recorded. Physical examination and standard hematology, blood chemistry, and urinalysis tests were performed throughout the study.

Statistical analyses

Statistical analyses were performed on the intent-to-treat population, defined as all randomized patients to whom study medication was dispensed.

For the primary efficacy analysis, the incidence of flares was ranked. Patients who discontinued were considered to have poorer control of AD than those who stayed in the study, which is in accordance with the method described by Gould.[21] Subjects discontinuing in their first 6 months in the study were ranked according to the number of flares they experienced over unit time in the study, whereas subjects completing 6 months in the study were ranked according to the number of flares recorded. The null hypothesis of no treatment difference was tested with the Wilcoxon rank sum test adjusted for center (Van Elteren test), with the 2-sided significance level set at 5%. This primary method of ranking was chosen because it took discontinuation into account, ranking discontinued patients according to the number of flares experienced per unit time in the study. All analyses were repeated on the 12-month data.

A sample size of 250 subjects with a pimecrolimus/vehicle ratio of 4:1 was sufficient to show a doubling of the proportion of subjects with 2 or fewer flares in 6 months from 25% to 50% by using the Wilcoxon rank sum test at an α value of 5% (2-sided significance with a power of >80%). Power was estimated by using simulations on one scenario. The percentage of rejections of the null hypothesis obtained from 1000 data sets provided the power estimation.

Efficacy according to the IGA, EASI, pruritus, and caregiver

assessment scales was evaluated by means of intent-to-treat analysis, with the last observation carried forward used to impute missing data, including end points.

Cumulative survival curves investigating time to first flare were constructed by using the Kaplan–Meier method.[22] The EASI was analyzed by using analysis of covariance, with the EASI at end point as the response and with treatment effect, center, and baseline EASI fitted. The following analysis of covariance model was fitted:

Response = Treatment + Center + EASI baseline.

Safety was assessed by comparing incidence rates of adverse events between the treatment groups. A time-to-event analysis was performed to determine the adjusted incidence of adverse events to account for the difference in duration of follow-up between the 2 treatment groups. Adverse events were coded with the MedDRA dictionary.

RESULTS

Patients

In total, 251 patients from 39 centers were randomized, of whom 204 were randomized to the pimecrolimus-based treatment regimen and 47 to the conventional treatment control group. A flow diagram of patient accounting and treatment outcome is provided in Fig 2.

The demographic and clinical characteristics of the patients are summarized in Table II. There were no clinically significant demographic differences between the 2 groups. In terms of baseline disease severity, the 2 groups were also similar, with a mean affected body surface area of 27.3% in the pimecrolimus group and 28.8% in the control group at baseline. The majority of patients in each group had moderate AD at baseline.

The mean ± SEM duration of follow-up was 321.3 ± 7.78 days in the pimecrolimus group and 263.3 ± 22.50 days in the control group. Almost twice as many patients withdrew in the control group than in the pimecrolimus group (34.8% vs 15.7%, respectively) in the first 6 months of the study, a trend that was maintained for the duration of the study (39.1% vs 24.5% at 12 months, respectively; $P = .016$, log-rank test on time to discontinuation). Significantly more patients in the control group than in the pimecrolimus group discontinued because of unsatisfactory therapeutic effect (30.4% vs 9.3% at 6 months and 32.6% vs 10.3% at 12 months, respectively).

Furthermore, the longer a patient remained in the study, the less often study medication had to be used to maintain disease control. The frequency of use of pimecrolimus for control of disease declined markedly the longer patients were in the study. From day 9 to day 29, patients used the treatment 75.2% of the time on average; from day 100 to day 183, this had declined to 51.7%, and from day 183 to the end of the study, it had declined to 47.8%.

Efficacy

As summarized in Fig 3, pimecrolimus treatment was associated with a significantly lower incidence of flares than conventional treatment ($P < .001$, Van Elteren test). In particular, 67.6% (95% CI, 61.2%-74.1%) of pimecrolimus-treated patients completed 6 months on study without a flare compared with 30.4% (95% CI, 17.1%-43.7%) of patients in the control group. This trend was

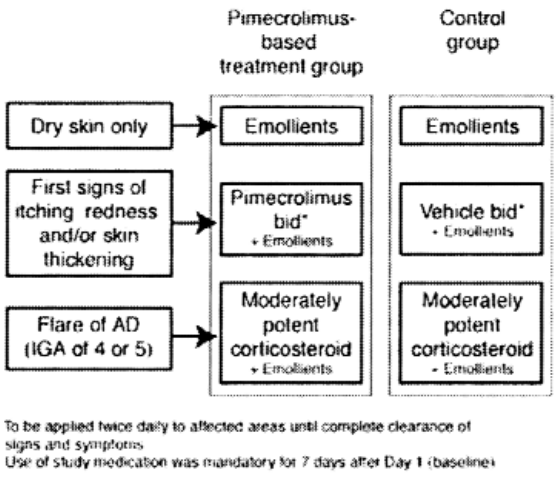

FIG 1. Study treatment scheme.

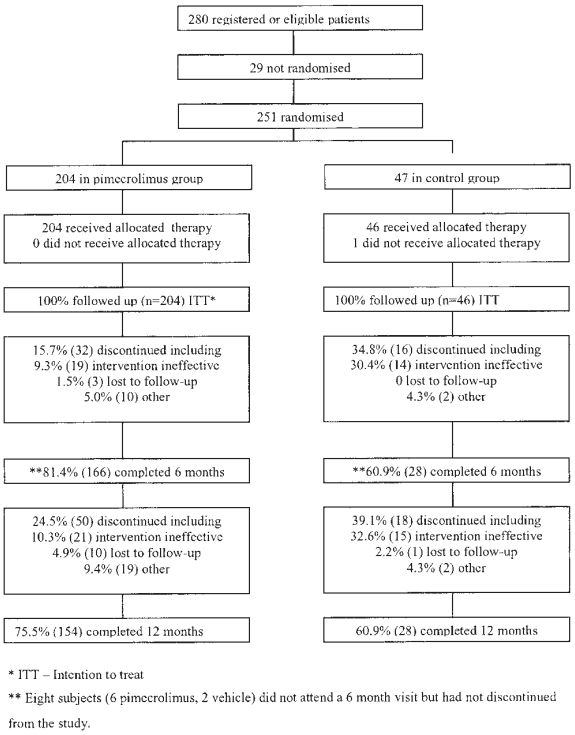

FIG 2. Flow diagram of treatment outcome.

maintained for the duration of the study: 56.9% (95% CI, 50.1%-63.7%) of patients in the pimecrolimus group completed 12 months in the study without a flare compared with 28.3% (95% CI, 15.2%-41.3%) in the control group. For patients who completed 6 and 12 months in the study, the absolute risk reduction[23] for flare was 37.2% and 28.2%, respectively. Fewer flares were observed in the pimecrolimus group, regardless of baseline disease severity. The absolute risk reduction for patients with baseline severity of mild, moderate, and severe or very severe who completed 6 months without a flare was 38.7%, 35.9%, and 33.3%, respectively, and therefore even patients with severe disease derived bene-

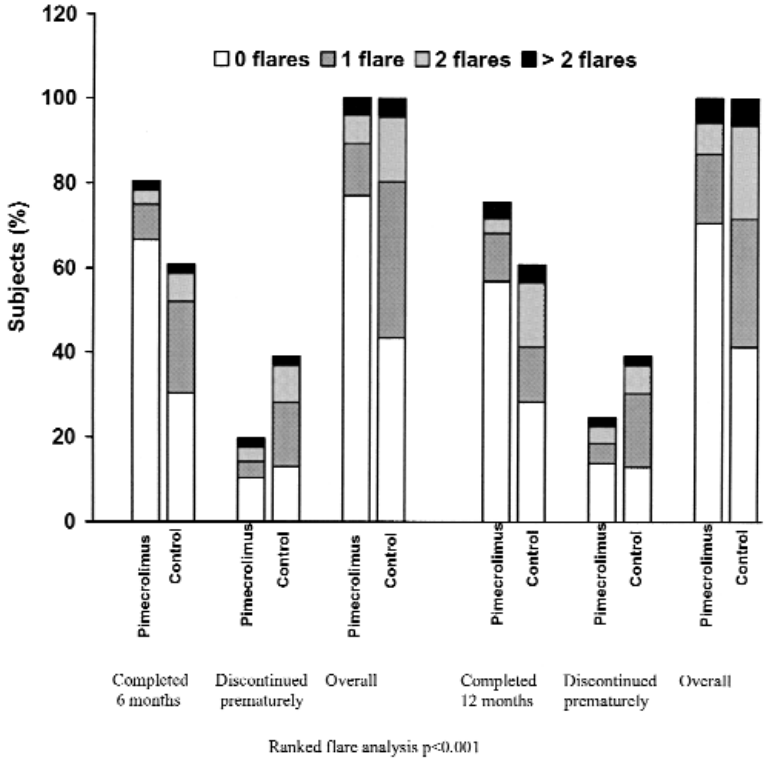

FIG 3. Incidence of flares of atopic dermatitis at 6 and 12 months.

TABLE I. Main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Diagnosis of AD according to the criteria of Seymour et al[18] AD affecting at least 5% of total body surface area IGA score of ≥2	Patients who had the following: • phototherapy or systemic therapy known or suspected to affect AD ≤1 mo before the first application of study medication, • topical therapy known or suspected to affect AD ≤7 days before the first application of study medication, and • systemic antibiotics ≤2 weeks before the first application of study medication. Patients who: • were immunocompromised or had a history of malignant disease, • had active skin infections, • had other infections that required treatment with prohibited medications (ie, generally medication that could affect a patient's AD), and • had other skin conditions that could affect the evaluation of study treatment.

fit from treatment. The analysis of time to first flare showed that treatment with pimecrolimus was associated with a significantly longer flare-free period ($P < .001$, log-rank test; Fig 4). In addition, the mean number of flares per unit time was lower in the pimecrolimus group than in the control group (1.0 vs 2.2 per 12 months; $P < .001$, Van Elteren test).

In total, 130 (63.7%) patients in the pimecrolimus group did not use a corticosteroid during the study compared with 16 (34.8%) patients in the control group. The proportion of study days on corticosteroid treatment was 3.2% in the pimecrolimus group compared with 6.2% in the control group.

The response of patients, as assessed by means of IGA, is summarized in Fig 5. By day 8 (the first postbaseline visit), an IGA score of 0 or 1 (clear or almost clear skin) had been achieved in 44.6% of pimecrolimus-treated patients compared with only 8.7% of patients receiving control treatment ($P < .001$). The maximum benefit was achieved by approximately day 22 in the pimecrolimus group compared with month 3 in the control group, and the magnitude of the effect was greater in the pimecrolimus group (54.9% vs 39.1% achieving an IGA of 0 or 1 by day 22, $P = .034$). At month 6, a significantly higher number of pimecrolimus-treated patients also had clear or nearly clear skin compared with those receiving

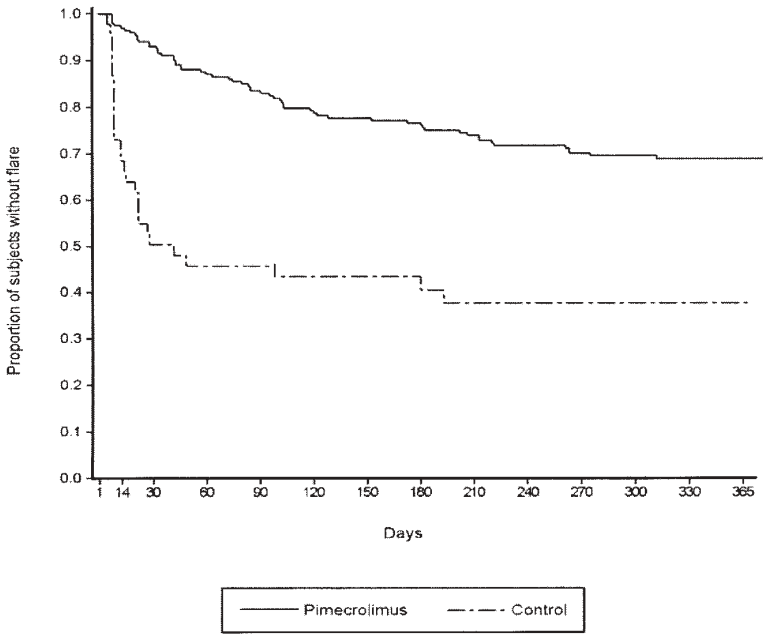

FIG 4. Kaplan-Meier analysis of time to first flare.

control treatment (52.9% and 37.0%, respectively; P = .03). Even at month 12, although not statistically significant, a higher number of patients in the pimecrolimus group (53.9%) had clear or nearly clear skin compared with 47.8% of patients in the control group.

The superior clinical response in the pimecrolimus group compared with that in the control group, as measured by means of EASI, pruritus, and caregiver assessment, is summarized in Table III.

Safety

Both treatments were well tolerated, and with the exception of viral infection not otherwise specified as to type, which was more common in the control group, there were no clinically significant differences between the treatment groups with respect to incidence of common adverse events (Table IV).

Local tolerability was good in both treatment groups. The incidence of application site reactions was low in both groups (6.5% vs 14.7%, pimecrolimus vs control), and there were no significant differences between the treatment groups (P = .104).

In total, 27.0% of pimecrolimus-treated patients and 27.6% of patients in the control group had at least one skin infection by the end of the study (P = .728). With the exception of viral rash not otherwise specified as to type and erysipelas, both of which were more common in the control group, there were no significant differences between the treatment groups in terms of adjusted incidence or time to first event for any skin infection (Table V).

No clinically relevant laboratory abnormalities were observed during the study.

TABLE II. Baseline demographic and clinical characteristics

	Pimecrolimus (n = 204)	Control (n = 46)
Age, mo (range)	12.2 (3-23)	11.8 (2-23)
Age distribution, %		
<1 y	47.1	45.7
>1 y	52.9	54.3
Sex, %		
Male	66.7	60.9
Female	33.3	39.1
Total body surface area involved, %		
Mean	27.3	28.8
Range	1.4†-95.0	3.0†-80.0
EASI*		
Mean	12.3	12.6
Range	1.2-58.0	1.6-45.5
IGA score, %		
1 (almost clear)	0	0
2 (mild disease)	32.8	39.1
3 (moderate)	57.4	47.8
4 (severe)	8.3	10.9
5 (very severe)	1.5	2.2

*EASI is a composite, validated scoring system objectively assessing both the severity of the 4 key signs of AD (ie, erythema, induration-papulation, excoriations, and lichenification) in the 4 EASI body regions (ie, head and neck, trunk, and upper and lower limbs) and the surface area involvement. We combed results from each region to give a total score of 0 to 72, which was age adjusted for the percentage of each body area involved.
†Eleven patients in the pimecrolimus group and 3 patients in the control had a baseline area involvement of less than 5%; most had just slightly less than 5%. For all analyses, total body surface area involvement was calculated by using the area component of EASI; however, when including patients in the study, investigators used a simple algorithm to check compliance with the 5% total body surface area involved inclusion criterion. The palm of the subject's hand was taken to be approximately 1% total body surface area.

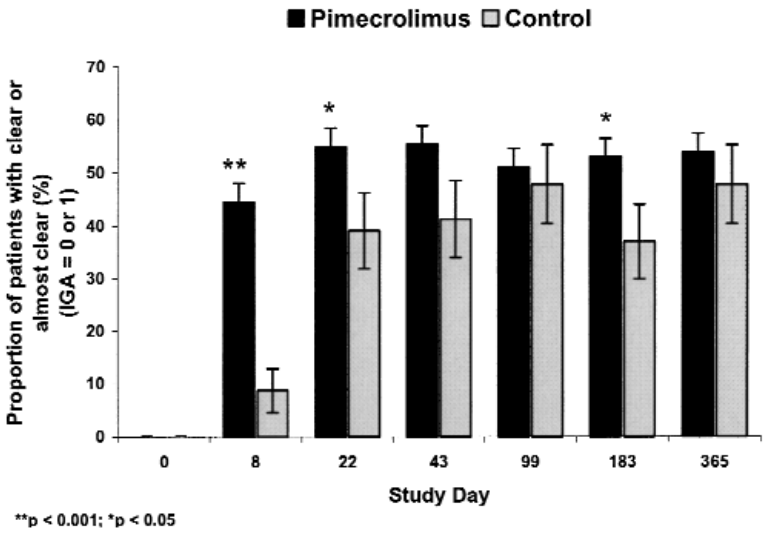

FIG 5. Number of patients with IGA score of 0 or 1 (clear or almost clear skin).

TABLE III. Change in EASI, pruritus, and caregiver assessment scores between baseline and month 12

	Pimecrolimus (n = 204)	Control (n = 46)	*P* value
EASI mean total score			
Baseline	12.3	12.6	
Day 43	3.9	7.7	<.0001
Month 6	5.0	6.9	.076
Month 9	4.7	6.7	.078
Month 12	5.0	5.9	.487
Change from baseline	–7.3	–5.7	
Pruritus score 0 or 1 (none or mild)			
Baseline, n (%)	68 (33.3)	13 (28.2)	
Day 43, n (%)	156 (76.5)	27 (58.7)	.016
Month 6, n (%)	149 (73.0)	25 (54.4)	.008
Month 9, n (%)	154 (75.5)	26 (56.6)	.009
Month 12, n (%)	157 (77.0)	29 (63.1)	.074
Caregiver assessment score 0 or 1 (complete or good disease control)			
Baseline	33 (16.2)	5 (10.9)	
Day 43	152 (74.5)	25 (54.4)	.013
Month 6	144 (70.6)	23 (51.0)	.016
Month 9	150 (73.5)	26 (56.5)	.058
Month 12	145 (71.0)	29 (63.0)	.337

DISCUSSION

This study demonstrates that a treatment strategy on the basis of early intervention with pimecrolimus twice daily for preventing flares and reducing dependence on corticosteroids was safe and provided superior disease control in infants with AD compared with a conventional regimen of emollients and moderately potent corticosteroids. In particular, pimecrolimus treatment was associated with a clinically significant effect on the course of the disease over 12 months, including a lower incidence of flares and better control of AD signs and symptoms. An imbalance caused by the premature discontinuation as a result of unsatisfactory therapeutic effect in the control group of patients with severe disease and the much higher level of corticosteroid consumption in the control group might largely explain the lack of significance between the treatment groups, as assessed by means of EASI from month 6 onward and by the pruritus severity assessment at month 12. To our knowledge, this is the first large, randomized controlled study focusing on the long-term efficacy and safety of therapeutic intervention in AD in infants.

Although more than 50% of all AD cases start in infancy, very little research has focused on therapeutic intervention in this age group.[24] AD is a chronic disease that can severely affect quality of life[25] and the infant–parent relationship. Therefore early therapeutic intervention with a view to preventing flares might be particularly advantageous in this patient group.

The treatment of AD in infants is complicated by pharmacokinetic considerations specific to this age group. Infants are known to be more sensitive than adults to systemic side effects after topical application of drugs because of the greater surface area/weight ratio.[26] This

TABLE IV. Adjusted incidence of common treatment emergency adverse events

Adverse event	Pimecrolimus, % (n = 204)	Control, % (n = 46)
Nasopharyngitis	56.9	46.2
Pyrexia	44.8	40.5
Teething	31.6	32.8
Diarrhea NOS	27.6	26.3
Upper respiratory tract infection NOS	27.3	25.3
Cough	26.0	16.5
Rhinitis NOS	24.0	15.8
Ear infection NOS	21.7	20.8
Chickenpox	19.6	15.6
Vomiting NOS	16.1	8.2
Otitis media NOS	14.9	15.5
Gastroenteritis NOS	14.8	14.9
Bronchitis NOS	14.6	16.2
Conjunctivitis NOS	13.9	13.9

NOS, Not otherwise specified.

TABLE V. Adjusted incidence of bacterial and viral skin infections

	Pimecrolimus, % (n = 204)	Control, % (n = 46)
Bacterial	12.7	9.1
Impetigo NOS	9.1	6.8
Bacterial infection NOS	1.6	0
Folliculitis	0.5	0
Furuncle (exc genital)	0.5	0
Bacterial genital infection NOS	0.6	0
Stye	0.6	0
Erysipelas	0	2.3
Viral	3.3	6.9
Herpes simplex	1.1	3.4
Eczema herpeticum	0.5	0
Molluscum contagiosum	1.2	0
Skin papilloma	0.5	0
Viral rash NOS	0	3.4

NOS, Not otherwise specified.

higher risk of systemic absorption in infants has been well documented for topical corticosteroids.[27] Significant effects on the hypothalamic-pituitary-adrenal axis have been reported after applications of even mild topical corticosteroids in infants.[13,28] Disease extent and patient age have been identified as important risk factors for systemic absorption of topical corticosteroids, with young pediatric patients with extensive AD being at most risk.[28] Because of the risk of adrenocortical suppression with long-term use in infants, topical corticosteroids are generally only used in short courses to treat acute flares, followed by maintenance treatment with emollients.[6,7,29] This conventional treatment approach has been shown to be effective for the short-term amelioration of signs and symptoms of AD. The long-term course of AD, however, is not affected, and many patients are not satisfied with current treatment options.[30-32]

Pimecrolimus is a nonsteroid selective inhibitor of activation of T cells and mast cells. Pharmacokinetic studies in pediatric patients have shown that systemic absorption of pimecrolimus is low, even in infants with large body surface area involvement.[33] This low level of systemic absorption might be explained by the pronounced lipophilicity of the molecule and by its high molecular weight.[14,16] Consequently, neither skin atrophy nor any of the systemic side effects associated with corticosteroids are expected with pimecrolimus.

In this study treatment in the pimecrolimus group was well tolerated, and notably, there were no significant differences between treatment groups with respect to the incidence of skin infections.

In conclusion, this study has demonstrated that pimecrolimus cream applied twice daily is safe and effective in the treatment of AD in infants aged 3 to 23 months. Early intervention with pimecrolimus to prevent progression to disease flare was proven to be significantly more effective than conventional management with emollients and moderately potent corticosteroids in modifying the long-term course of AD. Notably, in 57% of the infants, AD could be managed for 12 months without a flare and without having to resort to topical corticosteroids. Therefore pimecrolimus has the potential to establish a new and more effective approach to the management of AD, particularly in infants, for whom there are currently few treatment options.

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REFERENCES

1. Kapp A. Atopic dermatitis—the skin manifestation of atopy. Clin Exp Allergy 1995;25:210-9.
2. Werfel T, Kapp A. Atopic dermatitis and allergic contact dermatitis. In: Holgate S, Church M, Lichtenstein L, editors. Allergy. London: Mosby; 2001. p. 105-25.
3. Schultz LF. The epidemiology of atopic dermatitis. Monogr Allergy 1993;31:9-28.
4. Wadonda N, Golding J, Kennedy CTC, Archer CB, Dunnill MGS. Prevalence of atopic eczema in children between 0 and 30 months on Avon district. Br J Dermatol 2000;143(suppl 57):33.
5. Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. J Am Acad Dermatol 1994;30:35-9.
6. Hepburn D, Yohn JJ, Weston Wl. Topical steroid treatment in infants, children, and adolescents. Adv Dermatol 1994;9:225-54.
7. Raimer SS. Managing pediatric atopic dermatitis. Clin Pediatr 2000;39:1-14.
8. Gunther S. Incidence and degree of unwanted adverse effects of corticoids in childhood: results of dermatological studies in children with chronic diseases in the age group of 1–15 years. Z Hautkr 1976;51:569-79.
9. Hill CJ, Rosenberg A Jr. Adverse effects from topical steroids. Cutis 1978;21:624-8.
10. McLean CJ, Lobo RF, Brazier DJ. Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. Lancet 1995;345:330.

11. Ruiz-Maldonado R, Zapata G, Lourdes T, Robles C. Cushing's syndrome after topical application of corticosteroids. Am J Dis Child 1982;136:274-5.
12. Bode HH. Dwarfism following long-term topical corticosteroid therapy. JAMA 1980;244:813-4.
13. Queille C, Pommarede R, Saurat JH. Efficacy versus systemic effects of six topical steroids in the treatment of atopic dermatitis of childhood. Pediatr Dermatol 1984;1:246-53.
14. Meingassner JG, Grassberger M, Fahrngruber H, Moore HD, Schuurman H, Stütz A. A novel anti-inflammatory drug, SDZ ASM 981, for the topical and oral treatment of skin diseases: in vivo pharmacology. Br J Dermatol 1997;137:568-76.
15. Hultsch T, Muller KD, Meingasser JG, Grassberger M, Schopf RE, Knop J. Ascomycin macrolactam derivative SDZ ASM 981 inhibits the release of granule-associated mediators and of newly synthesized cytokines in RBL 2H3 mast cells in an immunophilin-dependent manner. Arch Dermatol Res 1998;290:501-7.
16. Grassberger M, Baumruker T, Enz A, Hiestand P, Hultsch T, Kalthof F, et al. A novel anti-inflammatory drug, SDZ ASM 981, for the treatment of skin diseases: in vitro pharmacology. Br J Dermatol 1999;147:264-73.
17. Queille-Roussel C, Paul C, Duteil L, LeFebvre M-C, Rapatz G, Zagula M, et al. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. Br J Dermatol 2001;144:507-13.
18. Seymour JL, Keswick BH, Hanifin JM, Jordan WP, Milligan MC. Clinical effects of diaper types on the skin of normal infants and infants with atopic dermatitis. J Am Acad Dermatol 1987;17:988-97.
19. Eichenfield LF, Lucky AW, Boguniewicz M, Langley RGB, Cherill R, Marshall K, et al. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol 2002;46:495-504.
20. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001;10:11-8.
21. Gould AL. A new approach to the analysis of clinical drug trials with withdrawals. Biometrics 1980;36:721-7.
22. Kaplan EL, Meier P. Non parametric estimation from incomplete samples. J Am Stat Assoc 1958;53:457-81.
23. Sackett D, Straus S, Richardson WS, Rosenberg W, Haynes RB, Evidence-based medicine. 2nd ed. New York: Churchill Livingston; 2000.
24. Hoare C, Li Wau P, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess 2000;4:1-191.
25. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. Br J Dermatol 2001;144:104-10.
26. Saurat JH. Systemic side-effects of topical preparation in children. Sem Hop 1982;58:1643-9.
27. Turpeinen M, Salo OP, Leisti S. Effect of percutaneous absorption of hydrocortisone on adrenocortical responsiveness in infants with severe skin disease. Br J Dermatol 1986;115:475-84.
28. Turpeinen M. Influence of age and severity of dermatitis on the percutaneous absorption of hydrocortisone in children. Br J Dermatol 1988;118:517-22.
29. Morley N. Minimising the use of topical steroids in children. Practitioner 1988;232:949-51.
30. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. Br J Dermatol 2000;142:931-6.
31. Fischer G. Compliance problems in pediatric atopic eczema. Aust J Dermatol 1996;37(suppl 1):10-3.
32. Fukaya M. Why do patients with atopic dermatitis refuse to apply topical corticosteroids? Dermatology 2000;201:242-5.
33. Harper J, Green A, Scott G, Gruendl E, Dorobek B, Cardno M, et al. First experience of topical SDZ ASM 981 in children with atopic dermatitis. Br J Dermatol 2001;144:781-7.