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Efficacy and Safety of Pimecrolimus Cream in the Long-Term Management of Atopic Dermatitis in Children

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ABSTRACT. *Objective.* Pimecrolimus cream (SDZ ASM 981), a nonsteroid inhibitor of inflammatory cytokines, is effective in atopic dermatitis (AD). We assessed whether early treatment of AD signs/symptoms with pimecrolimus could influence long-term outcome by preventing disease flares.

Methods. Early intervention with pimecrolimus was compared with a conventional AD treatment strategy (ie, emollients and topical corticosteroids). In this 1-year, controlled, double-blind study, 713 AD patients (2–17 years) were randomized 2:1 to a pimecrolimus-based or conventional regimen. Both groups used emollients for dry skin. Early AD signs/symptoms were treated with pimecrolimus cream or, in the conventional treatment group, vehicle to prevent progression to flares. If flares occurred, moderately potent topical corticosteroids were mandated. The primary efficacy endpoint was ranked flares at 6 months. Safety was monitored clinically, and a skin recall-antigen test was performed at study completion.

Results. Baseline Characteristics of the Patients. The mean age for both groups was approximately 8 years, and the majority of patients had moderate disease at baseline.

Patient Follow-up and Exposure to Study Medication. The mean duration of follow-up (\pm standard error) was 303.7 (\pm 5.30) days in the pimecrolimus group and 235.2 (\pm 9.40) days in the control group. The discontinuation rate was significantly higher in the control group than in the pimecrolimus group (51.5% vs 31.6% at 12 months), and proportionately more patients with severe or very severe disease discontinued in the control group. The

main reason for the higher discontinuation rate in the control group was unsatisfactory therapeutic effect (30.4% vs 12.4%). This resulted in a substantially higher mean number of study medication treatment days in the pimecrolimus group compared with the control group: 211.9 (69.8% of study days) versus 156.0 (66.3% of study days). Of those patients who completed 12 months on study, 14.2% and 7.0% of patients in the pimecrolimus and vehicle groups, respectively, used study medication continuously.

Efficacy. Patients in the pimecrolimus group experienced significantly fewer AD flares than those in the control group, according to the primary efficacy analysis on ranked flares of AD (Van Elteren test). The proportion of patients who completed 6 or 12 months with no flares was approximately twice as high in the pimecrolimus group compared with control (61.0% vs 34.2% at 6 months; 50.8% vs 28.3% at 12 months). Fewer flares were observed in the pimecrolimus group regardless of baseline disease severity, so even severe patients derived benefit from the treatment. The analysis of time to first flare showed that treatment with pimecrolimus was associated with a significantly longer flare-free period (log-rank test). Covariate analysis indicated a statistically significant effect on time to first flare of baseline Eczema Area and Severity Index score, and whether patients had "severe" or "very severe" disease at baseline according to the Investigators' Global Assessment, although patients in all baseline disease severity subgroups benefited from treatment. Age had no significant effect.

Fewer patients in the pimecrolimus group required topical corticosteroid therapy compared with control (35.0% vs 62.9% at 6 months; 42.6% vs 68.4% at 12 months), and patients in the pimecrolimus group spent fewer days on topical corticosteroid therapy (57.4% vs 31.6% [pimecrolimus vs control, respectively] spent 0 days on topical corticosteroid therapy, 17.1% vs 27.5% 1–14 days, and 25.5% vs 41.0% >14 days over the 12 months of the study). This steroid-sparing effect of pimecrolimus was evident despite pimecrolimus-treated patients being on study longer than patients in the control group. The average proportion of study days spent on second-line corticosteroids was 4.08% in the pimecrolimus group and 9.10% in the control group. Analysis of Eczema Area and Severity Index over time showed significantly lower median scores, thus indicating better disease control in the pimecrolimus group compared with the control group. Similar results were obtained from analysis of the Investigators' Global Assessment (not shown). The treatment groups were well balanced with respect to the number of patients using

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antihistamines during the study (57.2% vs 62.9%, pimecrolimus vs control, respectively).

Safety. There were no appreciable differences between treatment groups in the overall incidence of adverse events. The most frequent adverse events were common childhood infections and ailments, including nasopharyngitis, headache, and cough. The incidence of suspected drug-related adverse events was not significantly different in the pimecrolimus group (24.7% vs 18.7%—pimecrolimus vs control), and the incidence of serious adverse events was low (8.3% vs 5.2%—pimecrolimus vs control). Life-table analysis of incidence of adverse events revealed no significant differences between the treatment groups, except for cough.

Local tolerability was good in both treatment groups. The most common application site reaction reported was sensation of burning (10.5% vs 9.3%—pimecrolimus vs control). There were no major differences between treatment groups in the duration or severity of application site reactions, most of which were mild-to-moderate and transient, occurring within the first week of treatment.

Skin infections were reported in both groups. There were no between-group differences in the life-table analysis of time to first occurrence of bacterial skin infections nor in the adjusted incidence of bacterial skin infections. Although there were no significant differences between treatment groups in the incidence of individual viral skin infections, the incidence of grouped viral skin infections (12.4% vs 6.3%—pimecrolimus vs control) showed a slightly higher incidence in the pimecrolimus group.

Laboratory values and vital signs showed no significant between-group differences.

There were no significant differences between treatment groups in response to recall antigens in those patients who remained on study for 12 months.

Conclusions. Treatment of early AD signs/symptoms with pimecrolimus was effective in preventing progression to flares in more than half the patients, reducing or eliminating the need for topical corticosteroids. The benefits were consistently seen at 6 months across important disease severity subgroups and with respect to the various predefined efficacy endpoints. Furthermore, these benefits were sustained for 12 months, providing evidence that long-term treatment with pimecrolimus leads to better control of AD. Treatment with pimecrolimus was well tolerated and was not associated with clinically relevant adverse events compared with the conventional treatment group. The results reported here offer the prospect of effective long-term management of AD with reduced need for topical corticosteroids. *Pediatrics* 2002; 110(1). URL: <http://www.pediatrics.org/cgi/content/full/110/1/e2>; atopic dermatitis, SDZ ASM 981, pimecrolimus, long-term management, antiinflammatory, flares, Eczema Area and Severity Index, Investigators' Global Assessment, Elidel, randomized controlled study.

ABBREVIATIONS. AD, atopic dermatitis; IGA, Investigators' Global Assessment; EASI, Eczema Area and Severity Index.

Atopic dermatitis (AD) is predominantly a childhood disease, with 80% of patients presenting with signs or symptoms by the age of 5 years.¹ A steady increase in disease prevalence has been observed in most industrialized countries.² AD is typically a chronic disease, and one third of patients will have persistent disease through adulthood. AD has a significant impact on quality of life

and can constitute a considerable burden to the patient and society.³

For >40 years, standard treatment of AD has been regular applications of emollients to alleviate dry skin, and use of short courses of topical corticosteroids to treat disease flares. Although effective in treating acute manifestations of AD, topical corticosteroids, because of their side effects potential, cannot be used long term to control AD. Skin thinning and hypothalamic-pituitary-adrenal axis suppression are the potential topical corticosteroid side effects for children in whom the duration of treatment with moderately potent topical corticosteroids is generally restricted to short courses of 2 to 4 weeks.⁴⁻⁸ Consequently, many practitioners and patients are not satisfied with current treatment options, indicating a need for alternative therapies, particularly for the long-term management of AD.⁹⁻¹¹

Pimecrolimus (SDZ ASM 981), a new ascomycin macrolactam derivative, selectively blocks T-lymphocyte and mast cell inflammatory cytokine production. Both Th1 (interleukin-2, interferon- γ) and Th2 (interleukin-4, interleukin-10) type cytokines are blocked by pimecrolimus.¹² The short-term efficacy and safety of pimecrolimus has been demonstrated in AD.^{13,14} As a nonsteroid, pimecrolimus does not induce skin atrophy.¹⁵ Pharmacokinetic studies in adults and pediatric patients with extensive AD lesions have shown negligible absorption of pimecrolimus through the skin, greatly reducing the likelihood of systemic effects after topical application, even in infants with extensive skin lesions.¹⁶

In this study, we evaluated whether early treatment of AD signs and symptoms with pimecrolimus would influence long-term disease outcome by preventing progression to AD flares. The primary endpoint was the incidence of flares in 6 months.

METHODS

Study Conduct

From July through December 1999, eligible patients were enrolled at 53 centers in 13 countries (9 in Europe, the United States, Canada, South Africa, and Australia). The institutional review board at each center approved the protocol, and written informed consent was obtained from all participants or their legal guardians.

Study Population

Patients who were aged 2 to 17 years and had a diagnosis of AD according to the criteria of Williams et al¹⁷ were enrolled. The main inclusion criteria were AD affecting at least 5% of total body surface area and an Investigators' Global Assessment (IGA; see below) score of ≥ 2 . Patients were excluded if they had received phototherapy or systemic therapy known or suspected to affect AD up to 1 month before the first application of study medication, topical therapy known or suspected to affect AD up to 7 days before the first application of study medication, or systemic antibiotics up to 2 weeks before the first application of study medication. Also excluded were patients who had infections that required treatment with prohibited medications (ie, generally medication that could affect a patient's AD) or skin conditions that could affect the evaluation of study treatment.

Study Design

This was a 1-year, double-blind, controlled study. Patients were randomly assigned in a 2:1 ratio to receive either a pimecrolimus cream 1% treatment regimen or a control treatment regimen, respectively. Treatment assignments were balanced both within

and between centers. Randomization was performed using a validated system that automates the random assignment of treatment groups to randomization numbers. A block size of 6 was used. The randomization schedule was reviewed and locked after approval. The study treatment scheme is illustrated in Appendix 1.

For long-term management of AD, parents and caregivers were to apply study medication (ie, pimecrolimus or vehicle) twice daily to affected areas to treat at the first signs (ie, erythema) or symptoms (ie, pruritus) of AD to prevent the progression to flare. Treatment with study medication was to continue until complete clearance of signs and symptoms. In addition to study medication, emollients and moderately potent second-line topical corticosteroids were mandated. Emollients were used in both groups to treat dry skin. Second-line 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; IGA ≥ 4) and were to be administered according to the local country label. Treatment with corticosteroid was followed by 1 week of treatment with study medication for residual disease. In each participating country, 1 specific second-line topical corticosteroid was selected for use. The corticosteroids used in this study were 0.02% difluprednate cream, 0.25% prednicarbate cream, 0.1% hydrocortisone butyrate cream, 0.05% clobetasone butyrate cream, 0.02% triamcinolone acetonide cream, and 0.2% hydrocortisone valerate cream. Other concomitant medication allowed in the study included antihistamines/H1 blockers if a stable dose throughout the study could be ensured.

The control group received a conventional treatment: regular skin care with emollients and short-term treatment of flares with moderately potent topical corticosteroids. To keep the study blind, vehicle instead of pimecrolimus was used to prevent flares in the control group.

Primary and Secondary Outcome Measures

The primary efficacy endpoint was ranked flares of AD in 6 months (see "Statistical Analyses"). The incidence of flares was chosen as the primary efficacy endpoint 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 (a static 6-point measure of disease severity based on an overall assessment of skin lesions: 0 = clear—no inflammatory signs of AD; 1 = almost clear—just perceptible erythema and just perceptible papulation/infiltration; 2 = mild disease—mild erythema and mild papulation/infiltration; 3 = moderate disease—moderate erythema and moderate papulation/infiltration; 4 = severe disease—severe erythema and severe papulation/infiltration; 5 = very severe disease—severe erythema and severe papulation/infiltration with oozing/crusting) was assessed to be 4 or 5 (ie, at least severe erythema and severe infiltration/papulation). For the purpose of the analysis, to ensure that each flare was a clearly separate event, the definition of a flare also required that second-line corticosteroid therapy begin within 3 days of such a visit and be preceded by at least 7 days off second-line corticosteroid.

Secondary efficacy variables included ranked AD flares in 12 months, time to first flare, IGA, and Eczema Area and Severity Index¹⁸ (EASI). EASI is a composite AD scoring system in which the severity of the 4 key signs of AD (erythema, infiltration/papulation, lichenification, and excoriation) are assessed on a 4-point scale (0–3), and the area affected in each of the 4 EASI body regions (head/neck, trunk, upper extremities, and lower extremities) is estimated. The severity and area scores are used to calculate a single value, the EASI score. Possible EASI scores range from 0 (no disease anywhere on the body) to 72 (most severe disease on all parts of the body). The IGA and EASI were conducted by the investigators at every scheduled (baseline/day 1, weeks 2, 4, 7, 15, 27, 39, and 53) and unscheduled visit.

Safety assessments consisted of recording all adverse events and conducting physical examinations, vital signs, hematology, urinalysis, and clinical chemistry assessments. For assessing skin immune response to a standard panel of antigens (Multitest Immignost, Biosyn GmbH, Fellbach, Germany), a recall-antigen test was conducted on patients who completed 12 months on the study and for whom consent was received. In general, the test site was to be on the volar surface of the forearm, the volar surface of the upper arm, the medial or lateral surface of the thigh, or the paravertebral sites on the back. The test was applied to skin areas that had received no treatment with either study medication or

topical corticosteroids in the week before the test and where there was scant likelihood that treatment would be required in the week after the test; acneform, infected, or inflamed skin was excluded as a test area.

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 ranked as having poorer control of AD than those who stayed in the study, in accordance with the method described by Gould.¹⁹ Patients who discontinued in their first 6 months in the study were ranked according to the number of flares that they experienced over unit time on study, whereas patients who completed 6 months in the study were ranked according to the number of flares recorded. This primary method of ranking was chosen because it addressed the main clinical objective—management of AD—and took discontinuation into account in a clinically meaningful way, by ranking patients who discontinued in the first 6 months according to the number of flares experienced per unit time on study. The Wilcoxon rank sum test adjusted for center (Van Elteren test) was used to test treatment differences. All analyses performed with the 6-month data were repeated with the 12-month data. No correction for multiplicity of tests was performed.

Cumulative survival curves investigating time to first flare were constructed by the Kaplan-Meier method.²⁰ For investigating the effect of baseline variables with respect to time to first flare, a Cox proportional hazards model was fitted including the following factors: country, baseline EASI score, baseline IGA, age category, and treatment group. The EASI was analyzed using an analysis of covariance, with the EASI at endpoint as the response, with treatment effect, center, and baseline EASI fitted.

Safety analysis consisted of tabulation of the differences in incidence rates of adverse events between both randomization groups. To account for the difference in duration of follow-up between the 2 treatment groups, we performed a life-table analysis and compared differences in incidence of adverse events (adjusted incidence) using the log-rank test. Adverse events were coded using the MedDRA dictionary.

A sample size of 660 patients with a ratio of 2:1 for pimecrolimus to control was sufficient to show a doubling of the proportion of patients with 2 or fewer flares in 6 months from 25% to 50% incorporating >20% of dropouts using the Wilcoxon rank sum test at the $\alpha = 5\%$, 2-sided significance with a power of >80%. Power was estimated using simulations on different scenarios (different proportion of dropouts and different proportions of patients for each number of flares). The percentage of rejections of the null hypothesis obtained from 1000 data sets provided the power estimation. All analyses and summaries were performed using SAS version 6.12 (SAS Inc, Cary, NC), under a PC environment.

RESULTS

Recruited and Treated Patients

A flow diagram of patient accounting and treatment outcome is provided in Fig 1.

Baseline Characteristics of the Patients

At baseline, the demographic characteristics and disease severity were similar in both treatment groups (Table 1). The mean age for both groups was approximately 8 years, and the majority of patients had moderate disease at baseline.

Patient Follow-up and Exposure to Study Medication

The mean duration of follow-up (\pm standard error) was 303.7 (± 5.30) days in the pimecrolimus group and 235.2 (± 9.40) days in the control group. The discontinuation rate was significantly higher in the control group than in the pimecrolimus group (51.5% vs 31.6% at 12 months), and proportionately more

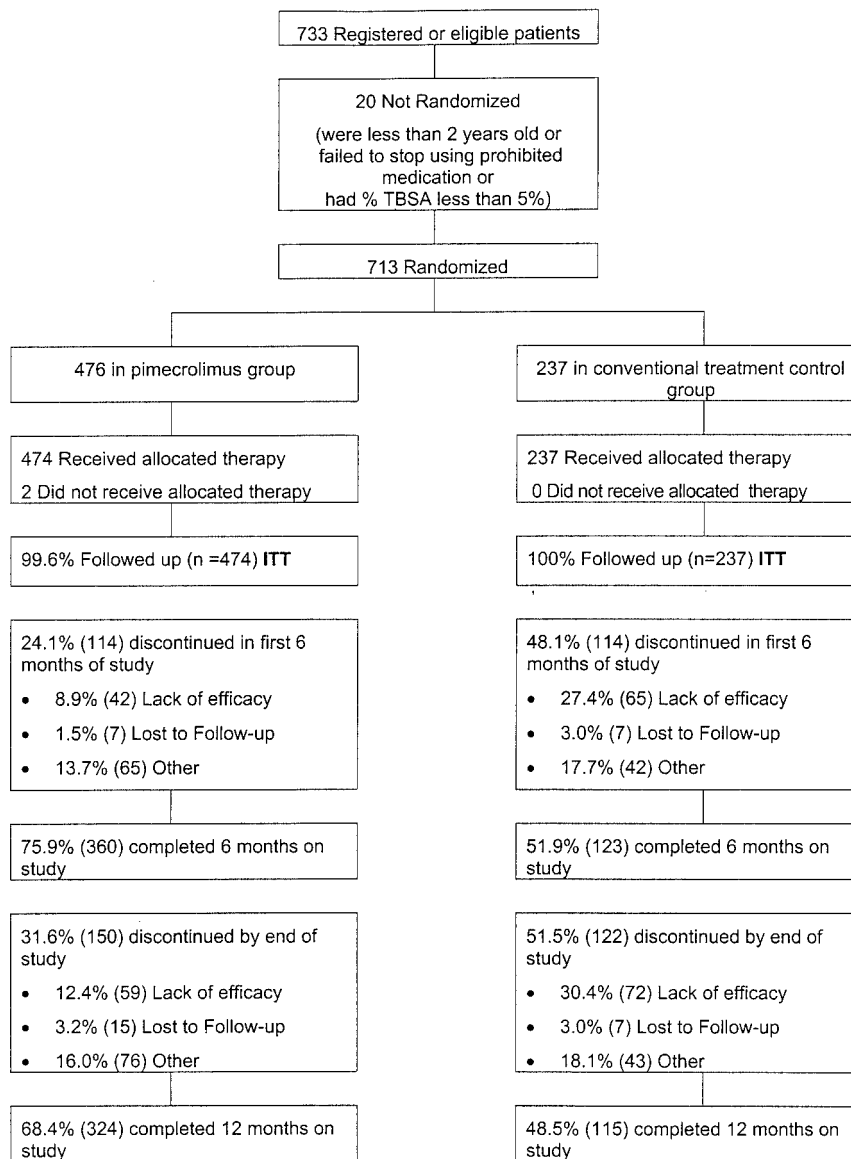


Fig 1. Flow diagram of treatment outcome.

patients with severe or very severe disease discontinued in the control group. The main reason for the higher discontinuation rate in the control group was unsatisfactory therapeutic effect (30.4% vs 12.4%). This resulted in a substantially higher mean number of study medication treatment days in the pimecrolimus group compared with the control group: 211.9 (69.8% of study days) versus 156.0 (66.3% of study days). Of those patients who completed 12 months on the study, 14.2% and 7.0% of patients in the pimecrolimus and vehicle groups, respectively, used study medication continuously.

Efficacy

Patients in the pimecrolimus group experienced significantly fewer AD flares than those in the control group, according to the primary efficacy analysis on ranked flares of AD ($P < .001$, Van Elteren test). The proportion of patients who completed 6 or 12 months with no flares was approximately twice as high in the pimecrolimus group compared with con-

trol (61.0% vs 34.2%, at 6 months; 50.8% vs 28.3%, at 12 months). These data are shown in Fig 2A. Fewer flares were observed in the pimecrolimus group regardless of baseline disease severity (Fig 2B), so even severe patients derived benefit from the 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 3A). Covariate analysis indicated a statistically significant effect on time to first flare of baseline EASI score and whether patients had "severe" or "very severe" disease at baseline according to IGA (Table 2), although patients in all baseline disease severity subgroups benefited from treatment. Age had no significant effect.

Fewer patients in the pimecrolimus group required topical corticosteroid therapy compared with control (35.0% vs 62.9% at 6 months; 42.6% vs 68.4% at 12 months), and patients in the pimecrolimus group spent fewer days on topical corticosteroid therapy (57.4% vs 31.6% [pimecrolimus vs control,

TABLE 1. Baseline Characteristics of the Patients

| Subjects | Pimecrolimus (n = 474) | Control (n = 237) |
|--------------------------------------|---------------------------|----------------------|
| Gender (%) | | |
| Male | 47.3 | 47.3 |
| Female | 52.7 | 52.7 |
| Age (y) | | |
| Mean | 8.0 | 7.9 |
| Range | 1–17 | 2–17 |
| Age distribution (%) | | |
| <2 y | 0.6 | 0 |
| 2<12 y | 73.4 | 75.1 |
| 12<18 y | 25.9 | 24.9 |
| EASI | | |
| Mean | 13.3 | 13.8 |
| Range | 0.6–61.2 | 1.2–61.3 |
| Total body surface area affected (%) | | |
| Mean | 24.2 | 23.8 |
| Range | 1.5–93.0 | 2.8–94.0 |
| IGA (%) | | |
| 1 (almost clear) | 0.2* | 0 |
| 2 (mild) | 26.2 | 27.8 |
| 3 (moderate) | 55.3 | 50.6 |
| 4 (severe) | 15.6 | 17.7 |
| 5 (very severe) | 2.7 | 3.8 |

* One patient had an IGA of 1 at baseline; however, this patient had a baseline EASI score of >10, ie, mild to moderate disease.

respectively] spent 0 days on topical corticosteroid therapy, 17.1% vs 27.5% 1–14 days, and 25.5% vs 41.0% >14 days during the 12 months of the study). This steroid-sparing effect of pimecrolimus was evident despite that pimecrolimus-treated patients were on the study longer than patients in the control group. The average proportion of study days spent on second-line corticosteroids was 4.08% in the pimecrolimus group and 9.10% in the control group.

Analysis of EASI over time showed significantly lower median scores, thus indicating better disease control in the pimecrolimus group compared with the control group (Fig 3B). Similar results were obtained from analysis of IGA (not shown). The treatment groups were well balanced with respect to the number of patients using antihistamines during the study (57.2% vs 62.9%, pimecrolimus vs control, respectively).

Safety

There were no appreciable differences between treatment groups in the overall incidence of adverse events (Table 3). The most frequent adverse events were common childhood infections and ailments, including nasopharyngitis, headache, and cough. The incidence of suspected drug-related adverse events was not significantly different in the pimecrolimus group (24.7% vs 18.7%, pimecrolimus vs control), and the incidence of serious adverse events was low (8.3% vs 5.2%, pimecrolimus vs control). The most frequently reported serious adverse events were skin infections, such as infected eczema (1 case in the pimecrolimus group), impetigo (2 cases in the pimecrolimus group, 1 case in the control group), and herpes simplex dermatitis (2 cases in the pimecrolimus group). The only serious adverse event assessed by the investigator as related to study medication was 1 of the cases of herpes simplex dermatitis, which resolved under appropriate antivi-

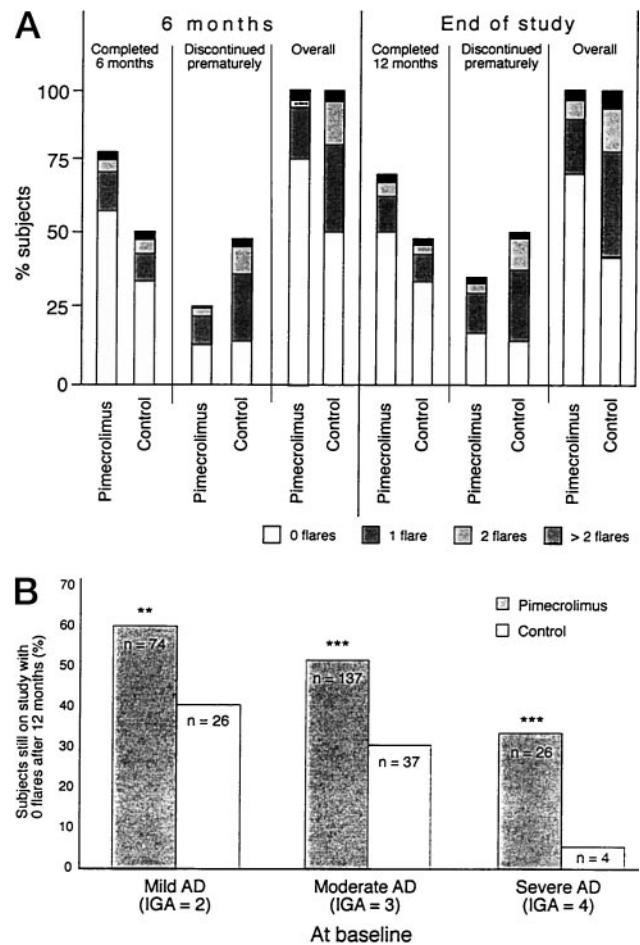


Fig 2. A, Incidence of flares (intention-to-treat population) at 6 and 12 months. B, Proportion of patients with no flares after 12 months by disease severity at baseline.

ral treatment. Life-table analysis of incidence of adverse events revealed no significant differences between the treatment groups, except for cough.

Local tolerability was good in both treatment groups. The most common application site reaction reported was sensation of burning (10.5% vs 9.3%, pimecrolimus vs control). There were no major differences between treatment groups in the duration or severity of application site reactions, most of which were mild to moderate and transient, occurring within the first week of treatment (not shown).

Skin infections were reported in both groups (Table 4). There were no between-group differences in the life-table analysis of time to first occurrence of bacterial skin infections or in the adjusted incidence of bacterial skin infections. Although there were no significant differences between treatment groups in the incidence of individual viral skin infections (Table 4), the incidence of grouped viral skin infections (12.4% vs 6.3%, pimecrolimus vs control) showed a slightly higher incidence in the pimecrolimus group ($P = .038$). Laboratory values and vital signs showed no significant between-group differences. There were no significant differences between treatment groups in response to recall antigens in those patients who remained on the study for 12 months (Table 5).

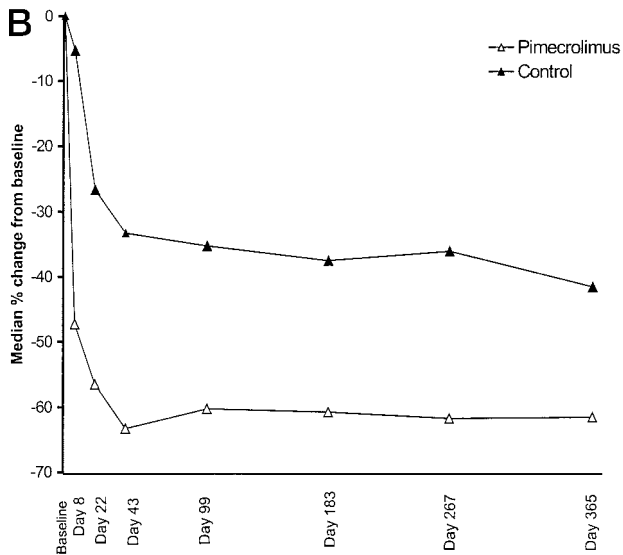
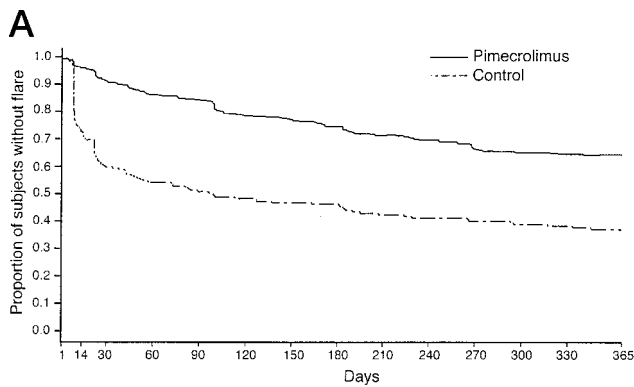


Fig 3. A, Kaplan-Meier estimate of time to first flare (intention-to-treat population). B, Reduction in median EASI over time.

TABLE 2. Effect of Covariates in Cox Proportional Hazards Model: Cox Regression Modeling of Time to First Flare

| Factor | Relative Risk | 95% CI | P Value |
|---------------------|---------------|---------------|---------|
| Age | | | |
| <2 y | 1.245 | (0.172–9.033) | .828 |
| 2–<12 y | 1.000 | | |
| 12–<18 y | 1.031 | (0.789–1.347) | .824 |
| Baseline EASI | 1.023 | (1.010–1.036) | <.001 |
| Baseline IGA | | | |
| Mild disease | 1.000 | | |
| Moderate disease | 1.367 | (0.982–1.903) | .064 |
| Severe disease | 2.443 | (1.598–3.735) | <.001 |
| Very severe disease | 2.661 | (1.332–5.316) | .006 |
| Treatment | | | |
| Pimecrolimus | 1.000 | | |
| Control | 2.824 | (2.228–3.580) | <.001 |

CI indicates confidence interval.

DISCUSSION

These results demonstrate that long-term treatment with pimecrolimus has substantial benefit for AD patients. Treatment of early AD signs or symptoms with pimecrolimus significantly reduced the incidence of flares and was associated with a reduction in topical corticosteroid use; indeed, more than half of the patients could eliminate corticosteroids altogether. Better long-term control of AD, assessed by EASI, was evident in the pimecrolimus group

TABLE 3. Adjusted Incidence of Most Common Adverse Events ($\geq 10\%$)

| Adverse Event | Pimecrolimus (n = 474; %) | Control (n = 237; %) | P Value* |
|-----------------------------|------------------------------|-------------------------|-------------|
| Nasopharyngitis | 28.9 | 27.1 | .944 |
| Headache | 23.0 | 21.5 | .576 |
| Bronchitis | 13.2 | 13.7 | .794 |
| Influenza | 14.6 | 9.5 | .083 |
| Cough | 19.3 | 11.8 | .045 |
| Pyrexia | 15.4 | 11.8 | .326 |
| Application site burning | 10.5 | 9.3 | .484 |

* P value from time to first occurrence analysis (log-rank test).

compared with control throughout the 1-year study. These benefits were apparent regardless of disease severity at the beginning of the study and were seen even in patients with severe disease at baseline.

Local tolerability was good in both groups, with no significant differences between the treatment groups for application-associated events. As expected in a population of children and adolescents, infections and childhood ailments were the most common adverse events. There was no significant association between the incidence of infection and the administration of pimecrolimus, except for a slightly significant higher incidence of grouped viral skin infections in the pimecrolimus group. No such significance, however, was seen with the incidences of individual viral skin infections, which were low in both treatment groups. The viral infections reported are common in this patient population. There was a slightly higher incidence of cough in the pimecrolimus group in this study. This was not seen consistently in all pimecrolimus clinical studies. It should be noted that the discontinuation rate was higher in the control group compared with the pimecrolimus group, mainly because of unsatisfactory therapeutic effect. Patients with severe AD were particularly at risk for early discontinuation in the control group, and these are the patients who are most likely to have asthma. It is tempting to hypothesize that asthma may be a confounding factor that could be contributing to the imbalance in cough. No patients discontinued study medication as a result of cough. Long-term treatment with pimecrolimus was not associated with a decrease in immune response to common recall antigens.

Although AD is a chronic disease, little research has focused on the long-term effect of AD drug therapies.¹⁰ Corticosteroids are efficacious in treating AD flares, but long-term use causes concern because of their potential for causing skin atrophy and other associated side effects, making them unsuitable for long-term management of AD. Consequently, for the past 40 years, most physicians have prescribed corticosteroids in short courses to control acute flares.¹⁰ In addition, the use of topical corticosteroids in the treatment of AD is not standardized: there is great variability of practice across physicians and countries. Until now there has been no broadly accepted treatment for preventing flares of AD. The regular use of emollients has been advocated to prevent flares of AD.²¹ Although legitimized by long use, this

TABLE 4. Adjusted Incidence of Bacterial and Viral Skin Infections

| Adverse Event | Pimecrolimus (n = 474; %) | Control (n = 237; %) | P Value* |
|------------------------------|------------------------------|-------------------------|-------------|
| Bacterial skin infection | 14.2 | 30.9 | .286 |
| Impetigo NOS | 8.3 | 26.7 | .079 |
| Folliculitis | 3.0 | 4.2 | .456 |
| Bacterial infection NOS | 1.7 | 1.0 | .662 |
| Stye | 0.6 | 0 | .227 |
| Abscess NOS | 0.5 | 0.7 | .876 |
| Staphylococcal infection NOS | 0.4 | 0 | .321 |
| Cellulitis | 0.2 | 0 | .515 |
| Streptococcal infection NOS | 0.2 | 0 | .487 |
| Viral skin infection | 12.4 | 6.3 | .038 |
| Herpes simplex | 3.0 | 2.8 | .558 |
| Skin papilloma | 2.8 | 0.6 | .125 |
| Molluscum contagiosum | 2.7 | 1.8 | .698 |
| Eczema herpeticum | 2.1 | 0.8 | .274 |
| Herpes zoster | 1.0 | 0 | .199 |
| Pityriasis rosea | 0.5 | 0 | .391 |
| Flat warts | 0.3 | 0 | .556 |
| Herpes viral infection NOS | 0.3 | 0 | .556 |
| Viral rash NOS | 0 | 0.4 | .157 |

NOS indicates not otherwise specified.

* P value from time to first occurrence analysis (log-rank test).

TABLE 5. Response to Recall Antigens at End of Study

| Skin Antigen | Pimecrolimus (n = 82; %) | Control (n = 30; %) | P Value* |
|---|-----------------------------|------------------------|-------------|
| Tetanus | 63.4 | 60.0 | .826 |
| Diphtheria | 42.7 | 23.3 | .079 |
| <i>Streptococcus</i> | 7.3 | 0 | .190 |
| Tuberculin | 17.1 | 13.3 | .776 |
| <i>Candida</i> | 13.4 | 3.3 | .176 |
| <i>Trichophyton</i> | 8.5 | 10.0 | .726 |
| <i>Proteus</i> | 18.3 | 6.7 | .151 |
| Negative control | 3.7 | 0 | .563 |
| Patients with ≥ 1 positive antigen | 73 | 67 | .820 |

* P value from time to first occurrence analysis (log-rank test).

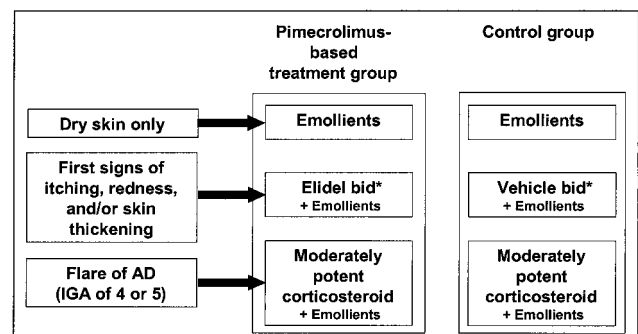
practice has never been evaluated rigorously in large clinical studies. In the control group in this study, emollients (and vehicle) alone were inadequate in preventing AD flaring in approximately two thirds of patients over 1 year.

To our knowledge, this represents the first large, randomized, controlled study to focus on long-term efficacy and safety of therapeutic intervention in AD. In addition to skin care with emollients, the treatment regimen evaluated in this study notably included pimecrolimus to treat early AD signs and symptoms to prevent progression to disease flare, reserving topical corticosteroids for flares not controlled by pimecrolimus. This represents a shift from current AD treatment concepts: emollients for skin care and reactive use of corticosteroids to treat disease flare.

CONCLUSION

The long-term use of pimecrolimus to treat early AD signs and symptoms prevented the progression to AD flares in more than half of the patients and reduced or eliminated the need for corticosteroids. The benefits were consistently seen at 6 months across important disease severity subgroups and with respect to the various predefined efficacy end-

points. Furthermore, these benefits were sustained for 12 months, providing evidence that long-term treatment with pimecrolimus leads to better control of AD. Treatment with pimecrolimus was well tolerated and was not associated with clinically relevant adverse events compared with the conventional treatment group.



* To be applied twice daily to affected areas until complete clearance of signs/symptoms.
Use of study medication was mandatory for 7 days after Day 1 (baseline)
AD, atopic dermatitis; IGA, Investigators' Global Assessment

Appendix 1. Study treatment scheme

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