Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: Results from 3 randomized, comparative studies

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Objective: To compare the efficacy and safety of tacrolimus ointment and pimecrolimus cream in adult and pediatric patients with mild to very severe atopic dermatitis (AD).

Methods: One thousand and sixty-five patients were randomized to treatment in 3 multicenter, randomized, investigator-blinded, 6-week studies.

Results: Based on the Eczema Area Severity Index (EASI), tacrolimus ointment was more effective than pimecrolimus cream at the end of the study in adults (54.1% vs. 34.9%, respectively; $P < .0001$), in children with moderate/severe disease (67.2% vs. 56.4%, respectively; $P = .04$), in the combined analysis (52.8% vs. 39.1%, respectively; $P < .0001$), and at week 1 in children with mild disease (39.2% vs. 31.2%, respectively; $P = .04$). Tacrolimus was also more effective than pimecrolimus based on the Investigator Global AD Assessment (IGADA), improvement in percentage of total body surface area affected, and improvement in itch scores ($P \leq .05$), with a faster onset of action. There was no significant difference in the incidence of adverse events (AEs), including application site reactions in the 2 studies involving 650 children. Adults treated with tacrolimus experienced a greater number of local application site reactions on day 1; both groups reported a similar incidence of application site reactions thereafter. More pimecrolimus-treated patients than tacrolimus-treated patients withdrew from the studies because of a lack of efficacy ($P \leq .03$) or adverse events ($P = .002$; pediatric mild).

Conclusion: Tacrolimus ointment is more effective and has a faster onset of action than pimecrolimus cream in adults and children with AD; their safety profiles are similar. (J Am Acad Dermatol 2005;52:810-22.)

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Tacrolimus and pimecrolimus, two nonsteroidal, topical calcineurin inhibitors, are currently approved for the management of AD. Tacrolimus ointment 0.03% is approved for the treatment of moderate to severe AD in patients 2 years of age and older, and 0.1% is approved for the treatment of moderate to severe AD in adult patients 16 years of age and older. Pimecrolimus cream 1% is approved for the treatment of mild to moderate AD in nonimmunocompromised patients over the age of 2. The safety and efficacy of both products have been demonstrated in short-term and long-term studies for up to 1 year.[1-12] Additional long-term studies have been conducted with tacrolimus ointment 0.1% and demonstrated no safety concerns in patients treated for up to 4 years.[13]

From a clinical perspective, the effectiveness of treatments for AD is evaluated on the basis of the rate with which patients respond to the therapy, the magnitude of the response, the decrease in the area affected, and the patient's subjective response, particularly the decrease in extent of itch. Results from independently conducted studies[9,10] suggest that tacrolimus ointment may be more effective than pimecrolimus cream in the treatment of AD, but no adequate, well-controlled studies comparing the efficacy of topical tacrolimus and pimecrolimus have been published. Kempers et al[14] recently published a randomized, investigator-blinded study comparing tacrolimus ointment to pimecrolimus cream in pediatric patients with moderate AD. In this study, clinical success as measured by a score of "clear" or "almost clear" was numerically higher in the tacrolimus treatment group when compared with the pimecrolimus treatment group; however, this study was not adequately powered to detect a significant difference in efficacy response rates.

The purpose of the studies reported here was to evaluate the efficacy and safety of tacrolimus ointment and pimecrolimus cream in adult and pediatric patients with mild, moderate, and severe AD. Three independent, prospective, randomized, investigator-blinded, multicenter studies were conducted to evaluate twice-daily application of these products in treating the signs and symptoms of AD. Each of the trials employed the same study design, differing only in the study population and strength of tacrolimus tested. Efficacy parameters included the Eczema Area and Severity Index (EASI), success as determined by achieving a score of "clear" or "almost clear" based on the Investigator Global AD Assessment (IGADA), decrease in the percentage of total body surface area (%BSA) affected by AD, and reduction in itch. The clinical response was evaluated at weeks 1, 3, and 6 to determine the onset of response. Data from each study were examined individually and in combined analysis for a direct comparison of tacrolimus ointment with pimecrolimus cream in the management of AD. A subgroup analysis of the data from patients with head/neck involvement at baseline as well as from patients with moderate AD at baseline was also performed.

Abbreviations used:

AD:	atopic dermatitis
BSA:	body surface area
%BSA:	percentage of total body surface area
EASI:	Eczema Area and Severity Index
EOS:	end of study
IGADA:	Investigator's Global Atopic Dermatitis Assessment
MedDRA:	Medical Dictionary for Regulatory Activities
VAS:	visual analog scale

METHODS

Study population

Two of the 3 multicenter studies conducted for the comparative analyses enrolled pediatric patients aged 2 to 15 years, whereas the third study enrolled patients at least 16 years of age. One of the pediatric studies included only those patients with AD that was mild in severity, and the other included patients with moderate to very severe disease. The adult study included patients over the spectrum of mild to very severe AD. To be eligible for participation in these studies, all patients had to meet the clinical criteria of Hanifin and Rajka[15] for the diagnosis of AD and have disease over at least 5% of their total body surface area (BSA). The severity of disease was rated according to the IGADA. Key exclusion criteria were any skin disorder other than AD in the area(s) to be treated in the study, extensive scarring or pigmentation in the area(s) to be treated in the study, or clinically infected AD. Patients whose disease would require the use of nonsteroidal immunosuppressants, light therapy, systemic and topical corticosteroids, topical H_1 and H_2 antihistamines, topical antimicrobials, and any other medicated topical agent were excluded from the study. Nonmedicated topical agents (such as emollients) were permitted only in the areas not being treated with study medication. Intranasal or inhaled corticosteroids were permitted if use was restricted to indications approved by the Food and Drug Administration and doses did not exceed the maximal approved doses. Use of sunscreens was permitted throughout the study. Written informed consent was obtained from all patients or their parents/legal guardian.

Table I. Patient accounting

Patient disposition	Combined analysis		Adult		Pediatric moderate to severe AD		Pediatric mild AD	
	Tacrolimus	Pimecrolimus	Tacrolimus 0.1%	Pimecrolimus 1%	Tacrolimus 0.1%	Pimecrolimus 1%	Tacrolimus 0.03%	Pimecrolimus 1%
Randomized	531	534	210	203	112	114	209	217
Evaluable for safety*	530	533	210	203	112	113	208	217
Evaluable for efficacy†	528	532	210	203	111	113	207	216
Completed‡	405	386	168	155	76	70	161	161
Discontinued	125	147	42	48	36	43	47	56
Adverse drug event	10	20	6	5	4	5	0§	10
Lack of efficacy	13‖	35	3¶	11	6	11	4¶	13
Lost to follow-up	69	69	22	27	14	18	33	24
Administrative#	33	23	11	5	12	9	10	9

Data expressed as number of patients.
*Defined as all randomized patients who applied study medication at least one time.
†Defined as all safety cohort patients who did not have any major randomization violation.
‡Defined as all patients who either completed the 6 weeks of the study or whose end of study visits occurred earlier than Week 6 because all lesions had cleared.
§$P = .002$.
‖$P = .001$.
¶$P = .03$.
#Includes treatment noncompliance; patient wished to withdraw for a reason other than lack of efficacy or adverse event deemed by investigator.

Table II. Baseline demographics*

Demographics	Combined analysis		Adult		Pediatric moderate to severe AD		Pediatric mild AD	
	Tacrolimus (n = 530)	Pimecrolimus (n = 533)	Tacrolimus 0.1% (n = 210)	Pimecrolimus 1% (n = 203)	Tacrolimus 0.1% (n = 112)	Pimecrolimus 1% (n = 113)	Tacrolimus 0.03% (n = 208)	Pimecrolimus 1% (n = 217)
Age (y) (mean ± SD)	19.6 ± 19.1	18.6 ± 18.1	39.6 ± 15.5	38.5 ± 14.0	6.3 ± 3.9	6.5 ± 3.9	6.5 ± 3.8	6.3 ± 3.7
Gender (% of patients)								
Male	45.5	43.9	41.0	38.4	50.9	55.8	47.1	42.9
Female	54.5	56.1	59.0	61.6	49.1	44.2	52.9	57.1
Race (% of patients)								
White	43.4	43.7	43.3	47.3	38.4	39.8	46.2	42.4
African American	34.7	34.0	39.5	36.5	41.1	39.8	26.4	28.6
Other	21.9	22.3	17.1	16.3	20.5	20.4	27.4	29.0

*Safety cohort.

The institutional review board or ethics committee at each center approved the protocol.

Study design

Each of the 3 studies was a prospective, randomized, investigator-blinded, multicenter comparative trial. Following a washout period of up to 4 weeks' duration (depending upon prestudy AD therapy), patients were randomized to receive either tacrolimus ointment or pimecrolimus cream. Study medication was applied twice daily to the affected area(s) for up to 6 weeks or until 1 week after the affected area(s) was completely cleared, whichever came first. Patients were randomized to treatment groups across all centers with a 1:1 randomization allocation. Patient numbers were assigned sequentially. In the pediatric studies, randomization was stratified by age. Group 1 consisted of patients who were 2 but younger than 7 years of age, and group 2 consisted of patients 7 to 15 years of age. In the adult study, randomization was stratified by disease severity. Group 1 consisted of patients with IGADA scores indicating mild or moderate disease; group 2 consisted of patients with IGADA scores indicating severe or very severe disease. Randomization and stratification were conducted by telephone through

Table III. Baseline disease severity*

Characteristics	Combined analysis		Adult		Pediatric moderate to severe AD		Pediatric mild AD	
	Tacrolimus (n = 528)	Pimecrolimus (n = 532)	Tacrolimus 0.1% (n = 210)	Pimecrolimus 1% (n = 203)	Tacrolimus 0.1% (n = 111)	Pimecrolimus 1% (n = 113)	Tacrolimus 0.03% (n = 207)	Pimecrolimus 1% (n = 216)
IGADA (% of pts)								
Mild	52.5	52.8	32.9	31.0	0.9†	1.8†	100.0	100.0
Moderate	35.6	32.9	46.7	44.3	81.1	75.2	0	0
Severe	9.7	11.8	15.7	19.2	16.2	21.2	0	0
Very severe	2.3	2.4	4.8	5.4	1.8	1.8	0	0
Head/neck involvement (% of pts)	66.1	67.9	62.9	65.0	71.2	77.0	66.7	65.7
EASI score (mean)	10.0	10.3	11.0	11.6	16.9	17.4	5.2	5.4
Total BSA % (mean)	19.5	19.9	19.1	19.8	30.8	31.6	13.8	13.8
Itch score, cm (least squares mean)	5.6	5.6	6.0	6.2	6.3	5.7	4.9	5.1

BSA, Body surface area; *EASI*, Eczema and Severity Index; *IGADA*, Investigator's Global Atopic Dermatitis Assessment.
*Efficacy cohort.
†These patients were enrolled in this study because of study center error.

a controlled randomization system at The EMMES Corporation (Rockville, Md). The system confirmed the patient's eligibility based on the inclusion/exclusion criteria and a patient number and treatment were then assigned. The medication was issued to each patient following the instructions obtained by the investigator's unblinded designee through the system.

Treatment

Commercially available tacrolimus ointment 0.03% or 0.1% (Protopic, Fujisawa Healthcare, Inc, Deerfield, Ill) or pimecrolimus cream 1.0% (Elidel, Novartis Pharmaceuticals Corp, East Hanover, NJ) were labeled "For Investigational Use Only" by the sponsor and provided to the investigational sites. Tacrolimus ointment 0.03% was evaluated in the pediatric study of patients with mild disease; tacrolimus ointment 0.1% was evaluated in both the pediatric study of patients with moderate to severe disease and in the adult study. The comparator agent in each trial was pimecrolimus cream 1%.

A thin layer of the assigned medication was applied to all affected areas twice daily, for up to 6 weeks. The study medication was applied at least 2 hours before bathing.

Changes to therapy during the course of the study were permitted following notification of the study investigator as follows: if the affected areas of AD increased in size or if the patient developed new lesions, these new areas were treated; if any individual lesion cleared, treatment applications continued in these areas for 1 additional week and thereafter, the cleared area(s) was excluded from further treatment, while the remaining lesions continued to be treated; and if all treated areas completely cleared before the week 6 visit, treatment continued in all areas for 1 additional week, followed by an end of study (EOS) evaluation. No treatments were continued beyond 6 weeks.

Blinding

A study coordinator, independently of the examining physician, placed a call to a centralized randomization center to obtain the next sequential patient number and drug assignment. Patients and the study coordinator were aware of the treatment assignment because commercially available products were used. The evaluating physician remained blinded to the assignment because patients were instructed not to bring their medications to the examination room, not to apply study drug on the day of their evaluation, and not to discuss any aspect of their study drug with the examining physician. The blinded investigator or designee was responsible for completing the patient case report forms.

Assessments

Patients were examined at baseline/day 1, week 1, week 3, and week 6/EOS. At the baseline visit, the investigator confirmed the diagnosis of AD using the Hanifin and Rajka criteria[15] and identified and evaluated all areas to be treated.

At all visits, the %BSA affected by AD as estimated from 4 designated body regions (head/neck, upper limbs, trunk, and lower limbs), and the Physician's Assessment of Individual Signs in each of these regions, were determined. The Physician's Assessment

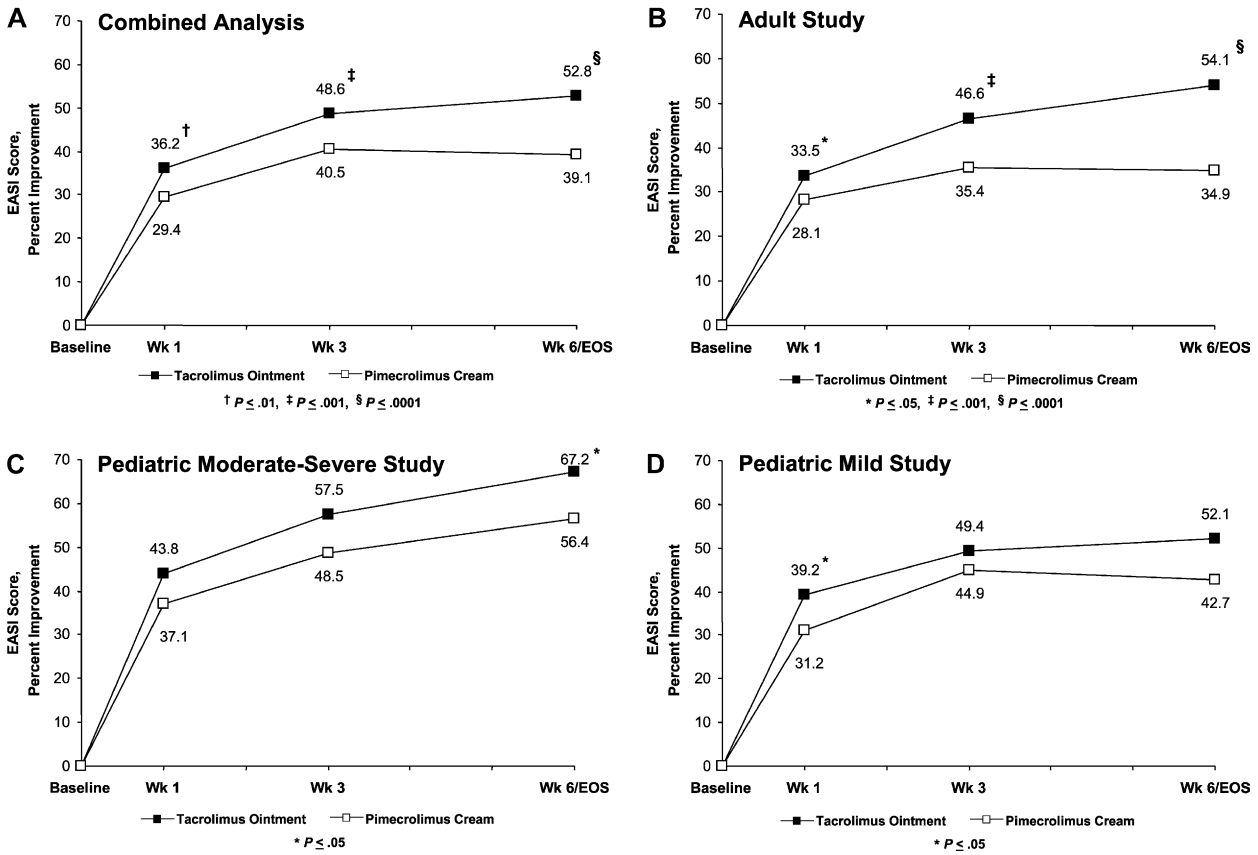

Fig 1. Percentage of improvement from baseline of EASI score in the combined analysis and individual studies; values are least squares means. *EOS,* End of study.

of Individual Signs grades the 6 signs of AD (erythema, edema/induration/papulation, excoriation, oozing/weeping/crusting, scaling, and lichenification) on a 4-point scale, ranging from absent to severe. The results of both these assessments were used to calculate the EASI score, a validated composite score that ranges from 0 (clear) to 72 (validated very severe).[16,17] Additional assessments conducted at each visit were the IGADA (a 6-category scale including the following categories: clear, almost clear, mild, moderate, severe, and very severe) and the patient's assessment of itch using a visual analog scale (VAS), graded on a scale of 0 cm (no itch) to 10 cm (worst itch imaginable). The VAS was to be completed by the patient or parent/legal guardian. Adverse events were recorded on baseline/day 1 (following application of drug) and at each post-baseline visit. For all patients who completed treatment early, the final visit was conducted before the scheduled week 6 visit.

End points

The primary outcome measure was the change in the EASI score from baseline to week 6/EOS. Secondary outcome measures included success of therapy, based on the IGADA where success equals "clear" or "almost clear" and failure equals all other IGADA ratings; %BSA affected; and patient's assessment of itch. Safety end points included the overall incidences of all adverse events reported by the patient or parent/guardian, or observed by the investigator, as well as the individual incidence rates of application site adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system.

Sample size estimation

The planned sample size for the moderate to severe pediatric study was 200 patients (100 per group) which, assuming a 40% success rate for tacrolimus and a 20% success rate for pimecrolimus, would provide 84% power to detect this difference (two-sided α= .05). The sample size for the pediatric study of mild AD and for the adult study was based upon a 50% success rate for tacrolimus and a 35% success rate for pimecrolimus. Thus, in order to have at least 80% power to detect this difference, a sample size of 366 (183 patients in each group) would be

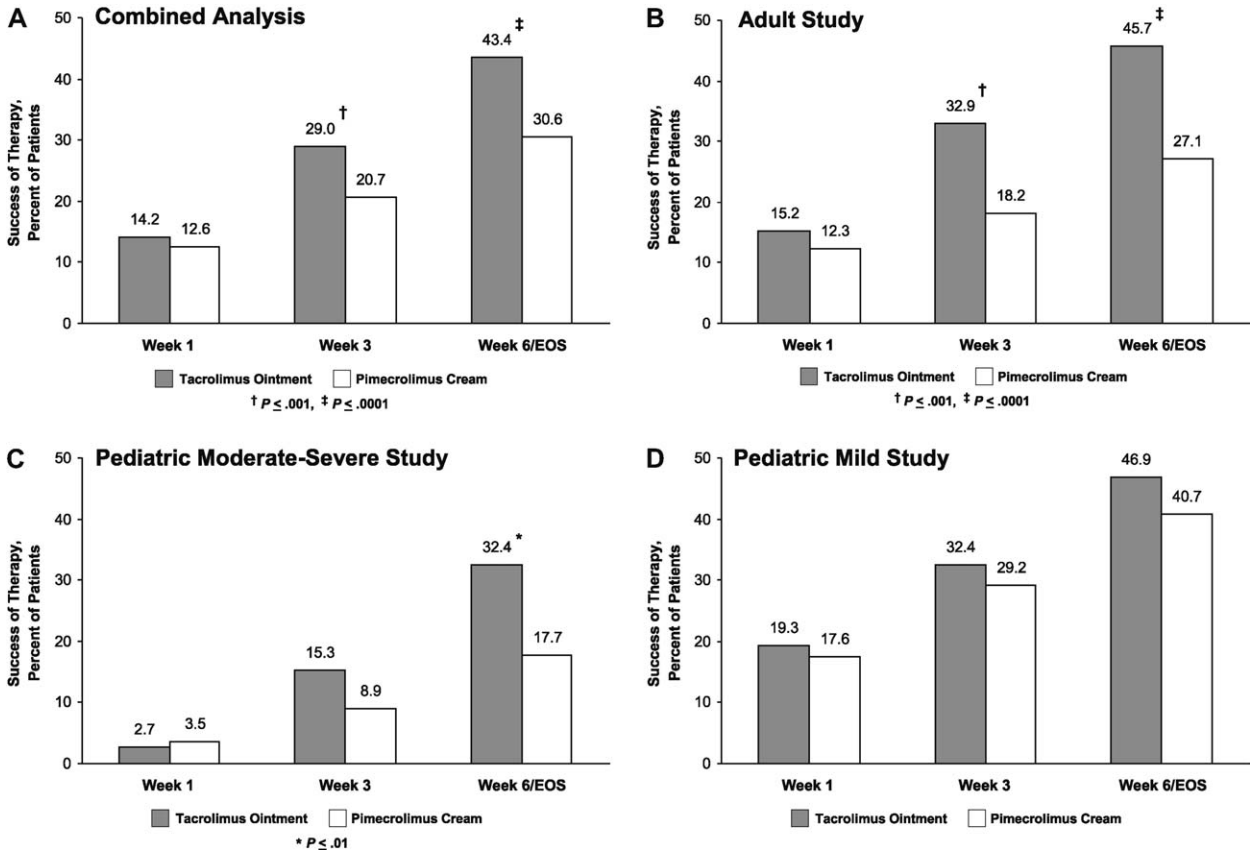

Fig 2. Percentage of patients achieving success of therapy in the combined analysis and individual studies. *EOS,* End of study.

needed (two-sided $\alpha \leq .05$). Because approximately 10% of patients were expected to withdraw from the study, the total sample size was estimated at 400 patients (200 per group).

Statistical analysis

All safety analyses were performed on the cohort of randomized patients who applied study medication at least once during the study (intention-to-treat). The efficacy cohort was composed of all patients in the safety cohort who did not have any major randomization violation (efficacy-evaluable).

Analyses of the primary outcome and the secondary outcomes of %BSA affected and patient's assessment of itch were performed using analysis of covariance in which least squares means calculated for each treatment group were adjusted for center and baseline values. A last-observation-carried-forward analysis was used for all missing efficacy data. Baseline values were carried forward as needed. Treatment success (which was based on the IGADA score) was analyzed using the Cochran-Mantel-Haenszel test stratified by study center. All statistical tests were two-sided, with $\alpha = .05$.

RESULTS

Study patients

Randomization for each study was initiated in November 2002 and was completed in May 2003 for the pediatric moderate to severe AD study (9 investigational sites) and in November 2003 for both the pediatric mild AD study (18 investigational sites) and the adult study (13 investigational sites). A total of 1065 patients were randomized: 531 to tacrolimus treatment and 534 to pimecrolimus treatment. The trial profile summaries for the 3 individual studies and the combined analysis are presented in Table I. The cohort for safety analyses (intention-to-treat) was composed of 530 tacrolimus patients and 533 pimecrolimus patients, whereas the cohort for efficacy analyses comprised 528 tacrolimus patients and 532 pimecrolimus patients.

A total of 76.4% (405/530) patients in the tacrolimus group and 72.4% (386/533) patients in the pimecrolimus group completed the study. Significantly more pimecrolimus-treated patients withdrew because of a lack of efficacy than tacrolimus-treated

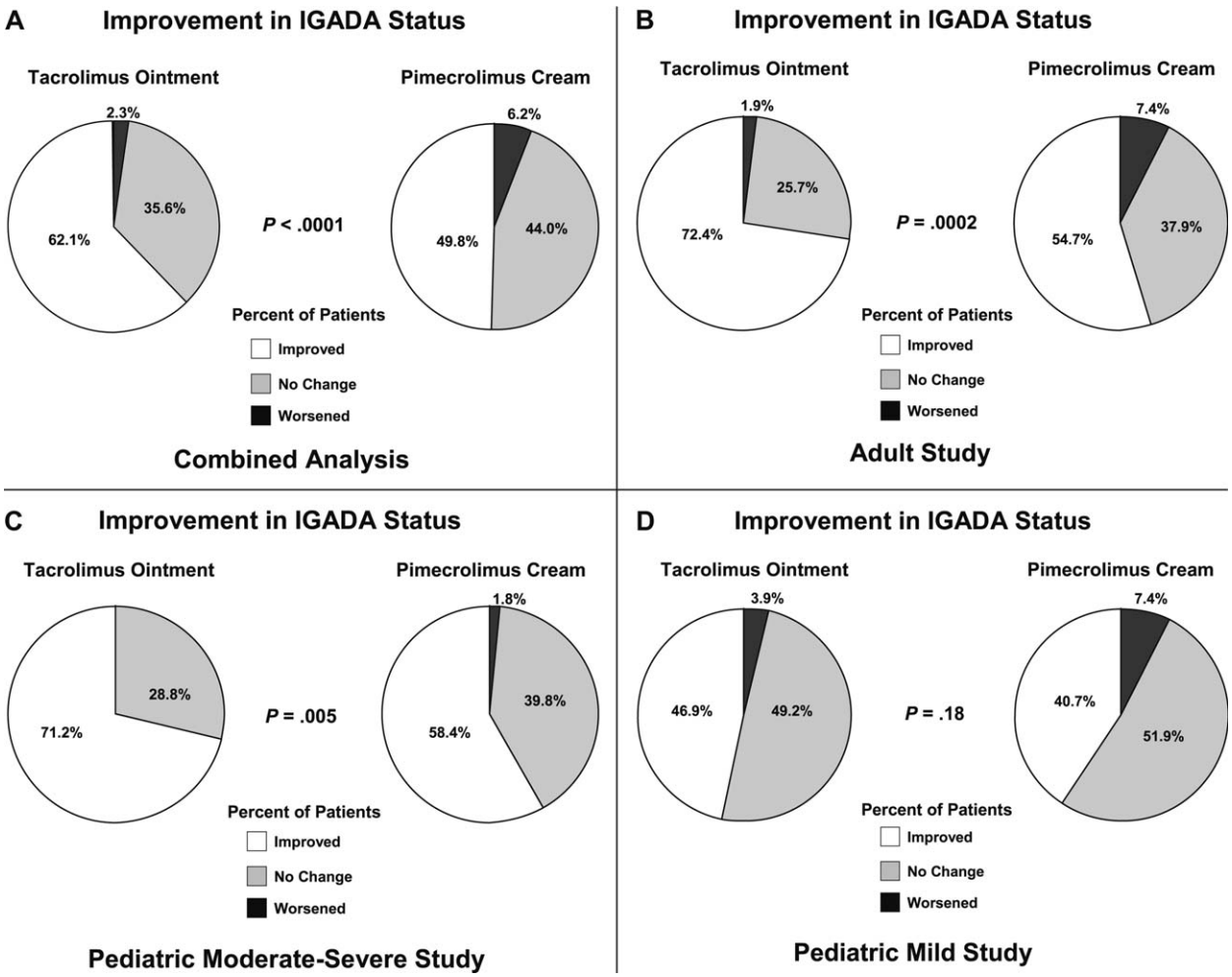

Fig 3. Improvement in IGADA status at end of study (percentage of patients who improved, had no change, or worsened) in the combined analysis and individual studies.

patients in both the adult and pediatric mild AD studies (P = .03). In the combined analysis, 2.5% (13/530) of tacrolimus patients withdrew because of a lack of efficacy compared with 6.6% (35/533) of pimecrolimus patients (P = .001). In the pediatric mild AD study, a greater number of pimecrolimus-treated patients compared with tacrolimus-treated patients withdrew because of adverse events (P = .002).

Baseline demographics (Table II) and baseline disease severity (Table III) were similar between treatment groups. Of 1060 efficacy-evaluable patients, 588 had mild AD, 363 had moderate AD, 114 had severe AD, and 25 had very severe AD at baseline.

Efficacy

Primary outcome measure

EASI score. At the end of treatment, the percentage of improvement from baseline, by reduction in EASI score, was significantly greater for tacrolimus ointment than for pimecrolimus cream in adults (54.1% vs. 34.9%, respectively; P<.0001), in pediatric patients with moderate to very severe AD (67.2% vs. 56.4%, respectively; P = .04), and in the combined analysis (52.8% vs. 39.1%, respectively; P < .0001; Fig 1). The corresponding reductions in raw scores were 5.1 for tacrolimus and 3.9 for pimecrolimus in the combined analysis (P = .0002). In the pediatric mild AD study, there was a statistically significant difference favoring tacrolimus over pimecrolimus at week 1 (39.2% vs. 31.2%, respectively; P = .04) and a trend for a continued advantage of tacrolimus compared with pimecrolimus at the end of treatment (52.1% vs. 42.7%, respectively; P = .07).

Among patients with moderate disease at baseline (n = 363), the percentage reduction in EASI score from baseline to study end was significantly greater for tacrolimus (63.3%) than for pimecrolimus (50.2%; P = .003).

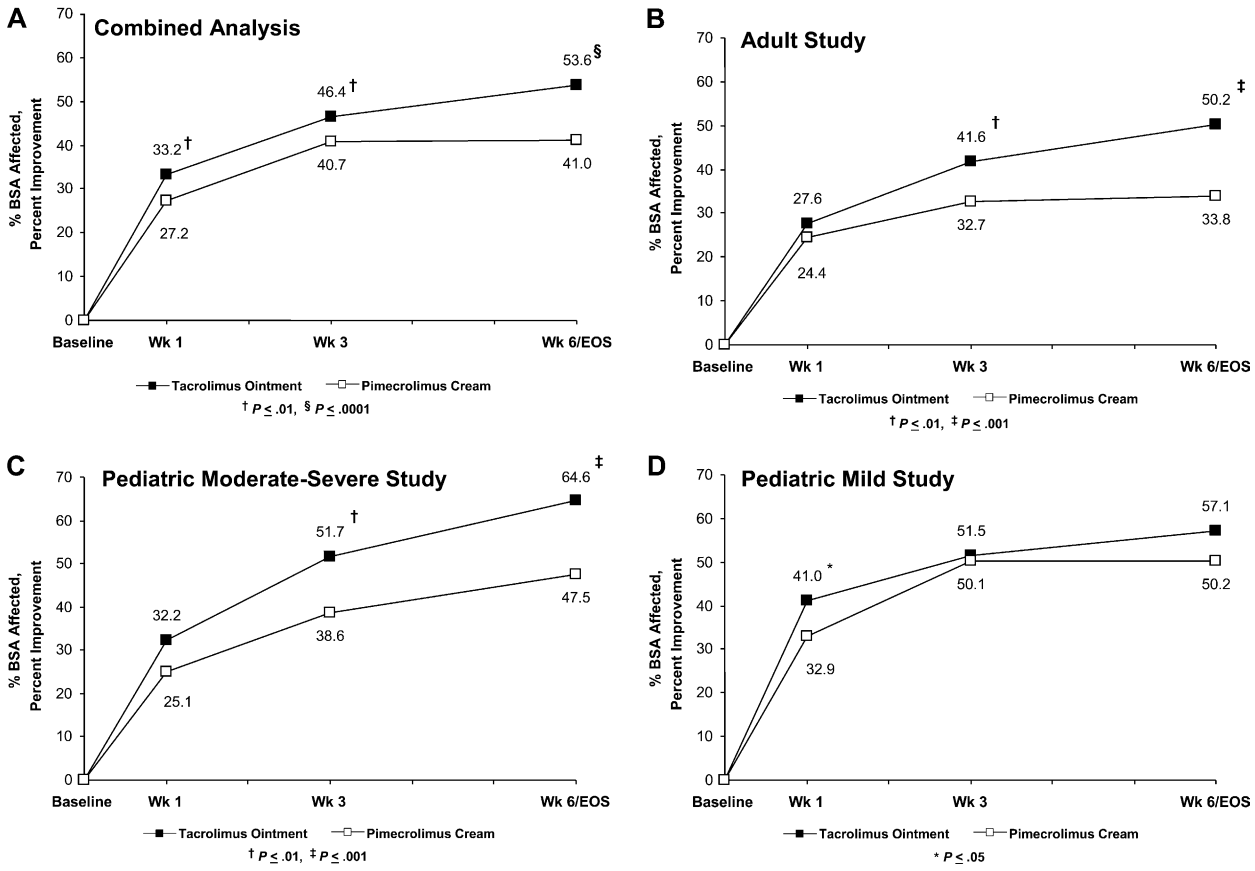

Fig 4. Percentage of improvement from baseline of %BSA affected in combined analysis and individual studies; values are least squares means. *EOS*, End of study.

At baseline, 710 of 1060 patients (67%) had head and/or neck involvement. Analysis of efficacy for treatment of the face and neck region revealed that tacrolimus was significantly more effective than pimecrolimus in reducing the signs and symptoms of AD. In the combined analysis, the percentage improvement from baseline to week 6/EOS was 57.0% for tacrolimus-treated patients compared with 42.0% for pimecrolimus-treated patients for AD involving the face and neck region ($P = .01$).

Secondary outcome measures

Success of therapy. Success of therapy, determined as achieving "clear" or "almost clear" status based on the IGADA, similarly supported superiority of tacrolimus over pimecrolimus at the end of treatment in adult patients, in pediatric patients with moderate to very severe disease, and in the combined analysis (Fig 2). In pediatric patients with mild disease, there was no significant difference between treatment groups in this measure of success at the end of treatment.

Results of the combined analysis demonstrated that at week 6/EOS, significantly more tacrolimus-treated patients (43.4%; 229/528) than pimecrolimus-treated patients (30.6%; 163/532) achieved treatment success ($P < .0001$) (Fig 2). Among adult and pediatric patients with moderate AD at baseline, 41.5% (78/188) of tacrolimus-treated patients compared with 26.9% (47/175) of pimecrolimus-treated patients were rated as clear or almost clear by study end ($P = .004$).

A comparison of IGADA scores at baseline and EOS in the combined analysis revealed that 62.1% (328/528) of tacrolimus-treated patients improved by one or more categories compared with 49.8% (265/532) of pimecrolimus-treated patients ($P = .0001$; Fig 3, *A*). In the individual studies, more tacrolimus-treated patients than pimecrolimus-treated patients improved by one or more categories (Fig 3, *B-D*). Across all studies, disease had worsened at the end of treatment among more pimecrolimus-treated patients than tacrolimus-treated patients (Fig 3).

Percentage of total BSA affected. The reduction in %BSA affected from baseline to week 6/EOS was greater for tacrolimus-treated patients than for pimecrolimus-treated patients in the adult study, in the pediatric moderate to very severe AD study,

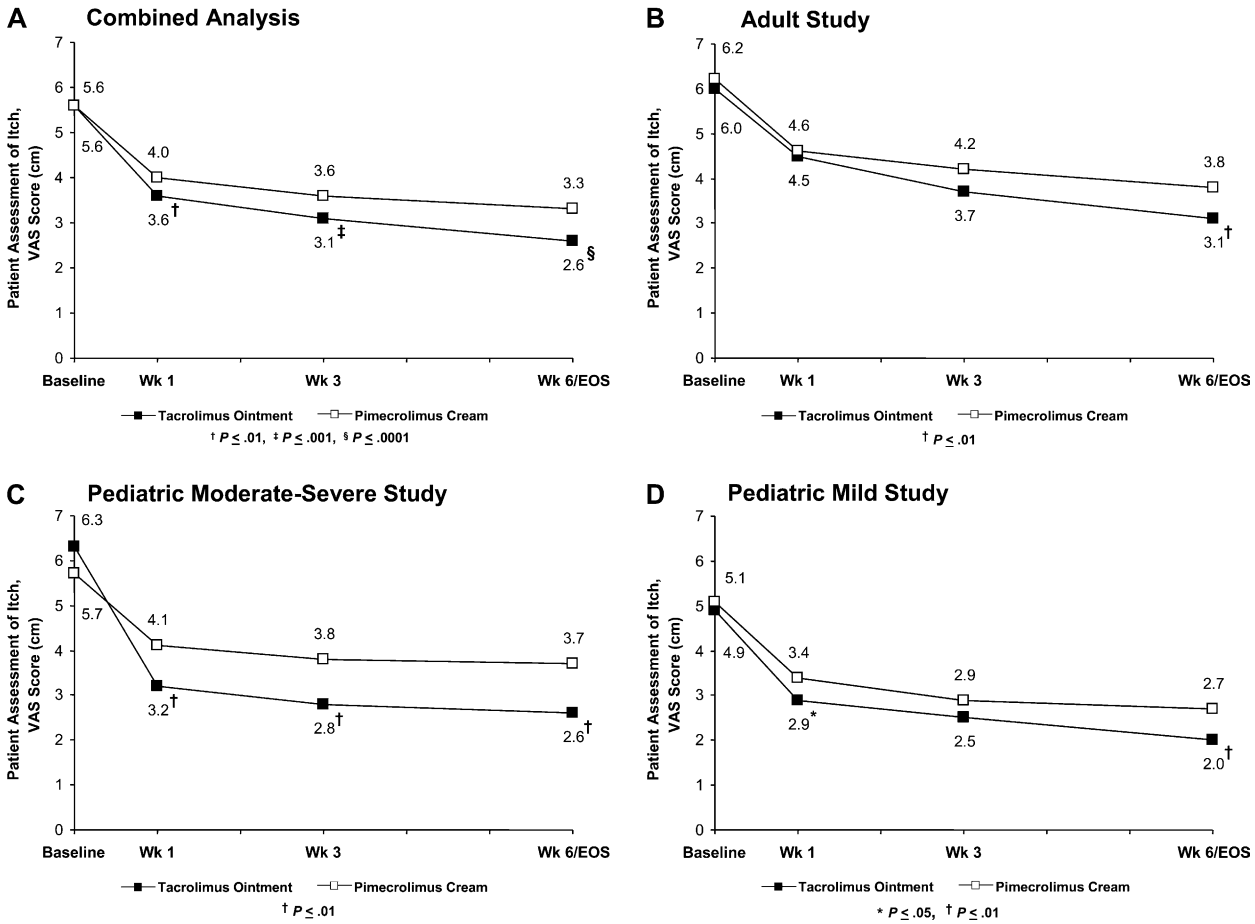

Fig 5. Patient assessment of itch—VAS scores over time in combined analysis and individual studies; values are least squares means. *EOS*, End of study.

and in the combined analysis. This difference was significant at week 3 and persisted through the end of study (Fig 4). As was similarly observed with the EASI scores, a statistically significant greater improvement in %BSA affected was observed in pediatric patients with mild disease at week 1 treated with tacrolimus ($P = .02$). At EOS, tacrolimus-treated pediatric patients with mild AD had a greater reduction in %BSA affected than pimecrolimus-treated pediatric patients with mild disease, but this difference was not statistically significant (57.1% vs 50.2%; $P = .15$). In the combined analysis, a significant reduction of 53.6% in %BSA affected was observed for tacrolimus-treated patients versus a 41.0% reduction for pimecrolimus-treated patients at the end of treatment ($P < .0001$).

Patient assessment of itch. In all 3 studies (adult, pediatric moderate to very severe AD, and pediatric mild AD) at week 6/EOS, the reduction in itch score by VAS was significantly greater in tacrolimus ointment–treated patients compared with pimecrolimus cream–treated patients (Fig 5). Statistically significant differences in itch scores between tacrolimus and pimecrolimus treatments were observed by week 1 in both pediatric studies. In the combined analysis, the least squares mean itch score at baseline was 5.6 cm in both treatment groups and decreased to 2.6 cm for tacrolimus and 3.3 cm for pimecrolimus by the EOS ($P < .0001$; Fig 5).

Time to response

Data from the individual studies, as well as the combined analysis, demonstrate that the better response to tacrolimus ointment compared with pimecrolimus cream was apparent as early as week 1, with continued significance in differences between groups through study end for EASI scores, %BSA affected, and itch (Figs 1, 4, and 5). In the combined analysis, the percentage improvement in EASI score from baseline to week 1 was 36.2% for tacrolimus and 29.4% for pimecrolimus ($P = .002$) and the percentage improvement from baseline to week 1 in %BSA affected was 33.2% for tacrolimus and 27.2% for pimecrolimus ($P = .003$). Similarly,

Table IV. Adverse events

Adverse event	Combined analysis		Adult		Pediatric moderate to severe AD		Pediatric mild AD	
	Tacrolimus (n = 530)	Pimecrolimus (n = 533)	Tacrolimus 0.1% (n = 210)	Pimecrolimus 1% (n = 203)	Tacrolimus 0.1% (n = 112)	Pimecrolimus 1% (n = 113)	Tacrolimus 0.03% (n = 208)	Pimecrolimus 1% (n = 217)
Any adverse event	113 (21.3)	106 (19.9)	67 (31.9)*	47 (23.2)	14 (12.5)	23 (20.4)	32 (15.4)	36 (16.6)
Withdrawal due to adverse event	10 (1.9)	20 (3.8)	6 (2.9)	5 (2.5)	4 (3.6)	5 (4.4)	0 (0)	10 (4.6)†
Application site reactions								
Burning	58 (10.9)	51 (9.6)	41 (19.5)‡	23 (11.3)	6 (5.4)	8 (7.1)	11 (5.3)	20 (9.2)
Pruritus	37 (7.0)	38 (7.1)	20 (9.5)	13 (6.4)	6 (5.4)	11 (9.7)	11 (5.3)	14 (6.5)
Pain	11 (2.1)	8 (1.5)	6 (2.9)	2 (1.0)	1 (0.9)	2 (1.8)	4 (1.9)	4 (1.8)
Erythema	5 (0.9)	9 (1.7)	1 (0.5)	4 (2.0)	2 (1.8)	1 (0.9)	2 (1.0)	4 (1.8)
Skin infection	2 (0.4)	4 (0.8)	0 (0)	2 (1.0)	2 (1.8)	2 (1.8)	0 (0)	0 (0)
Acne	2 (0.4)	2 (0.4)	1 (0.5)	2 (1.0)	0 (0)	0 (0)	1 (0.5)	0 (0)
Herpes simplex	2 (0.4)	1 (0.2)	1 (0.5)	1 (0.5)	0 (0)	0 (0)	1 (0.5)	0 (0)

Data expressed as number of patients (percentage).
*P = .05
†P = .002.
‡P = .02.

between baseline and week 1, a significant difference in itch score was observed in tacrolimus ointment–treated patients compared with pimecrolimus cream–treated patients (P = .003). With regard to treatment success as determined by IGADA (Fig 2), the difference between treatment groups became significant by week 3, when 29.0% (153/528) of tacrolimus-treated patients were clear or almost clear of their AD compared with 20.7% (110/532) of pimecrolimus-treated patients (P = .001).

Safety

The reported adverse events from the 3 individual studies and combined analysis are summarized in Table IV. In all studies, regardless of treatment, the most common adverse events were local application site reactions, including stinging or burning. In both pediatric studies, there were no significant differences in the incidence rate of adverse events, including local application site reactions between tacrolimus-treated and pimecrolimus-treated patients. In the adult study, application site burning occurred more frequently in the tacrolimus-treated patients than the pimecrolimus-treated patients (P = .02). This difference (11.4%, or 24/210 tacrolimus-treated patients vs. 4.9%, or 10/203 pimecrolimus-treated patients) occurred early in treatment; by week 1, the rates of local application site reactions in tacrolimus-treated and pimecrolimus-treated patients were comparable.

Overall, reported adverse events were similar in both tacrolimus and pimecrolimus treatment groups. In general, adverse events were mild in severity and rarely led to treatment discontinuation. In the pediatric mild AD study, significantly more patients withdrew from the study because of an adverse event associated with pimecrolimus treatment (4.6%) than with tacrolimus treatment (0%; P = .002: Table IV).

In the combined analysis, the occurrence of application site burning was similar between treatment groups at all time points. There were no significant differences between treatment groups in the incidence of application site burning or pruritus in adult and pediatric patients with moderate disease at baseline.

Across all 3 studies, there were 4 reports of acne and 3 reports of herpes simplex, with similar incidences between treatment groups. There were no reports of eczema herpeticum in either treatment group.

DISCUSSION

Tacrolimus ointment and pimecrolimus cream are nonsteroidal topical calcineurin inhibitors approved for the treatment of AD. The trials reported herein are the first published investigations that directly compared the efficacy and safety of these 2 topical agents in pediatric and adult patients with AD of varying degrees of severity. Although the safety and efficacy of tacrolimus ointment and of pimecrolimus cream have been established in the treatment of AD, these studies demonstrate that tacrolimus ointment is more effective than pimecrolimus cream in managing the signs and symptoms of AD, and that adverse events—including local application site

reactions—are comparable following the application of either product. The percentage reductions from baseline in EASI score and %BSA affected were significantly greater in the tacrolimus group than in the pimecrolimus group at EOS for adults and pediatric patients with moderate to severe disease and at week 1 in pediatric patients with mild disease. Treatment success (defined as "clear" or "almost clear") occurred in significantly more tacrolimus-treated patients than pimecrolimus-treated patients, and study withdrawal because of lack of efficacy occurred in significantly fewer tacrolimus-treated patients than pimecrolimus-treated patients.

Clinical response was faster in tacrolimus ointment–treated patients, as demonstrated by statistically significantly greater improvement in several efficacy measures; improvement was evident by week 1. A rapid response to therapy is most desirable, especially for pruritus, one of the most bothersome symptoms of AD. As early as week 1 and continuing to study end, itch score was significantly lower in tacrolimus-treated patients compared with pimecrolimus-treated patients in both pediatric studies and in the combined analysis. As early as week 1, the percentage reductions in EASI score and %BSA affected were significantly greater in the tacrolimus group compared with the pimecrolimus group. Treatment success with tacrolimus occurred earlier and was of greater magnitude compared with pimecrolimus. By week 3 and continuing through study end, AD had cleared or almost cleared in significantly more tacrolimus-treated patients than pimecrolimus-treated patients.

Both tacrolimus and pimecrolimus were well tolerated. There was no difference in the incidence of adverse events, including application site reactions between tacrolimus-treated and pimecrolimus-treated pediatric patients. In the adult study, more patients experienced local application site reactions on day 1 of tacrolimus treatment than on initiation of pimecrolimus treatment; however, there was no difference in the adverse event rates at week 1 and subsequent time points. In the individual studies, more pediatric patients with mild AD withdrew from pimecrolimus cream treatment because of adverse events.

Because both tacrolimus ointment and pimecrolimus cream are currently approved for the treatment of patients with moderate AD, an analysis of this subgroup was performed. In adult and pediatric patients with moderate AD, the percentage reduction in EASI score from baseline to study end was significantly greater in tacrolimus-treated patients compared with pimecrolimus-treated patients. Tacrolimus-treated patients with moderate AD also achieved significantly greater treatment success as measured by achieving a score of "clear"/"almost clear" compared with the pimecrolimus-treated patients with moderate AD. As was similar to the overall findings, both topical calcincurin inhibitors were well tolerated and had similar safety profiles in patients with moderate AD.

In a recently published study comparing tacrolimus ointment 0.03% and pimecrolimus cream 1% in pediatric patients with moderate AD, similar results were observed by Kempers et al.[14] Using a similar investigator global scale with success defined as "clear" or "almost clear," more tacrolimus ointment–treated patients were rated a success at the end of the study than pimecrolimus cream–treated patients, although this difference was not statistically significant. Because the primary objective of that study was not efficacy, the sample size was inadequate to detect a statistically significant difference in this parameter. Also similar was the discontinuation rate related to a lack of efficacy; more pimecrolimus-treated patients discontinued the study because of a lack of efficacy as compared with tacrolimus-treated patients—a finding which is consistent with the results reported here.

The results in the 2 reports differ with regard to efficacy on AD of the head and neck. Kempers et al[14] reported a greater mean reduction from baseline in BSA affected for pimecrolimus-treated patients with head and neck involvement; however, this difference was not statistically significant. The studies reported here showed significantly greater efficacy for tacrolimus ointment when compared with pimecrolimus cream in treating AD signs and symptoms of the head and neck.

The focus of Kempers et al[14] report was tolerability. Local application site reactions reported in either treatment group were similar: at all time points for warmth/stinging/burning, at all time points (except day 4) for erythema/irritation, and at all time points (except day 29) for itching (where exceptions indicated a significantly higher incidence in the tacrolimus group). Both treatments were well tolerated, with no unexpected adverse reactions reported. In the adult study reported here, similar adverse events and local reaction rates were noted at all time points except day 1, where there was a higher incidence for tacrolimus-treated patients. In both pediatric studies, including patients with mild, moderate, or severe disease, there was no difference in adverse reactions, including local application site reactions.

In conclusion, tacrolimus ointment is more effective and has a more rapid onset of action compared with pimecrolimus cream in the management of AD in both adult and pediatric populations.

The incidence of adverse events, including local application site reactions, was low and comparable in tacrolimus-treated and pimecrolimus-treated patients. The results of these 3 studies in adults and children with mild, moderate, and severe disease support the superior efficacy of tacrolimus ointment when compared with pimecrolimus cream in the treatment of AD.

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APPENDIX

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