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Tacrolimus Ointment 0.03% Is Safe and Effective for the Treatment of Mild to Moderate Atopic Dermatitis in Pediatric Patients: Results From a Randomized, Double-Blind, Vehicle-Controlled Study

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ABSTRACT. *Objective.* This study was designed to compare the safety and efficacy of tacrolimus ointment 0.03% with vehicle ointment for the treatment of mild to moderate atopic dermatitis (AD) in pediatric patients.

Methods. A total of 317 patients (2–15 years of age) with mild to moderate AD were randomized to receive tacrolimus ointment or vehicle ointment twice daily in a 6-week, multicenter, double-blind study. Efficacy evaluations, including the Investigators' Global Atopic Dermatitis Assessment, eczema area and severity index, percentage of total body surface area affected, and patient assessment of itch occurred at baseline, day 4, and weeks 2, 4, and 6. Cutaneous adverse events were recorded to evaluate safety.

Results. At the end of study, 50.6% (80 of 158) of the patients were treated successfully with tacrolimus ointment based on Investigators' Global Atopic Dermatitis Assessment scores, a significant improvement compared with patients treated with vehicle ointment (25.8% [41 of 159]). The percent improvement from baseline in eczema area and severity index scores was also significantly greater in tacrolimus-treated patients (54.8%) compared with vehicle-treated patients (20.8%). There was also a significant improvement in the percentage of total body surface area affected of tacrolimus-treated patients (50.5% reduction from baseline) compared with vehicle-treated patients (16.4%). Patient itch scores were significantly lower in tacrolimus-treated patients (2.1) versus vehicle-treated patients (3.7). Overall, the incidence of cutaneous adverse events reported was similar for both treatment groups. There was no significant difference in the incidence of burning or stinging between treatment groups. Significantly fewer tacrolimus-treated patients

prematurely discontinued from the study because of a cutaneous adverse event in the treatment area or experienced increased itching and erythema at the application site.

Conclusion. Monotherapy with tacrolimus ointment 0.03% is a safe and effective treatment alternative for pediatric patients with mild to moderate AD. *Pediatrics* 2005;116:e334–e342. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2638; *atopic dermatitis, pediatrics, tacrolimus ointment, topical immunomodulatory agents.*

ABBREVIATIONS. AD, atopic dermatitis; UV, ultraviolet; BSA, body surface area; IGADA, Investigators' Global Atopic Dermatitis Assessment; EOS, end of study; EASI, eczema area and severity index; %BSA, percentage of total body surface area.

Atopic dermatitis (AD) is a recurrent inflammatory skin disease, with intense pruritus as its hallmark symptom, and often follows a chronic, relapsing course.¹ It frequently affects children, with symptoms developing in 65% of patients before 1 year of age and in 90% by 5 years of age.² Although many children will outgrow the condition by 10 years of age, 60% remain symptomatic as adults.² If not outgrown in childhood, the condition progresses to adulthood, with recurrent flares that may be severe and sometimes debilitating. The prevalence of AD in the United States is projected to be between 7% and 17% of school-aged children and has increased greatly over the past 40 years.³

Several quality-of-life issues have been reported in children with AD, including sleep disturbances, changes in activity, irritability, and self-consciousness.^{4–8} AD exacts a marked toll on the children and their families through both direct and indirect financial expenses of medical care. Even more significant are the stressful impacts of sleep deprivation, missed school and work, and the time spent on the daily care and treatments for AD.⁹ The family stress related to the care of children with AD is similar to or significantly greater than that of children with type 1 diabetes mellitus.¹⁰

The mainstay of therapy for AD, including mild to moderate disease, has been the liberal use of emollients and topical corticosteroids while avoiding allergens and other triggers for prevention of flares.

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Indeed, topical corticosteroids have been the cornerstone of treatment for AD for >40 years.¹ Topical immunomodulators, antihistamines, and antibiotics are also used for the treatment of AD, although severe cases may require systemic corticosteroids, phototherapy with ultraviolet light types A and B (UVA and UVB), and/or immunosuppressants. It is unfortunate that the adverse effects of stronger topical corticosteroids such as striae, atrophy, and telangiectasia limit the long-term use of these agents. Moreover, there is a paucity of data to show that the long-term use of topical corticosteroids is without potential systemic effects, especially adverse effects on linear bone growth in children and hypothalamic-pituitary-adrenal axis suppression. When topical corticosteroids are applied to extensive body surface areas (BSAs), they can be absorbed systemically; systemic complications include Cushing's syndrome, adrenal suppression, loss of bone density, hypertension, cataracts, and growth retardation in children.¹¹⁻¹⁴ The degree of systemic absorption will vary depending on the potency and amount of the drug applied and the extent of skin surface area as well as the nature of the skin in areas where it is applied. When applied to broken skin or to areas on which the stratum corneum are thinnest, such as the face, eyelids, and genitals, drug penetration is more rapid and extensive than when applied to areas of thick stratum corneum such as the palms of the hands and soles of the feet. For this reason, mid- to high-potency corticosteroids are not used routinely on the face, which is an area commonly affected by AD. Because the use of topical corticosteroids is limited by the area affected and the duration of treatment needed, some clinicians have called for additional investigation into treatment alternatives, and interest in alternatives such as tacrolimus ointment has increased.¹⁵

Protopic (tacrolimus) ointment, available since December 2000, is a topical immunomodulator indicated for short-term and intermittent long-term therapy of both adult (0.03% and 0.1% concentrations) and pediatric (0.03% concentration) patients with moderate to severe AD. Tacrolimus acts through inhibition of calcineurin to suppress T-cell activation, inhibit inflammatory cytokine release, and reduce the stimulatory activity of antigen-presenting cells. Topical applications of tacrolimus ointment result in minimal systemic absorption, do not cause a decrease in collagen synthesis or skin thickness, and have not been associated with limiting adverse events thus far.¹⁶⁻²¹

Tacrolimus ointment (0.03% and 0.1%) has been clinically shown to reduce the extent, severity, and symptoms of moderate to severe AD in children as young as 2 years of age and to be safe and effective for long-term use for up to 4 years.²²⁻²⁷ However, it has not been evaluated for treatment of mild to moderate cases. This study was designed to investigate the safety and efficacy of tacrolimus ointment 0.03% monotherapy in pediatric patients with mild to moderate AD.

Study Design and Conduct

This was a multicenter, randomized, double-blinded, vehicle-controlled study conducted between September 2001 and November 2002. Eligible patients were randomized in a 1:1 allocation to receive either tacrolimus ointment 0.03% (Protopic; Astellas Pharma US, Inc) or a vehicle ointment. There was a centralized computer-generated randomization code with sequential assignment of patient numbers within each site, and there was no stratification. Patients, caregivers, investigators, and clinical staff were blinded to treatment. The vehicle ointment was identical in composition, appearance, texture, and odor to the emollient base of the active treatment. Each of the 18 study sites obtained institutional review board approval, and patients or their legal guardians gave written informed consent before enrollment.

Patient Selection

Pediatric patients between 2 and 15 years of age with a diagnosis of mild or moderate AD involving 2% to 30% of the BSA were enrolled in the study. Diagnosis of AD was made by using Hanifin and Rajika criteria.²⁸ The degree of severity was rated by using the Investigators' Global Atopic Dermatitis Assessment (IGADA) using scores based on the Physician Assessment of Individual Signs (Tables 1 and 2). Patients were required to meet the entrance criteria and follow specific prestudy and concomitant therapy restrictions. Patients were excluded from the study if they had a skin disorder other than AD in the area to be treated, clinically infected AD, a known hypersensitivity to macrolides or any of the excipients of the ointment, or previous use of tacrolimus ointment for AD or if they were pregnant or nursing.

Treatment Plan

A thin coating of either tacrolimus or vehicle ointment was applied twice daily (~12 hours apart) to areas affected with AD at least 2 hours before bathing for up to 6 weeks by patients or caregivers. Treatment was continued for an additional week after any individual lesions cleared. Thereafter, the cleared area(s) was excluded from additional treatment, while all remaining lesions continued to be treated. If all treated areas completely cleared before the week-6 visit, treatment continued in all areas for 1 additional week and was followed by an end-of-study (EOS) visit. No treatments continued beyond 6 weeks. Nonsteroidal immunosuppressants, other investigational drugs, systemic corticosteroids, UV light therapy (UVA, UVB), as well as concomitant topical medications (including topical corticosteroids, topical H1 and H2 antihistamines, and topical antimicrobials) were not allowed during the treatment period; patients were required to have a washout period of up to 4 weeks, depending on AD treatment before study. Intranasal or inhaled corticosteroids were permitted if use was restricted to FDA-approved indications and doses did not exceed the maximal approved doses. Use of sunscreen was allowed, and application of nonmedicated emollients was permitted on nontreatment areas. Use of cosmetics on treatment sites was prohibited. Oral antihistamines were allowed only if the patient was on a stable dose at baseline; however, the dosage could be decreased or discontinued (but not increased) during the study.

TABLE 1. IGADA

Clear	No evidence of disease with the exception of residual pigment changes and/or xerosis
Almost clear	Affected areas have minimal disease
Mild	Majority of affected areas have individual assessment scores* of 1 in ≥ 3 signs and symptoms of AD
Moderate	Majority of affected areas have individual assessment scores* of 2 in ≥ 3 signs and symptoms of AD
Severe	Majority of affected areas have individual assessment scores* of 3 in ≥ 3 signs and symptoms of AD
Very severe	All of affected areas have individual assessment scores* of 3 in ≥ 3 signs and symptoms of AD

* Individual assessment scores are defined in Table 2.

TABLE 2. Physician Assessment of Individual Signs*

	Individual Assessment Score			
	Absent	Mild	Moderate	Severe
Signs, <i>n</i>	0	1	2	3
Erythema	None	Faint erythema	Prominent redness	Deep, intense red color
Edema, induration, papulation	None	Dermal swelling in limited areas discernable by touch	Definite dermal swelling of the skin in several areas	Dermal swelling, indurated skin in widespread areas
Excoriations	None	Slight evidence of scratching, no broken skin	Linear marks on skin, epidermal (fluid, crusts) or dermal (blood) injury	Many weepy or hemorrhagic lesions
Oozing, weeping, crusting	None	Faint signs of oozing	Definite oozing or crust but with ≤5 sites per area	Marked and extensive
Scaling	None	Slight flaking in limited areas, mostly fine scales	Visible flaking over many portions of the body, coarser flakes	Obvious flaking covering most body areas, course thick scales
Lichenification	None	Skin markings minimally exaggerated	Skin markings exaggerated to a criss-cross pattern	Skin markings visibly exaggerated to a deep criss-cross pattern

* Separate assessments were made for lesions on 4 different areas of the body: head and neck, upper limbs, trunk, and lower limbs.

Primary and Secondary Efficacy Outcome Measures

The primary efficacy end point was treatment success rate, which was defined as the percentage of patients with IGADA scores designated as “clear” or “almost clear” at week 6/EOS, and failure was designated as all other IGADA ratings (Table 1). Secondary efficacy end points included eczema area and severity index (EASI) scores, percentage of total BSA (%BSA) affected, and patient assessment of itch. The EASI is a validated composite score having a maximum value of 72 that is calculated from scores assigned to 4 of the individual signs of AD (erythema, induration/papulation, excoriation, and lichenification) combined with the %BSA affected in head and neck, upper limbs, trunk, and lower limbs.²⁹ Severity of itch was based on marks made by patient or caregiver (parent/guardian) on a 10-cm visual analog scale (VAS), on which 0 cm was “no itch” and 10 cm was “worst itch imaginable.” All outcome measures were assessed at baseline/day 1, day 4, and weeks 2, 4, and 6/EOS.

Safety Outcome Measures

Safety end points were the overall incidence rates of cutaneous adverse events reported by the patient or caregiver or observed by the investigator, the overall incidence rates of serious drug-related adverse events, and the specific incidence rates of application-site adverse events. Cutaneous adverse events were recorded at baseline after the application of study drug and at each subsequent visit; these events included skin burning or stinging, increased itching, skin erythema, folliculitis, skin infection, acne, warts, molluscum, herpes simplex, eczema herpeticum, and herpes zoster. Eczema herpeticum was captured as a separate event from herpes simplex.

Sample-Size Estimation

Sample size was based on the binomial distribution with the objective to detect a difference in success rate between the vehicle group and the tacrolimus group with 80% power and a 2-sided .05 significance level. Based on estimated success rates of 40% for tacrolimus and 25% for vehicle, ~152 patients would be required for each treatment group.

Statistical Analysis

All patients who were dispensed the study drug were included in all data analyses (intent-to-treat population). The primary efficacy end point (success rate) was analyzed by comparing the number of successes in each treatment group using the row mean scores for the Cochran-Mantel-Haenszel test adjusted for study center. An analysis of covariance was performed for secondary efficacy end points with treatment group and study center as factors and the baseline value as covariate. Missing efficacy data were imputed by using the last observation carried forward. Safety data were tabulated, and *P* values for differences between

treatment groups were calculated by using the Pearson χ^2 test or Fisher’s exact test as appropriate. All statistical tests were 2-sided with a significance level of $\alpha = .05$.

RESULTS

Patient Accounting

A total of 317 patients were enrolled in the study (158 in the tacrolimus-ointment group and 159 in the vehicle-ointment group), and all were included in the safety and efficacy analyses (Fig 1). A total of 81.6% (129 of 158) of tacrolimus-treated patients and 61.6% (98 of 159) of vehicle-treated patients completed the trial (defined as patients who either completed 6 weeks of the trial or discontinued early because they reached the primary end point before the scheduled week 6 visit). The reasons for withdrawal from the study are shown in Fig 1. A significantly greater percentage of vehicle-treated patients (38.4%) withdrew prematurely from the study compared with tacrolimus-treated patients (18.4%; $P < .0001$). Withdrawal resulting from lack of efficacy occurred in 2.5% of patients in the tacrolimus-treated group compared with 12.6% of the patients in the vehicle-treated group ($P = .0007$). Application-site adverse events led to withdrawal in 2.5% (4 of 158) of tacrolimus-treated patients compared with 7.5% (12 of 159) of vehicle-treated patients ($P = .04$).

Patient Demographics and Baseline Disease Characteristics

Patient demographics and baseline disease characteristics were similar between treatment groups (Table 3). The mean age for both groups was ~7 years with comparable proportions of patients distributed between 2 and 6 years and 7 and 15 years. There was a similar distribution of mild or moderate AD for both treatment groups, with the majority (~60%) of patients in each group having mild disease. At baseline, the mean EASI score was ~6, and the mean %BSA affected was ~12% for the 2 treatment groups.

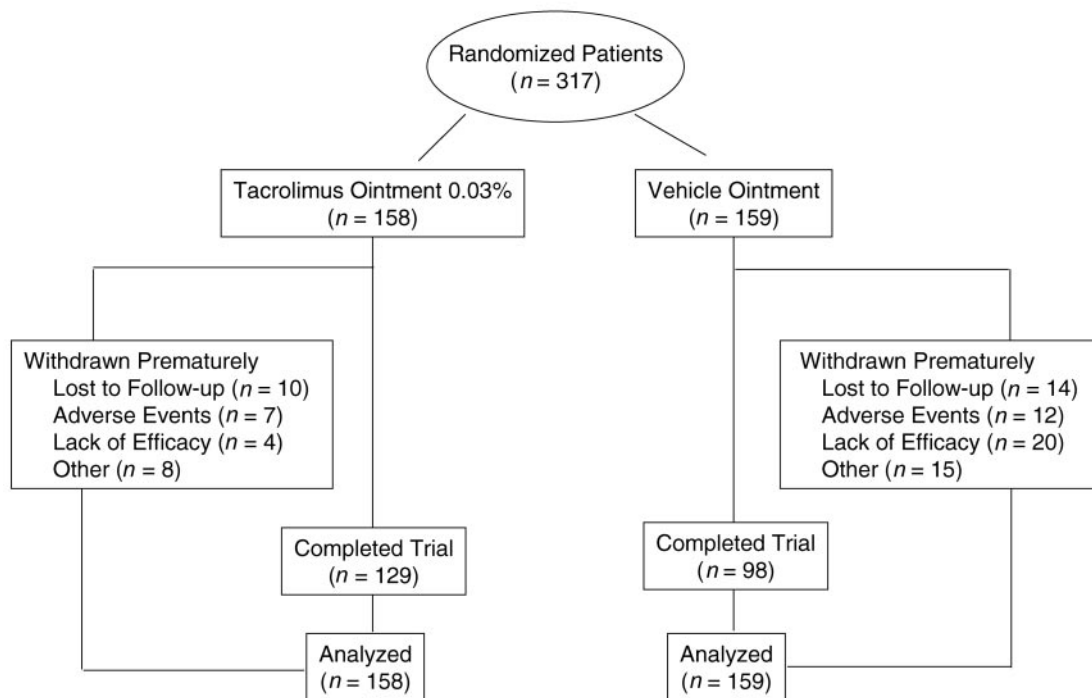


Fig 1. Clinical trial profile.

TABLE 3. Patient Demographics and Baseline Disease Characteristics

	0.03% Tacrolimus (n = 158)	Vehicle (n = 159)
Gender, %		
Male	47	47
Female	53	53
Race, %*		
White	65	71
Black	23	23
Asian	6	4
Other	5	1
Age, y, mean (SD)	6.7 (4.0)	7.0 (4.1)
Age distribution, %		
2–6 y	56	54
7–15 y	44	46
AD severity, %†		
Mild	61	60
Moderate	39	40
Head/neck involvement, %	59	54
%BSA		
Mean (SD)	12.3 (9.1)	12.5 (7.7)
Median	9.5	12.0
Range	2.0–47.5	2.0–30.0
EASI score‡		
Mean (SD)	5.9 (4.6)	6.3 (4.5)
Median	4.6	5.0
Range	0.5–22.0	0.3–20.8
Itch score, cm, least-squares mean	4.9	4.9

* Numbers may not add up to 100% because of rounding.

† Based on IGADA score.

‡ Range: 0–72.

Efficacy

IGADA Score

The overall success rate, defined as the percentage of patients clear or almost clear of their AD at the EOS, was significantly higher in patients treated with tacrolimus ointment (50.6% [80 of 158]) compared with vehicle ointment (25.8% [41 of 159]; $P < .0001$;

Fig 2). Among patients characterized with mild AD at baseline ($n = 193$), the success rate was 56.7% (55 of 97) after treatment with tacrolimus compared with 32.3% (31 of 96) after treatment with vehicle ($P = .0007$). Among patients with moderate AD at baseline ($n = 124$), the success rate was 41.0% (25 of 61) after treatment with tacrolimus compared with 15.9% (10 of 63) after treatment with vehicle ($P = .001$). Nineteen percent (30 of 158) of tacrolimus-treated patients reached the study end point of being clear or almost clear of their AD as early as day 4, compared with 11.9% (19 of 159) of the vehicle-treated patients ($P = .06$); this success rate was significantly greater for tacrolimus-treated patients at all subsequent time points ($P < .0001$; Fig 3).

EASI Score

At baseline, EASI scores were comparable between treatment groups (Table 3). By day 4, the percent improvement from baseline (by reduction in EASI score) was significantly greater for the tacrolimus-treated group than for the vehicle-treated group (32.5% vs 16.3%; $P = .0004$; Fig 4A). The treatment differences in favor of tacrolimus ointment continued throughout all subsequent study visits, with an improvement of 54.8% in tacrolimus-treated patients and 20.8% in vehicle-treated patients at the EOS ($P < .0001$; Fig 4A).

A total of 94 of 158 tacrolimus-treated patients and 86 of 159 vehicle-treated patients had head and/or neck involvement at baseline. Tacrolimus ointment was significantly more effective in reducing the signs and symptoms of AD in the head and neck region, with a 59.1% improvement from baseline to week 6/EOS compared with a 3.9% worsening from baseline to the EOS for patients treated with vehicle ($P = .006$; Fig 4B). A significant difference between treat-

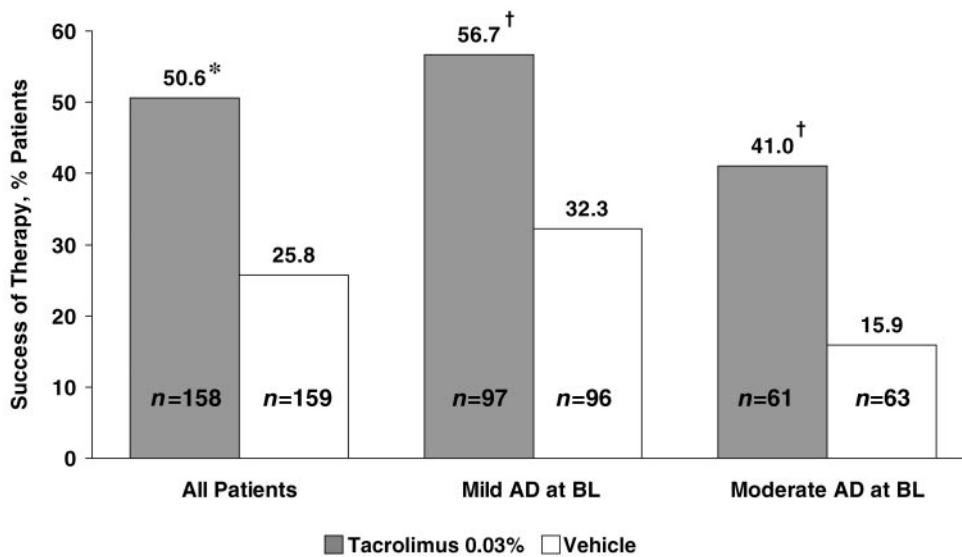


Fig 2. Percentage of patients achieving success of therapy at EOS. BL indicates baseline. * $P < .0001$; † $P \leq .001$.

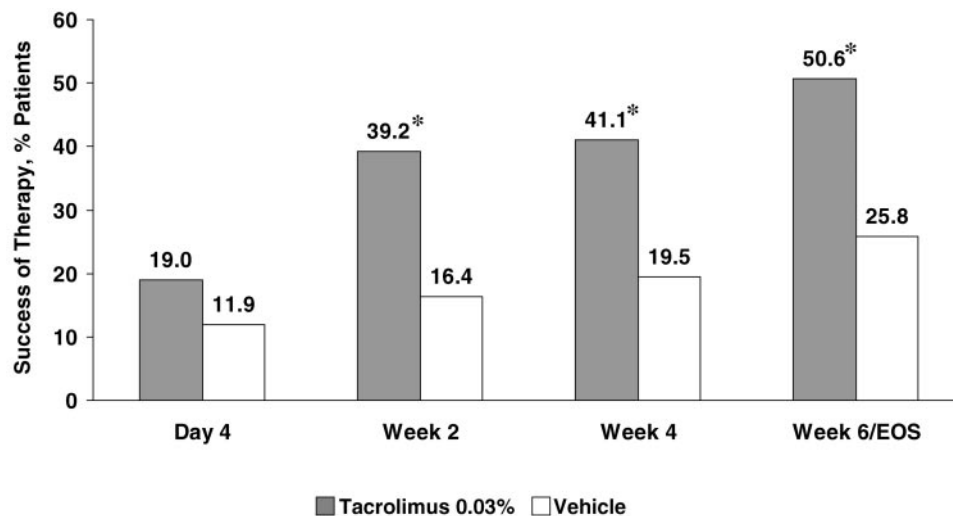


Fig 3. Percentage of patients achieving success of therapy by study visit. * $P < .0001$.

ment groups in improvement in the head and neck region was observed as early as day 4, and differences remained significant at every time point through week 6 ($P \leq .01$).

%BSA Affected

The %BSA affected was not significantly different for the 2 groups at baseline (Table 3). By day 4, the mean percent improvement (by reduction from baseline) was significantly greater in tacrolimus-treated patients (25.3%) than in vehicle-treated patients (12.2%; $P = .001$; Fig 4C). The difference was significant at all time points, with a 50.5% reduction for tacrolimus-treated patients and a 16.4% decrease for vehicle-treated patients ($P < .0001$) at week 6/EOS (Fig 4C).

Patient Assessment of Itch

The least-squares mean itch score at baseline was 4.9 cm for both treatment groups and decreased to 3.1 and 3.9 for tacrolimus-treated and vehicle-treated

patients, respectively, by day 4 ($P = .001$; Fig 4D). By the EOS, the least-squares mean itch score in the tacrolimus-treated group was significantly reduced to 2.1, compared with 3.7 in the vehicle-treated group ($P < .0001$; Fig 4D).

Safety

The overall incidence of adverse events was similar with tacrolimus and vehicle: 36.7% for tacrolimus-treated patients and 45.3% for vehicle-treated patients ($P = .12$). Early withdrawal from the study because of application-site adverse events occurred in significantly fewer tacrolimus-treated patients than vehicle-treated patients (2.5% vs 7.5%, respectively; $P = .04$). The most frequent cutaneous adverse event observed during the treatment period in both groups was increased itching, which was reported by 23.4% (37 of 158) of patients in the tacrolimus-treated group and 33.3% (53 of 159) in the vehicle-treated group ($P = .05$; Fig 5). Skin erythema was reported by 7.6% (12 of 158) of patients in the tacrolimus-

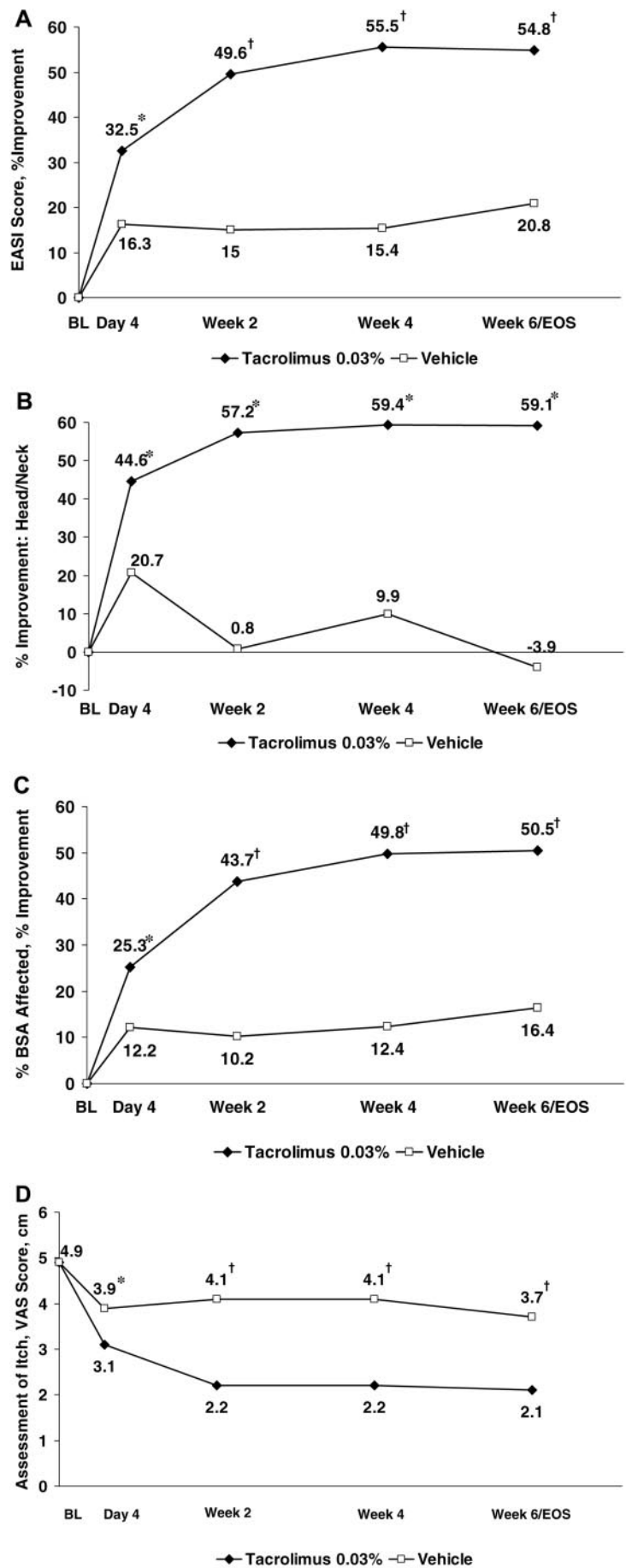


Fig 4. Percent improvement from baseline (BL) in EASI score (A); signs and symptoms of AD in the head/neck region (B); %BSA affected (C); and the reduction in patient assessment of itch-VAS scores over time (D). Values are least-squares means. A, * $P = .0004$; † $P < .0001$. B, * $P < .01$. C, * $P = .001$; † $P < .0001$. D, * $P = .001$; † $P < .0001$.

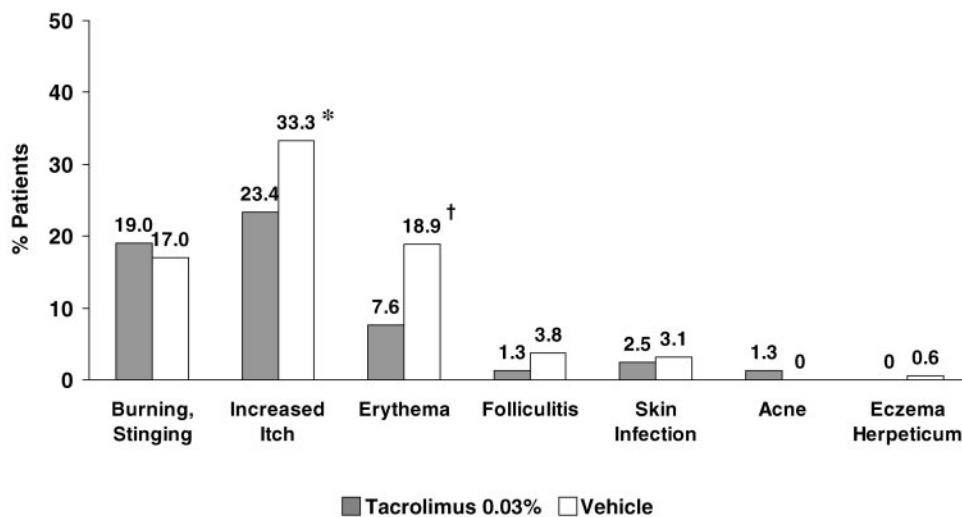


Fig 5. Incidence of cutaneous adverse events. * $P = .05$; † $P = .003$.

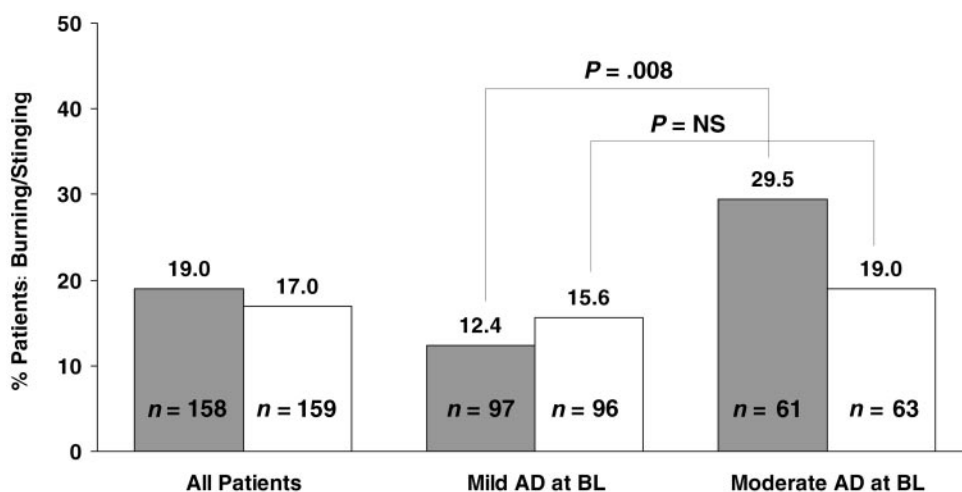


Fig 6. Incidence of burning/stinging by baseline disease severity and for all patients. There was no significant difference between vehicle and tacrolimus ointment treatment groups in any of these patient subsets. NS indicates not significant.

treated group and 18.9% (30 of 159) in the vehicle-treated group ($P = .003$; Fig 5). The incidence of skin burning or stinging between treatment groups was not significantly different, with 19.0% (30 of 158) of patients treated with tacrolimus ointment and 17.0% of patients (27 of 159) treated with vehicle ointment reporting this application-site event ($P = .64$; Fig 6). The skin burning/stinging incidence rates were also comparable among those patients with mild AD at baseline (12.4% vs 15.6%, respectively; $P = .51$; Fig 6) and moderate AD at baseline (29.5% vs 19.0%, respectively; $P = .28$; Fig 6). A significantly higher incidence of skin burning or stinging after topical application of tacrolimus ointment was seen in those patients with moderate AD at baseline (29.5% [18 of 61]), compared with patients having mild AD at baseline (12.4% [12 of 97]; $P = .008$; Fig 6). Folliculitis, skin infection, and acne were reported in a small number of patients and were comparable between treatment groups. None of the patients in either group experienced warts, molluscum, herpes simplex, or herpes zoster. A single case of eczema herpeticum was reported in a patient treated with the

vehicle ointment. There were no serious adverse events.

DISCUSSION

Previous studies have established the beneficial effects of tacrolimus ointment in patients with moderate to severe AD.²²⁻²⁷ When tacrolimus ointment is used to treat moderate to severe AD, children generally respond to treatment within the first week with an improvement in signs and symptoms, assessment of itch and %BSA affected.²²⁻²⁶ Transient burning and itching typically decreases after the first few days of treatment, and no increase has been reported in the incidence of infections or other adverse events when used long-term for up to 4 years.²⁷ Because of the limitations of topical corticosteroid therapy, a nonsteroidal treatment alternative is needed for children with mild to moderate AD.

In this study, the majority of enrolled patients had mild disease at baseline. In this subgroup, as well as in the subgroup of patients with moderate AD at baseline, treatment with tacrolimus ointment 0.03% resulted in a significantly higher success rate than

treatment with vehicle ointment. At all postbaseline visits except day 4, the percentage of patients with treatment success was statistically superior for tacrolimus compared with vehicle. Significant improvements in EASI scores and %BSA affected were also observed after treatment with tacrolimus ointment 0.03% compared with vehicle ointment at all postbaseline visits throughout the study. In addition to the healing of the skin, the "itch-scratch" cycle becomes a primary focus of treatment of AD. If scratching is unchecked, secondary irritation and/or infection with redness, swelling, cracking, weeping, scaling, and crusting may result. In this study, a profound reduction in itch within the first 4 days was noted, indicating that tacrolimus ointment was effective in breaking the "itch-scratch" cycle. This significant reduction in the itch score after tacrolimus treatment compared with vehicle treatment continued throughout the entire study period.

The overall incidence of cutaneous adverse events was similar for tacrolimus and vehicle. Furthermore, significantly fewer tacrolimus-treated patients experienced increased itching and erythema at the application site or discontinued prematurely from the study because of a cutaneous adverse event in the treatment area. It is important to note that there was no difference between treatments in the incidence of burning or stinging. The occurrence of this local irritation event was apparently related to baseline disease severity, with a significantly higher incidence found after topical application of tacrolimus in patients with moderate disease at baseline compared with patients having mild disease. These rates are lower than those previously reported, in which 34% to 43% of pediatric patients with moderate to severe disease (mean EASI score: 23; mean %BSA affected: 48%) reported skin burning after topical tacrolimus application.²³ Despite the hypersensitivity exhibited by atopic patients, this local irritation proved to be transient and decreased in prevalence with continued use. Lawrence³⁰ also reported data from 2 large multicenter trials involving 4350 pediatric patients and 4372 adult patients with AD that revealed that local application-site reactions of skin burning and pruritus were more frequent in patients with severe disease than in those with mild disease. Fortunately, the speed with which tacrolimus ointment healed the atopic skin resulted in few reports of treatment discontinuations for this initial irritability.

Rather than solely evaluate the improvement in the signs and symptoms of AD from baseline in pediatric patients in an open-label study, this study compared the effects of tacrolimus ointment 0.03% with a vehicle control ointment over a 6-week period in a double-blind fashion. Ointments have an intrinsic emollient effect on the skin,³¹ and applying emollients to achieve skin hydration is an approach used to prevent AD flares. This beneficial effect of emollient use was observed in this study with improvement from baseline in patients treated with the vehicle ointment, particularly the patients who had milder AD. The vehicle ointment tested in this study was identical to the emollient base in the tacrolimus ointment, consisting of white petrolatum, white wax,

and other petroleum derivatives added to enhance drug solubility and absorption. Although some patients prefer the texture of creams, most dermatologists recommend ointments for patients with AD, because ointments increase hydration by impeding transepidermal water loss. In addition, the excipients in creams can be irritating to the sensitive skin of an AD patient.

CONCLUSIONS

This study demonstrates that tacrolimus ointment 0.03% has a rapid onset of action and can be used safely and effectively for treating mild to moderate AD in pediatric patients. At the end of treatment, slightly more than half of the patients treated with tacrolimus ointment 0.03% were clear or almost clear of their AD and had experienced a rapid reduction in their itching. Tacrolimus ointment 0.03% may be used safely on all skin surfaces, including the face and intertriginous areas, without the potential long-term consequences of topical corticosteroids, especially skin atrophy and striae, and provides a steroid-free alternative to traditional AD treatment in pediatric patients.

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REFERENCES

1. Hanifin JM, Cooper KD, Ho VC, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines." *J Am Acad Dermatol*. 2004;50:391-404
2. National Institutes of Health, US Department of Health and Human Services. Handout on health: atopic dermatitis. NIH publication 03-4272. 1999. Available at: www.niams.nih.gov/hi/topics/dermatitis/index.html#link_a. Accessed July 26, 2005
3. Laughter D, Istvan JA, Tofte SJ, Hanifin JM. The prevalence of atopic dermatitis in Oregon schoolchildren. *J Am Acad Dermatol*. 2000;43:649-655
4. Bender BG, Leung SB, Leung DYM. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J Allergy Clin Immunol*. 2003;111:598-602
5. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *J Eur Acad Dermatol Venereol*. 2002;16:455-462
6. Paller AS, McAlister RO, Doyle JJ, Jackson A. Perceptions of physicians and pediatric patients about atopic dermatitis, its impact, and its treatment. *Clin Pediatr (Phila)*. 2002;41:323-332
7. Drake L, Prendergast M, Maher R, et al. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *J Am Acad Dermatol*. 2001;44:S65-S72

8. Chamlin SL, Frieden IJ, Williams ML, Chren M. Effects of atopic dermatitis on young American children and their families. *Pediatrics*. 2004;114:607–611
9. Kemp AS. Cost of illness of atopic dermatitis in children: a societal perspective. *Pharmacoeconomics*. 2003;21:105–113
10. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child*. 1997;76:159–162
11. Castanedo-Cazares JP, Lopez-Lucio RH, Moncada B. Cushing syndrome following the prescription of antifungal, antibiotic, corticosteroid cream. *Int J Dermatol*. 2003;42:318
12. Ermis B, Ors R, Tastekin A, Ozkan B. Cushing's syndrome secondary to topical corticosteroids abuse. *Clin Endocrinol (Oxf)*. 2003;58:795–796
13. Aalto-Korte K, Turpeinen M. Bone mineral density in patients with atopic dermatitis. *Br J Dermatol*. 1997;136(2):172–175
14. Walker BR, Best R, Shackleton CHL, Padfield LP, Edwards CRW. Increased vasoconstrictor sensitivity to glucocorticoids in essential hypertension. *Hypertension*. 1996;27:190–196
15. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments of atopic eczema. *Health Technol Assess*. 2000;4(37):1–191
16. Alaiti S, Kang S, Fiedler VC, et al. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. *J Am Acad Dermatol*. 1998;38:69–76
17. Harper J, Smith C, Rubins A, et al. A multicenter study of the pharmacokinetics of tacrolimus ointment after first and repeated application to children with atopic dermatitis. *J Invest Dermatol*. 2005;124:695–699
18. Kapp A, Allen BR, Reitamo S. Atopic dermatitis management with tacrolimus ointment (Protopic). *J Dermatolog Treat*. 2003;14(suppl 1):5–16
19. Rubins A, Gutmane R, Valdmane N, Stevenson P, Foster C, Undre N. Pharmacokinetics of 0.1% tacrolimus ointment after first and repeated application to adults with moderate to severe atopic dermatitis. *J Invest Dermatol*. 2005;125:68–71
20. Reitamo S, Rissanen J, Remitz A, et al. Tacrolimus Ointment does not affect collagen synthesis: results of a single-center randomized trial. *J Invest Dermatol*. 1998;111:396–398
21. Kyllönen H, Remitz A, Mandelin JM, Elg P, Reitamo S. Effects of 1-year intermittent treatment with topical tacrolimus monotherapy on skin collagen synthesis in patients with atopic dermatitis. *Br J Dermatol*. 2004;150:1174–1181
22. Kang S, Lucky AW, Pariser D, Lawrence I, Hanifin JM. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *J Am Acad Dermatol*. 2001;44:S58–S64
23. Paller A, Eichenfield LF, Leung DYM, Stewart D, Appell M. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol*. 2001;44:S47–S57
24. Reitamo S, Van Leent EJM, Ho V, et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol*. 2002;109:539–546
25. Boguniewicz M, Fiedler VC, Raimer S, Lawrence ID, Leung DYM, Hanifin JM. A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. *J Allergy Clin Immunol*. 1998;102:637–644
26. Reitamo S, Harper J, Bos JD, et al. 0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomized double-blind controlled trial. *Br J Dermatol*. 2004;150:554–562
27. Hanifin JM, Leung DYM, Paller A, Rico J. Tacrolimus ointment monotherapy is safe and effective for the long-term treatment (more than 3 years) of atopic dermatitis in pediatric patients [abstract]. *J Allergy Clin Immunol*. 2003;111(2):S130
28. Hanifin JM, Rajika G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)*. 1980;92:44–47
29. 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. EASI Evaluator Group. *Exp Dermatol*. 2001;10:11–18
30. Lawrence I. Three studies in pediatric and adult patients demonstrate that tacrolimus ointment is safe and effective in the treatment of atopic dermatitis. *Acta Dermatovenerol Croat*. 2003;11(2):126–132
31. Loden M. The skin barrier and use of moisturizers in atopic dermatitis. *Clin Dermatol*. 2003;21:145–57

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