Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis

Sakari Reitamo, MD,[a] Malcolm Rustin, MD,[b] Thomas Ruzicka, MD,[c] Frédéric Cambazard, MD,[d] Kirsti Kalimo, MD,[e] Peter S. Friedmann, MD,[f] Erwin Schoepf, MD,[g] Mourad Lahfa, MD,[h] Thomas L. Diepgen, MD,[i] Harryono Judodihardjo, MD,[j] Andreas Wollenberg, MD,[k] John Berth-Jones, FRCP,[l] and Thomas Bieber, MD,[m] for the European Tacrolimus Ointment Study Group*

Helsinki and Turku, Finland, London, Southampton, Cardiff, and Coventry, United Kingdom, Dusseldorf, Freiburg, Heidelberg, Munich, and Bonn, Germany, and Saint Etienne and Paris, France

Background: Vehicle-controlled studies have demonstrated the efficacy and safety of tacrolimus ointment for patients with atopic dermatitis.

Objective: This study was undertaken to compare 0.03% and 0.1% tacrolimus ointment with 0.1% hydrocortisone-17-butyrate ointment, a midpotent to potent topical corticosteroid, in the treatment of adult patients with moderate-to-severe atopic dermatitis.

Methods: Patients applied ointment twice daily to all affected areas for 3 weeks in this multicenter, randomized, double-blind, parallel-group study. The primary endpoint was the modified eczema area and severity index (mEASI) mean area under the curve as a percentage of baseline.

Results: Five hundred seventy patients were randomized and received treatment. Discontinuations included 22 of 193 patients from the 0.03% tacrolimus group, 22 of 191 patients from the 0.1% tacrolimus group, and 17 of 186 patients from the hydrocortisone butyrate group. The median mEASI mean area under the curve as a percentage of baseline was 47.0%, 36.5%, and 36.1% for patients who received 0.03% tacrolimus, 0.1% tacrolimus, and 0.1% hydrocortisone butyrate, respectively. There was no statistically significant difference between 0.1% tacrolimus and 0.1% hydrocortisone butyrate; however, the lower improvement in mEASI for 0.03% tacrolimus was statistically significant when compared with 0.1% tacrolimus ($P < .001$) or hydrocortisone butyrate ($P = .002$). Skin burning and pruritus at the application site showed a higher incidence in the tacrolimus treatment groups than in the hydrocortisone butyrate group ($P < .05$). Laboratory parameters showed no treatment differences and no marked changes over time.

Conclusions: The efficacy of 0.1% tacrolimus ointment was similar to that of 0.1% hydrocortisone butyrate ointment and was lower for 0.03% tacrolimus ointment. No serious safety concerns were identified. (J Allergy Clin Immunol 2002;109:547-55.)

Key words: *Tacrolimus, FK506, atopic dermatitis, efficacy, safety, ointment, topical*

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease. It is characterized by episodes of intense pruritus and multiple lesions with erythema, excoriations, erosions accompanied by a serous exudate, lichenification, papules, dry skin, and a susceptibility to cutaneous infections.[1] AD tends to run in families and often coexists with other atopic diseases, such as rhinitis, asthma, and allergic conjunctivitis. The immune pathology of AD is not precisely understood. Skin lesions have infiltrates of basophils, eosinophils, and cells of the mononuclear phagocyte lineage and T cells. Elevated IgE is found in 60% to 80% of patients with AD. Patients also usually have elevated eosinophil counts.

Treatment options for AD are few, with topical corticosteroids being the principal treatment for acute episodes.[2] Secondary treatments with UV light irradiation or immunosuppressive drugs generally do not replace topical corticosteroids but rather act as steroid-sparing therapies. Emollients are important in extending treatment-free periods. The development of new corticosteroid preparations, with an aim to reduce side effects, has not significantly changed the risk/benefit ratio. The limitations regarding the use of topical corticosteroids

From [a]the Department of Dermatology, Hospital for Skin and Allergic Diseases, University of Helsinki, Helsinki; [b]the Department of Dermatology, Royal Free Hospital, London; [c]Heinrich-Heine-Universität, Hautklinik, Dusseldorf; [d]Hôpital Nord, Service de Dermatologie, St Etienne; [e]the Department of Dermatology, University Hospital of Turku, Turku; [f]Southampton General Hospital, Southampton; [g]Klinikum der Albert-Ludwigs-Universität, Universitäts-Hautklinik, Freiburg; [h]Hôpital Saint-Louis, Service de Dermatologie, Paris; [i]Universitätsklinikum Heidelberg, Institut und Poliklinik für Arbeits-und Sozialmedizin, Heidelberg; [j]the Department of Dermatology, University of Wales College of Medicine, Cardiff; [k]Klinik und Poliklinik für Dermatologie und Allergologie, Ludwig-Maximilians-University, Munich; [l]the Department of Dermatology, Walsgrave Hospital, Coventry; and [m]Klinik und Poliklinik für Dermatologie, Klinikum der Universität, Bonn.

*Additional members of the European Tacrolimus Ointment Study Group are listed in the Appendix.

Supported by Fujisawa GmbH, Munich, Germany.

Received for publication July 2, 2001; revised November 19, 2001; accepted for publication November 19, 2001.

Reprint requests: Sakari Reitamo, MD, Department of Dermatology, Hospital for Skin and Allergic Diseases, University of Helsinki, Meilahdentie 2, 00250 Helsinki, Finland.

0091-6749/2002 $35.00 + 0 **1/85/121832**

doi:10.1067/mai.2002.121832

Abbreviations used
AD: Atopic dermatitis
BSA: Body surface area
EASI: Eczema area and severity index
mAUC: Mean area under the curve
mEASI: Modified eczema area and severity index

relate to the wide distribution of steroid-responsive elements in various cells and tissues. In general, the most clinically relevant are atrophogenicity, growth restriction in children, poor long-term control of AD, and, in some patients, therapeutic resistance.[3]

Tacrolimus ointment, formulated for the treatment of AD, is the first in a class of topical immunomodulators. Its mechanism of action is based on calcineurin inhibition. Tacrolimus inhibits the phosphatase activity of calcineurin and thereby the dephosphorylation of the nuclear factor of activated T-cell protein, a transcription factor necessary for the expression of inflammatory cytokines.[4,5] Downregulation of the expression of the high-affinity IgE receptor in Langerhans cells and inhibition of the release of inflammatory mediators from mast cells and basophils by tacrolimus may also serve as targets in the immune therapy of AD.[6-9] Large, multicenter, randomized, vehicle-controlled studies in adults and children have shown that tacrolimus ointment is effective and safe in the treatment of AD.[10-14] The safety and efficacy of tacrolimus ointment monotherapy has been demonstrated for periods of up to 1 year in adults and children.[15,16] Unlike topical corticosteroids, tacrolimus ointment does not interfere with collagen synthesis or cause skin atrophy.[17] Like topical corticosteroids, it is associated with a reduction in staphylococcal skin colonization in AD lesions.[18] Systemic absorption is minimal.[19]

The present study was undertaken to compare the efficacy and safety of tacrolimus ointment with a topical corticosteroid reference therapy. Hydrocortisone butyrate ointment, 0.1%, a midpotent to potent topical corticosteroid, was chosen for the reference therapy. A stronger topical corticosteroid or a treatment period of longer than 3 weeks with the selected corticosteroid would have placed patients at an unacceptable risk for skin atrophy and other side effects, especially because the face and neck were not excluded from treatment. More potent (super or ultrahigh potency) topical corticosteroids are recommended only for very short periods in skin areas that are lichenified (thickened), with the face and neck entirely excluded.

METHODS

Study design

The primary focus of this phase III, comparative, multicenter, randomized, double-blind, parallel-group study was to assess the efficacy and safety of 0.03% and 0.1% tacrolimus ointment and 0.1% hydrocortisone butyrate ointment in adult patients with moderate-to-severe AD. The study was performed at 27 centers in 8 European countries; the ethics committee from each center reviewed the protocol and granted approval of the study before its implementation.

The study consisted of a screening visit within 7 days before the baseline visit, a baseline (day 0, treatment allocation) visit, visits on days 3 and 7 and weeks 2 and 3 of treatment, and a follow-up visit 2 weeks after treatment was completed (week 5).

Patient selection

Male and female patients, 16 to 70 years old, with a diagnosis of AD on the basis of the criteria of Hanifin and Rajka[20] were eligible for study participation. Patients were also required to have an AD severity grading of moderate to severe according to the criteria of Rajka and Langeland[21] and disease involvement of at least 5% of the total body surface area (BSA). The main exclusion criterion was a serious skin disorder other than AD that required treatment. All patients gave written informed consent.

Randomization and blinding

Patients were randomized in parallel groups (1:1:1) to receive 0.03% tacrolimus ointment, 0.1% tacrolimus ointment, or a commercial preparation of 0.1% hydrocortisone butyrate ointment (Alfason, Yamanouchi).

The sponsor (Fujisawa GmbH, Munich) supplied each center with a unique block of sequentially ordered patient numbers from a randomization list. Randomization (assignment of a patient number) occurred in the order that patients passed the selection criteria on the baseline visit. For treatment allocation, an ointment supply box bearing a unique patient number was dispensed. Study ointments were provided in identical tubes to safeguard blinding, and the ointment supply boxes bore no information that might have revealed the identity of the study ointment.

Treatment

Treatment consisted of a thin layer of ointment applied twice daily to all areas of actively diseased skin. Patients were instructed to continue treatment for the entire 3-week treatment period, regardless of whether clearance was realized.

Prohibited therapies during the study comprised topical and systemic corticosteroids, antihistamines and antimicrobials, coal tar, topical nonsteroidal anti-inflammatory drugs, nonsteroidal immunosuppressants, UV light treatments (UVA and UVB), hypnotics and sedatives, and other investigational drugs. Wash-out periods for these therapies ranged from 5 days to 6 weeks. Inhaled or intranasal corticosteroids were restricted to 1 mg/d. Bath oil and nonmedicated emollients were allowed.

Assessments

At baseline (day 0), days 3 and 7 and weeks 2 and 3 of treatment, and 2 weeks after completing treatment (week 5), investigators rated erythema, edema-induration-papulation, excoriations, and lichenification on a scale of 0 to 3 and estimated the percentage of the total BSA affected by AD (0%-100%) for 4 body regions (head and neck, trunk, upper limbs, and lower limbs). Patients assessed the intensity of itching experienced during the previous 24 hours using a 10-cm visual analogue scale with 0 cm to indicate "no itch" and 10 cm to indicate "worst itch imaginable." These assessments were used to calculate the modified eczema area and severity index (mEASI). The mEASI is a variant of the eczema area and severity index (EASI) developed by Hanifin et al.[22] The mEASI is identical to the EASI except that in the latter an assessment of itching is not included. Itching was included in the mEASI because it is considered a primary symptom of AD.[16] Both the EASI and the mEASI have the advantage of including severity scores for individual symptoms of AD weighted according to the extent of affected BSA. The method for calculating the EASI and mEASI for adult patients with AD was recently described.[12]

TABLE I. Demographics and baseline characteristics and reasons for withdrawal of patients

		Tacrolimus	
	Hydrocortisone butyrate 0.1%	**0.03%**	**0.1%**
No.	186	193	191
Age, y (mean ± SD)	30.8 ± 10.3	31.1 ± 11.5	32.4 ± 11.4
Male/female ratio, %	46.8/53.2	43.5/56.5	42.9/57.1
White, No. (%)	182 (97.8)	183 (94.8)	184 (96.3)
Duration of AD, y (median)	24.0	23.0	25.0
Duration of current episode, mo (median)	9.5	7.8	13.3
Moderate-severe AD, %	44.6/55.4	46.1/53.9	50.8/49.2
Percentage affected BSA (median)	36.3	35.0	30.0
Affected body region, No. (%)			
Head and neck	178 (95.7)	180 (93.3)	183 (95.8)
Upper limbs	186 (100.0)	190 (98.4)	190 (99.5)
Trunk	170 (91.4)	174 (90.2)	172 (90.1)
Lower limbs	164 (88.2)	170 (88.1)	163 (85.3)
Withdrawn from study, No. (%)	17 (9.1)	22 (11.4)	22 (11.5)
Reason for withdrawal, No. (%)			
Adverse event	3 (1.6)	7 (3.6)	8 (4.2)
Withdrawal of consent	4 (2.2)	6 (3.1)	6 (3.1)
Noncompliance or lost to follow-up	6 (3.2)	3 (1.5)	4 (2.1)
Prohibited therapy	2 (1.1)	4 (2.1)	3 (1.6)
Lack of efficacy	2 (1.1)	2 (1.0)	1 (0.5)

Investigators also assessed overall clinical improvement in the physician's global evaluation of clinical response. "Cleared" indicated an improvement of 100%, "excellent" indicated improvement of 90% to 99%, "marked" indicated improvement of 75% to 89%, "moderate" indicated improvement of 50% to 74%, "slight" indicated improvement of 30% to 49%, "no appreciable improvement" indicated improvement of 0% to 29%, and "worse" indicated improvement of less than 0%.

Adverse events were monitored on an ongoing basis. An adverse event was defined as any undesirable experience that occurred to a patient during the clinical trial, regardless of whether it was considered related to the study drug. Causally related adverse events were those assessed by the investigator as having a highly probable, probable, possible, or not assessable relationship to the study drug or adverse events for which such an assessment was not made. Except where noted, adverse event data are presented irrespective of the causality assessment.

Laboratory assessments (haematology and clinical chemistry, including assessments for renal and hepatic function) were performed at the screening visit, 7 days after starting treatment (day 7), at the end of treatment (week 3), and at the end of the study (week 5).

Statistical analyses

The primary analysis was based on the intent-to-treat population, which comprised all patients who were randomized and received at least one application of study ointment. The primary endpoint was the mEASI mean area under the curve (mAUC) as a percentage of baseline. On the basis of a phase II study (which used a different efficacy parameter, 10), it was estimated that about 180 patients per treatment group would be required for an ANOVA with an α value of .05 and a power of 90% to detect a difference of 15% among the 3 treatment groups. Before unblinding of the data, it was discovered that the data did not have a normal distribution; thus a nonparametric method (the Wilcoxon rank sum test) was adopted. All continuous variables (the mEASI mAUC as a percentage of baseline, as well as the percentage decrease of mEASI, EASI, pruritus, and affected BSA from baseline to the end of treatment) were tested by using the Wilcoxon rank sum test. The χ^2 test was used to compare treatment groups in the physician's global evaluation of clinical response.

A dictionary, based on COSTART (coding symbols for thesaurus of adverse reaction terms), was used to code investigator terms. The term "skin burning" was used to refer to the sensation of skin burning or smarting. "Allergic reaction" included investigator terms such as allergic rhinitis and allergic conjuctivitis. "Flu syndrome" was used to code investigator terms such as "cold," "common cold," "flu," "influenza," and "upper respiratory tract infection." Comparison of treatment groups for the incidence of adverse events was carried out with Fisher exact test.

RESULTS

Patients

Of the 571 patients randomized, 1 patient (in the hydrocortisone butyrate group) never received treatment; thus 570 patients were included in the intent-to-treat population. Approximately 90% of patients across treatment groups completed the study; withdrawals included 22 (11.4%) of 193 patients from the 0.03% tacrolimus group, 22 (11.5%) of 191 patients from the 0.1% tacrolimus group, and 17 (9.1%) of 186 patients from the hydrocortisone butyrate group (Table I).

Demographic and baseline characteristics were similar among treatment groups (Table I). Comparison of the mean age of patients (about 31 years across treatment groups) with the median duration of AD (about 25 years) indicates that most patients experienced onset of the disease during

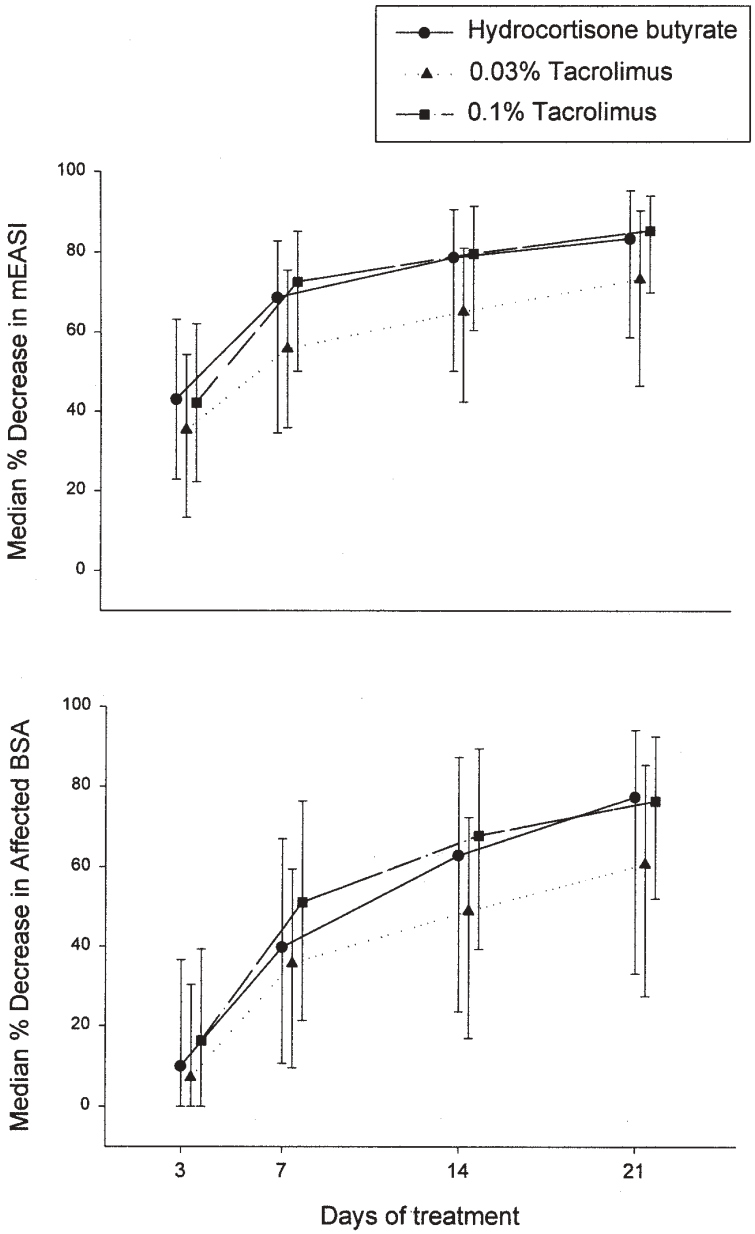

FIG 1. Median percentage decreases from baseline (and upper and lower quartiles) in mEASI and affected BSA. The mEASI considers the affected BSA and the severity of erythema, edema, excoriations, lichenification, and itching. Differences between 0.1% and 0.03% tacrolimus and between 0.1% hydrocortisone butyrate and 0.03% tacrolimus were significant ($P < .05$).

childhood. The affected BSA was extensive at baseline (a median of approximately one third of the total BSA across treatment groups), and most patients had active disease on all body regions, including the head and neck.

Efficacy

The mEASI mAUC as a percentage of baseline showed that, averaged over the 3-week course of treatment, patients had a median improvement of 53.0% with 0.03% tacrolimus (ie, from 100.0% at baseline to a median of 47.0% over the entire treatment period), 63.5% with 0.1% tacrolimus (ie, from 100% at baseline to a median of 36.5% over the entire treatment period), and 63.9% with hydrocortisone butyrate (ie, from 100% at baseline to a median of 36.1% over the entire treatment period). There was no statistically significant difference

TABLE II. Incidence of most common adverse events

COSTART term	Hydrocortisone butyrate	Tacrolimus	
		0.03%	0.1%
No.	186	193	191
Application site, No. (%)			
Skin burning	24 (12.9)	87 (45.1)	113 (59.2)
Pruritus	18 (9.7)	39 (20.2)	29 (15.2)
Folliculitis	13 (7.0)	15 (7.8)	15 (7.9)
Skin erythema	1 (0.5)	4 (2.1)	7 (3.7)
Maculopapular rash	2 (1.1)	1 (0.5)	5 (2.6)
Nonapplication site, No. (%)			
Flu syndrome (eg, flu, cold, upper respiratory tract infection)	12 (6.5)	8 (4.1)	12 (6.3)
Allergic reaction (eg, allergic rhinitis, allergic conjunctivitis)	12 (6.5)	6 (3.1)	5 (2.6)
Headache	14 (7.5)	10 (5.2)	9 (4.7)
Herpes simplex	1 (0.5)	5 (2.6)	3 (1.6)

The most common adverse events were present in at least 5 patients in any treatment group. An overall comparison of treatment groups showed descriptive *P* values of less than .05 for skin burning and pruritus.
COSTART, Coding symbols for thesaurus of adverse reaction terms.

between 0.1% tacrolimus and 0.1% hydrocortisone butyrate; however, the lower improvement in mEASI for 0.03% tacrolimus was statistically significant when compared with that of 0.1% tacrolimus ($P < .001$, Wilcoxon rank sum test) or hydrocortisone butyrate ($P = .002$, Wilcoxon rank sum test). Separate analysis of the head and neck showed similar findings compared with the analysis of combined body regions in all 3 treatment groups (data not shown).

Fig 1 presents percentage decreases from baseline in the mEASI and percentage of affected BSA. For all 3 treatment groups, improvement was apparent 3 days after the start of treatment, with improvement continuing until completion of treatment at week 3. Consistent with the mEASI mAUC, there was no significant difference between 0.1% tacrolimus and 0.1% hydrocortisone butyrate in the percentage decrease (from baseline to the end of treatment) of the mEASI or affected BSA. Differences between 0.1% tacrolimus and 0.03% tacrolimus and between 0.1% hydrocortisone butyrate and 0.03% tacrolimus were associated with descriptive *P* values of less than .05 (Wilcoxon rank sum test). Findings for the EASI and pruritus (data not shown) were similar to those for the mEASI and affected BSA.

In the physician's global evaluation of clinical response, 51.4% of patients who received 0.1% hydrocortisone butyrate, 37.6% of patients who received 0.03% tacrolimus, and 49.2% of patients who received 0.1% tacrolimus experienced excellent improvement or clearance (≥90% improvement) by the end of treatment. Again, the difference between 0.1% tacrolimus and 0.1% hydrocortisone butyrate was not statistically significant. Pairwise comparisons between 0.1% tacrolimus and 0.03% tacrolimus and between 0.1% hydrocortisone butyrate and 0.03% tacrolimus were associated with descriptive *P* values of less than .05 (χ^2 test). At least marked improvement was observed in 70.5% of patients who received 0.1% hydrocortisone butyrate, 58.2% of patients who received 0.03% tacrolimus, and 76.5% of patients who received 0.1% tacrolimus. At least moderate improvement was observed in 79.2%, 79.9%, and 85.0% of patients, respectively (Fig 2). Patients who had a rating of at least moderate improvement at the end of treatment and continued to adhere to prohibited therapy restrictions were assessed 2 weeks after stopping treatment (week 5). In all 3 treatment groups, only about half of the patients maintained at least moderate improvement after 2 weeks without treatment (Fig 2). Follow-up for other efficacy endpoints showed similar findings, with patients, on average, showing a better condition at follow-up than at baseline but a worse condition than observed at the end of treatment (data not shown).

Safety

Adverse events experienced by at least 5 patients in any treatment group are presented in Table II. Skin burning and pruritus were the only adverse events to show a higher incidence in the tacrolimus treatment groups than in the hydrocortisone butyrate group ($P < .05$, Fisher exact test). These signs of local irritation were transient, decreasing in prevalence over time (Table III). A separate analysis of adverse events of the head and neck showed the same overall findings as the analysis that included all body regions (data not shown).

Only one patient had a serious adverse event during treatment for which a causal relationship with the study ointment was considered possible. A 32-year-old male patient in the 0.1% tacrolimus group experienced skin burning and pruritus at treated areas in combination with

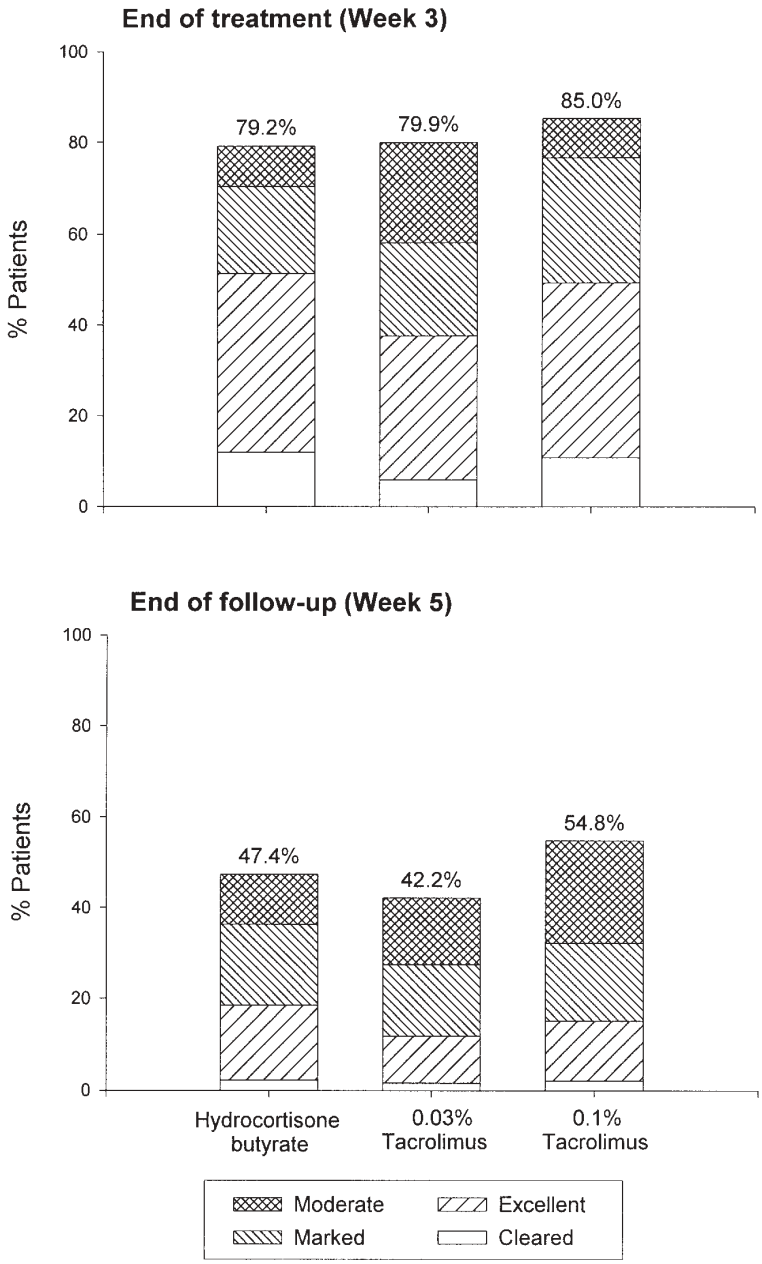

FIG 2. Physician's global evaluation of clinical response at the end of treatment and the end of follow-up. The population for analysis at the end of treatment was an intent-to-treat population, with 183, 189, and 187 patients, respectively, included in the 0.1% hydrocortisone butyrate group, the 0.03% tacrolimus group, and the 0.1% tacrolimus group. The difference in the proportion of patients who had clearance or excellent improvement was significant between 0.1% and 0.03% tacrolimus and between 0.1% hydrocortisone butyrate and 0.03% tacrolimus ($P < .05$). The population for analysis of follow-up included only patients who had at least moderate improvement at the end of treatment and continued prohibited therapy restrictions, with 135, 128, and 146 patients, respectively.

scaling and flush and insomnia. This cluster of events occurred on the first day of application. Treatment was discontinued the same evening, and the episode resolved.

Except for skin burning and skin irritation at the application site, adverse events that led to treatment discontinuation were complications typically associated with AD. A skin irritation adverse event led to discontinuation in 2 patients who received 0.03% tacrolimus and 6 patients who

TABLE III. Prevalence of application site skin burning and pruritus over time

	Hydrocortisone butyrate 0.1%		Tacrolimus 0.03%		Tacrolimus 0.1%	
	n	Patients (%)	n	Patients (%)	n	Patients (%)
Skin burning						
Days 1-4	186	23 (12.4)	193	82 (42.5)	191	108 (56.5)
Days 5-8	180	4 (2.2)	188	39 (20.7)	184	33 (17.9)
Week 2	177	4 (2.3)	184	27 (14.7)	181	21 (11.6)
Week 3	173	2 (1.2)	177	12 (6.8)	172	15 (8.7)
Pruritus						
Days 1-4	186	13 (7.0)	193	36 (18.7)	191	27 (14.1)
Days 5-8	180	10 (5.6)	188	18 (9.6)	184	11 (6.0)
Week 2	177	5 (2.8)	184	15 (8.2)	181	8 (4.4)
Week 3	173	5 (2.9)	177	8 (4.5)	172	4 (2.3)

received 0.1% tacrolimus. Infection adverse events that led to discontinuation were skin infection (2 patients in the hydrocortisone butyrate group and 2 patients in the 0.1% tacrolimus group) and herpes simplex infection (2 patients in the 0.03% tacrolimus group and 1 patient in the 0.1% tacrolimus group). No cases of eczema herpeticum were reported during the study. Four additional patients had an adverse event that led to discontinuation: worsening of AD in the hydrocortisone butyrate group and urticaria, rash, and ophthalmitis in the 0.03% tacrolimus group.

As expected for a population of patients with AD,[1,23] laboratory measurements showed mean eosinophil counts and lactate dehydrogenase concentrations above the normal range at baseline and at all study visits. There were no meaningful differences among treatment groups. All other mean laboratory values were within the normal range during the study and showed no marked changes over time or treatment differences. Changes in laboratory values reported as adverse events included one patient in the 0.03% tacrolimus group with a mild transient decrease in white blood cell count below the normal range and 2 patients in the hydrocortisone butyrate group and 1 patient in the 0.03% tacrolimus group who reported increases in liver function enzyme activities.

DISCUSSION

Findings from this study indicate that the efficacy of 0.1% tacrolimus ointment is comparable with that of 0.1% hydrocortisone butyrate ointment, a midpotent to potent topical corticosteroid used as a standard therapy in AD. The mEASI mAUC as a percentage of baseline and all secondary endpoints showed no significant difference between treatment with 0.1% hydrocortisone butyrate and treatment with 0.1% tacrolimus ointment. Improvement was also substantial for patients who received 0.03% tacrolimus but was significantly lower than in the other 2 treatment groups. This was a short-term (3-week) study. It would be of interest to conduct a long-term study in which patients were treated for several months to compare 0.1% tacrolimus ointment with 0.1% hydrocortisone butyrate ointment or another midpotent to potent standard topical corticosteroid.

These findings are consistent with the US phase III vehicle-controlled studies in adults with AD, which showed both 0.03% and 0.1% tacrolimus ointment to be effective but with greater efficacy for 0.1% than 0.03% tacrolimus.[12] Findings from the present study are also consistent with a study conducted in Japan that showed the efficacy of 0.1% tacrolimus ointment to be similar to that of 0.1% betamethasone-valerate ointment in the treatment of adult patients with AD.[24] Betamethasone ointment, like hydrocortisone butyrate ointment, is classified in Europe as a potent topical corticosteroid.[25] Topical preparations of hydrocortisone butyrate and betamethasone valerate have shown comparable clinical efficacy in the treatment of eczematous skin lesions[26] and are equipotent in inducing skin thinning,[27] decreasing collagen synthesis,[28] and inhibiting proliferation of cultured human skin fibroblasts.[29]

This study was not designed to assess relapse or rebound; however, the average condition of patients at the follow-up visit was better than that recorded at baseline.

Because tacrolimus ointment offers a potential advantage to topical corticosteroids for the treatment of skin of the face and intertriginous areas (tacrolimus ointment does not reduce collagen synthesis or skin thickness[17]), separate analyses for the head and neck were carried out. These analyses showed similar efficacy and safety results for the head and neck compared with the analysis for combined body regions. Long-term efficacy without evidence of skin atrophy or other safety risks has been shown in a noncomparative study in which 316 adult patients received tacrolimus ointment for up to 1 year.[15] The long-term efficacy and safety of tacrolimus ointment monotherapy is of particular benefit for patients with persistent disease on the face and flexure regions, for whom long-term treatment with topical cor-

ticosteroids would be inappropriate because of an unacceptable risk of skin atrophy.

This study has also shown that treatment with tacrolimus ointment is safe. Only transient local burning and pruritus showed a treatment relation with tacrolimus ointment. It is possible that baseline disease severity contributed to the heightened local irritation at the start of treatment, with the skin becoming more resilient as it heals. The actual episode of skin burning lasts only about 10 minutes.[13,16] No adverse events away from the application site or infection adverse events showed a statistically significant difference in incidence. Folliculitis was a common infection adverse event that was equally prevalent in all 3 treatment groups; it is possible that the occlusive properties of the ointment vehicles contributed to its development.

We conclude that the efficacy of 0.1% tacrolimus ointment is comparable with that 0.1% hydrocortisone butyrate ointment, a midpotent to potent topical corticosteroid. Clinical improvement was also substantial for patients who received 0.03% tacrolimus but lower than that observed with 0.1% tacrolimus and 0.1% hydrocortisone butyrate. Findings from this study indicate that both 0.1% and 0.03% tacrolimus are safe for the treatment of AD. This new treatment option offers an alternative to topical corticosteroids for patients with moderate-to-severe AD.

We thank Connie Grogan for editorial support and Ulrich Beyer and Ruthild Sautermeister for support in the statistical analyses.

REFERENCES

1. Leung DYM. Atopic dermatitis: new insights and opportunities for therapeutic intervention. J Allergy Clin Immunol 2000;105:860-76.
2. Leung DYM, Hanifin JM, Charlesworth EN, et al. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
3. Goerz G, Lehmann P. Topical treatment with corticosteroids. In: Ruzicka T, Ring J, Przybilla B, editors. Handbook of atopic eczema. Berlin: Springer Verlag; 1991. p. 375-90.
4. Goto T, Kino T, Hatanaka H, at al. Discovery of FK-506, a novel immunosuppressant isolated from *Streptomyces tsukubaensis*. Transplant Proc 1987;19:4-8.
5. Tocci MJ, Markovich DA, Collier KA, et al. The immunosuppressant FK506 selectively inhibits expression of early T cell activation genes. J Immunol 1989;143:718-26.
6. Panhans-Groß A, Novak N, Kraft S, Bieber T. Human epidermal Langerhans cells are targets for the immunosuppressive macrolide tacrolimus (FK506). J Allergy Clin Immunol 2001;107:345-52.
7. Wollenberg A, Sharma S, von Bubnoff D, Geiger E, Haberstok J, Bieber T. Topical tacroilmus (FK506) leads to profound phenotypic and functional alterations of epidermal antigen presenting dendritic cells in atopic dermatitis. J Allergy Clin Immunol 2001;107:519-25.
8. De Paulis A, Stellato C, Cirillo R, Ciccarelli A, Oriente A, Marone G. Anti-inflammatory effect of FK506 on human skin mast cells. J Invest Dermatol 1992;99:723-8.
9. Reitamo S. Tacrolimus: a topical immunomodulatory therapy for atopic dermatitis [editorial]. J Allergy Clin Immunol 2001;107:445-8.
10. Ruzicka T, Bieber T, Schoepf E, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. N Engl J Med 1997;337:816-21.
11. Boguniewicz M, Fiedler VC, Raimer S, et al. A randomized, vehicle-controlled trial of tacrolimus ointment for the treatment of atopic dermatitis in children. J Allergy Clin Immunol 1998;102:637-44.
12. Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E, the Tacrolimus Ointment Study Group. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: Part I, efficacy. J Am Acad Dermatol 2001; 44:S28-38.
13. Paller A, Eichenfield LF, Leung DYM, Steward D, Appell M, the Tacrolimus Ointment Study Group. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. J Am Acad Dermatol 2001;44:S47-57.
14. Soter NA, Fleischer AB, Webster GF, Monroe E, Lawrence I, the Tacrolimus Ointment Study Group. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. J Am Acad Dermatol 2001;44:S39-46.
15. Reitamo S, Wollenberg A, Schöpf E, et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. Arch Dermatol 2000;136:999-1006.
16. Kang S, Lucky AW, Pariser D, Lawrence I, Hanifin JM, the Tacrolimus Ointment Study Group. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol 2001;44:S58-64.
17. 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;111:396-8.
18. Remitz A, Kyllönen H, Granlund H, Reitamo S. Tacrolimus ointment reduces staphylococcal colonization of atopic dermatitis lesions [letter]. J Allergy Clin Immunol 2001;107:196-7.
19. Alaiti S, Kang S, Fiedler VC. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. J Am Acad Dermatol 1998;38:69-76.
20. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980;92:44-7.
21. Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol 1989;144:13-4.
22. Hanifin JM, Thurston M, Ornoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol 2001;10:11-8.
23. Mukai H, Noguchi T, Kamimura K, Nishioka K, Nishiyama S. Significance of elevated serum LDH (lactate dehydrogenase) activity in atopic dermatitis. J Dermatol 1990;17:477-81.
24. FK506 Ointment Study Group. Phase III comparative study of FK506 ointment versus betamethasone valerate ointment in atopic dermatitis (trunk/extremities) [in Japanese]. Nishinihon J Derm 1997;59:870-9.
25. Reynolds JEF, editor. Martindale: the extra pharmacopoeia. London: The Pharmaceutical Press; 1993.
26. Thormann J, Brodhagen H. Clinical trial comparing hydrocortisone-17-butyrate to betamethasone-valerate in a series of patient with eczematous skin lesions. Dermatologica 1976;152(Suppl 1):209-14.
27. Dykes PJ, Hill S, Marks R. Assessment of the atrophogenicity potential of corticosteroids by ultrasound and by epidermal biopsy under occlusive and nonocclusive conditions. In: Christophers F, Schoepf E, Kligman AM. Topical corticosteroid therapy: a novel approach to safer drugs. New York: Raven Press; 1988.
28. Haapasaari K-M, Risteli J, Koivukangas V, Oikarinen A. Comparison of the effect of hydrocortisone, hydrocortisone-17-butyrate and betamethasone on collagen synthesis in human skin in vivo. Acta Derm Venereol (Stockh) 1995;75:269-71.
29. Korting HC, Kerscher MJ, Schäfer-Korting. Topical glucocorticoids with improved benefit/risk ratio: do they exist? J Am Acad Dermatol 1992;27:87-92.

APPENDIX

Additional members of the European Tacrolimus Ointment Study Group:

Johannes Ring, MD (Technische Universitaet Muenchen, Munich, Germany); Gerd Plewig, MD (Dermatologische Klinik and Poliklinik, Munich, Germany); Alexander Kapp, MD (Dermatologische Klinik and Poliklinik der Medizinischen Hochschule Hannover, Hannover, Germany); Manige Fartasch, MD (Dermatologische Universitaets Klinik, Erlangen, Germany); Kristian Thestrup-Pedersen, MD (Marselisborg Hospital, Aarhus, Denmark); L. Iglesias Diez, MD (Servicio de Dermatologia, Madrid, Spain); F. Camacho Martinez, MD (Hospital Clinico Universitario, Sevilla, Spain); M. Lecha Carralero, MD (Hospital Clinic i Provincial, Barcelona, Spain); Kristina Turjan-

maa, MD (Tampere Universitiy Central Hospital, Tampere, Finland); Claire Beylot, MD (Hopital du Haut-Leveque, Pessac, France); Gerard Guillet, MD (Hôpital A. Morvan, Brest, France); Patrice Plantin, MD (Centre Hospitalier Laennec, Quimper, France); J. A. A. Hunter, MD (The University of Edinburgh, Edinburgh, United Kingdom); C. E. M. Griffiths, MD (University of Manchester, Hope Hospital, Salford, United Kingdom); Carla Bruijnzeel-Koomen, MD (University Hospital/Academisch Ziekenhuis Utrecht, Netherlands); J. Austad, MD (Rikshospitalet, Oslo, Norway); Elke Bornhövd, MD (Ludwig-Maximilians-University, Munich, Germany); J. L. Perrot, MD (Hôpital Nord, Dermatology, St Etienne, France); Louis Dubertret, MD (Hôpital Saint-Louis, Service de Dermatologie, Paris, France); Anita Remitz, MD, and Håkan Granlund, MD (Hospital for Skin and Allergic Diseases, University of Helsinki, Helsinki, Finland).