Development of new treatment modalities for atopic dermatitis
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Chapter 8

Safety and Efficacy of 1 Year of Tacrolimus Ointment Monotherapy in Adults With Atopic Dermatitis

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SUMMARY

Objective: To investigate the safety and efficacy of using 0.1% tacrolimus ointment for long-term treatment of atopic dermatitis.

Design: Open-label, noncomparative study with 6 to 12 months of follow-up. Setting: Outpatient departments in 30 study centers in 11 European countries.

Patients: We enrolled 316 patients aged 18 years and older with moderate to severe atopic dermatitis, 200 for 6 months and 116 for 12 months; 77.5% of patients completed the study.

Intervention: Twice-daily application of 0.1% tacrolimus ointment on all affected skin. Visits were scheduled on day 1; after 1, 2, and 4 weeks of treatment; and monthly thereafter.

Main Outcome Measures: Safety assessments included monitoring of adverse events, clinical laboratory values, and tacrolimus blood concentrations. Efficacy end points included a combined score (modified Eczema Area and Severity Index) and an investigator's global assessment.

Results: Local irritation, adverse events such as burning sensation (47% of patients), pruritus (24% of patients), and erythema (12% of patients) were common but tended to occur only when initiating treatment. Laboratory values showed no marked changes over time. Systemic absorption was minimal, with the maximum tacrolimus blood concentration being less than 1 ng/mL in 76% of patients. All efficacy end points showed improvement. The mean (SD) modified Eczema Area and Severity Index score was 23.7 (12.6) at day 1, 13.5 (11.3) at week 1, 6.1 (9.2) at month 6, and 6.1 (8.1) at month 12. Marked or excellent improvement or clearance of disease was reported in 54%, 81%, and 86% of patients at week 1, month 6, and month 12, respectively.

Conclusion: Up to 1 year of tacrolimus ointment use was safe and effective in patients with atopic dermatitis.
INTRODUCTION

Atopic dermatitis, an inflammatory skin disease with a chronically relapsing course, is characterized by episodes of intense pruritus, multiple lesions with erythema, excoriation, erosions accompanied by a serous exudate, accentuated skin markings (lichenification), fibrotic papules, severely dry skin, and a susceptibility to cutaneous infections. Atopic dermatitis often coexists with other atopic diseases, especially allergic respiratory diseases. There are no biochemical markers for atopic dermatitis, but patients typically have elevated serum IgE levels, eosinophil counts, and lactate dehydrogenase concentrations.1-4 Topical corticosteroids are the standard treatment for acute lesions of atopic dermatitis. However, they carry a risk of local side effects such as skin atrophy and striae and systemic side effects. Thus, use of high-potency topical corticosteroids is indicated only for short periods and for a limited area of treatment. Weak topical corticosteroids are preferred for regions of skin that are particularly thin and more susceptible to skin atrophy, such as the face.2 Tacrolimus ointment is the first potential new topical therapy for atopic dermatitis since the introduction of corticosteroids some 40 years ago. Tacrolimus is a novel macrolide molecule discovered for its ability to inhibit T-cell activation.5 SDZ ASM has a structure and activity similar to tacrolimus and might also be efficacious in atopic dermatitis when applied topically.6 The local action of tacrolimus on the skin of patients with atopic dermatitis seems to involve T cells, Langerhans cells, mast cells, and basophils.7 Short-term studies8-10 in adults and children have shown that tacrolimus ointment is effective and safe in the treatment of atopic dermatitis. Systemic absorption is minimal.11 Unlike topical corticosteroids, tacrolimus ointment does not cause skin atrophy; 7 days of application under occlusion in adults did not compromise collagen synthesis or cause skin thinning.12 Because atopic dermatitis is a chronic disease, there is a need for long-term assessment of patients treated with tacrolimus ointment. This study was undertaken to assess the safety and efficacy of tacrolimus ointment monotherapy for either 6 or 12 months in patients with moderate to severe atopic dermatitis.

PATIENTS AND METHODS

Study design
The primary focus of this long-term, open-label, noncomparative, multicenter phase 3 study was to assess the long-term safety of 0.1% tacrolimus ointment in adults with atopic dermatitis. The study was performed at 30 centers in 11 European countries; the ethics committee of each center reviewed the protocol.
and granted approval of the study before its implementation. Patients were assigned to either 6 or 12 months of study participation at entry. It was planned to enroll approximately 300 patients, with the first 120 to be assigned 12 months of participation. The sample size and duration of exposure were based on guidelines from the International Conference on Harmonisation that describe the extent of population exposure required to assess clinical safety with long-term use of a drug. The study consisted of a screening visit within 30 days before the baseline visit; a baseline visit (day 1); visits 1, 2, and 4 weeks after treatment initiation; and monthly visits thereafter.

**Patient selection**

Men and women aged 18 years and older with a diagnosis of atopic dermatitis based on the criteria of Hanifin and Rajka were eligible for study participation. Patients were also required to have an atopic dermatitis severity grading of moderate to severe according to the criteria of Rajka and Langeland and disease involvement of 5% to 60% of the total body surface area. The main exclusion criterion was a serious skin disorder other than atopic dermatitis. All patients gave informed consent.

**Treatment**

At baseline, investigators assessed areas to be treated, dispensed the first ointment supply box, and explained the dosing procedure to the patient. Treatment consisted of a thin coat of 0.1% tacrolimus ointment applied twice daily to areas of actively diseased skin. The treatment area could extend up to 60% of the total body surface area; this was extended to 100% of the total body surface area by protocol amendment after all patients had been enrolled. Patients were instructed to continue application for 1 week after cessation of itch and to change the treatment areas or select new areas based on the presence of itch. The treated area was assessed by the investigator at each study visit. Prohibited therapies were other investigational drugs, UV-A and UV-B light treatments, nonsteroidal immunosuppressive agents, and topical corticosteroids. Restricted therapies included systemic corticosteroids (2 treatment periods of 2 weeks each separated by 3 months and no treatment within the 4 weeks preceding the Recall Antigen Test) and nonsteroidal anti-inflammatory drugs (2 weeks of treatment within any 3-month period). Allowed therapies were bath oil, nonmedicated emollients, inhaled corticosteroids (patients with an immediate history of taking >1 mg/d were excluded), antihistamines, and anti-infective agents. ASSESSMENTS 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 to be related to use of the study drug. "Causally related" adverse
events were those assessed by the investigator as having a highly probable, probable, possible, not assessable relation to the study drug or adverse events for which such an assessment was not made. Except as noted, adverse event data are presented irrespective of the causality assessment. Laboratory assessments (hematology, clinical chemistry, and renal and hepatic function) were performed at the screening visit; day 1; weeks 1, 2, and 4; and once a month thereafter. The Recall Antigen Test was used at selected centers (based on experience) to assess delayed-type hypersensitivity reactions as an indirect measure of cellular immune response (Multitest CMI; Institut Mérieux, Lyon, France). At baseline and after 6 and 12 months, skin testing was carried out using an 8-pronged applicator containing 7 preloaded antigens and 1 vehicle control. Results were given as the sum of the diameters from positive reactions (Mérieux score) and the mean number of positive reactions.16 A test reaction of at least 2 mm in diameter (the mean of the maximum diameter and the diameter orthogonal to it) was regarded as positive. For determination of tacrolimus concentrations, whole blood samples were collected at day 1, week 1, week 2, month 1, month 3, and the last visit. The samples were assayed for tacrolimus concentration using a validated high-performance liquid chromatography method with repeated mass spectrometry. The limit of quantification was 0.025 ng/mL; intra-assay precision was 14.7% of the quantification limit.17 On day 1 of treatment; weeks 1, 2, and 4; and once a month thereafter, investigators rated erythema, edema/induration/papulation, excoriations, and lichenification on a scale from 0 to 3 and estimated the percentage of total body surface area affected by atopic dermatitis (0%-100%) for 4 body regions (head and neck, trunk, upper limbs, and lower limbs). Patients assessed the intensity of itch experienced during the previous 24 hours using a 10-cm visual analog scale, with 0 cm indicating "no itch" and 10 cm indicating "worst itch imaginable." These assessments were used to calculate the modified Eczema Area and Severity Index (mEASI). The mEASI is a variant of the EASI.18 The mEASI is identical to the EASI except that in the latter an assessment of itch is not included. Itch was included in the mEASI because it is considered a primary symptom of atopic dermatitis.14 The EASI and the mEASI have the advantage of including severity scores for individual symptoms of atopic dermatitis weighted according to the extent of affected body surface area. For each body region (head and neck, upper limbs, trunk, and lower limbs), the following steps were carried out: (1) an affected area score of 0 to 6 was assigned for the percentage of affected body surface area (0%-100%); (2) the individual ratings for erythema, edema/induration/papulation, excoriations, and lichenification were summed (0-3 for each of the 4 symptoms); (3) the sum of the individual symptoms (maximum = 12) was multiplied by the affected area score (maximum = 6) for a maximum of 72; (4) the head and neck subtotal was
multiplied by 0.1, the upper limb subtotal by 0.2, the trunk subtotal by 0.3, and the lower limb subtotal by 0.4, and all components were summed (maximum EASI = 72); and (5) the patient's assessment of itch was converted to an ordinal scale of 0 to 3 and then multiplied by the investigator's total affected area score (0-6) for a maximum itch score of 18. The EASI was summed with the itch score for a maximum mEASI of 90 (the sum of 72 and 18). Investigators also assessed overall clinical improvement using the following terms: cleared, 100%; excellent, 90% to 99%; marked, 75% to 89%; moderate, 50% to 74%; slight, 30% to 49%; no appreciable improvement, 0% to 29%; and worse, less than 0%.

Statistical analyses
The evaluable population comprised patients who received at least 1 application of tacrolimus and had at least 1 assessment after baseline. Data were summarized by descriptive statistics and frequency counts. The Mérieux score included only data from patients who had at least 1 positive reaction. A global dictionary, based on COSTART (coding symbols for thesaurus of adverse reaction terms), was used to code investigator terms. Some COSTART terms warrant explanation. The COSTART term "flu syndrome" was used to code investigator terms such as "cold," "common cold," "flu," "influenza," and "upper respiratory tract infection." Investigator terms for the COSTART term "infection" included "tonsillitis" and "viral infection," and "allergic reaction" was used to summarize events such as "conjunctivitis" and "rhinitis." "Alcohol intolerance" refers to facial flushing or facial skin irritation after consumption of alcoholic beverages. "Lack of drug effect" was used for investigator terms describing exacerbation or worsening of atopic dermatitis. "Skin burning" was used to refer to the sensation of skin burning or smarting. Adverse events were summarized by frequency counts. Cox regression analyses were used to assess any effect of cumulative ointment use on the time to first occurrence of selected adverse events.
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RESULTS

Patients
Of 341 patients screened, 316 were eligible for study entry. Two hundred patients were assigned to treatment for 6 months and 116 for 12 months. In total, 245 patients (77.5%) completed the study; 246 patients completed at least 6 months of therapy and 68 completed at least 12 months of therapy. Patient demographic and baseline characteristics are presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Patient Demographic and Baseline Disease Characteristics and Reasons for Withdrawal From the Study</th>
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<tbody>
<tr>
<td><strong>Planned Exposure</strong></td>
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<tr>
<td><strong>Age, mean ± SD (range), y</strong></td>
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<tr>
<td><strong>Age, median (range), y</strong></td>
</tr>
<tr>
<td><strong>Ethnic group, No. (%)</strong></td>
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<tr>
<td><strong>White</strong></td>
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<tr>
<td><strong>Black</strong></td>
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<tr>
<td><strong>Asian</strong></td>
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<tr>
<td><strong>Duration of episode, mo</strong></td>
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<tr>
<td><strong>Mean, SD</strong></td>
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<tr>
<td><strong>Median (range)</strong></td>
</tr>
<tr>
<td><strong>Severity of atopic dermatitis, No. (%)</strong></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
</tr>
<tr>
<td><strong>Severe</strong></td>
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<tr>
<td><strong>Total % affected body surface area, median (range)</strong></td>
</tr>
<tr>
<td><strong>Head and neck involvement, No. (%)</strong></td>
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<tr>
<td><strong>Reason for withdrawal, No. (%)</strong></td>
</tr>
<tr>
<td><strong>Lack of efficacy</strong></td>
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<tr>
<td><strong>Prohibited therapy</strong></td>
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<tr>
<td><strong>Adverse event</strong></td>
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<tr>
<td><strong>Administrative</strong></td>
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</tbody>
</table>

Comparison of the mean age of patients (31 years in the total study population) with the mean duration of atopic dermatitis (25 years in the total study population) indicates that most patients experienced onset of the disease during childhood. The long duration of the current episode (with a mean of several years) reflects a patient population with persistent disease. The affected body surface area was extensive at baseline (a median of approximately one third of total body surface area), and most patients had active disease on all body regions, including the head and neck. In total, 162 patients (51.3%) had a history of hay fever, 155 (49.0%) had a history of asthma, and 198 (62.7%) had other types of allergies; 259 patients (82.0%) had family members with a history of atopy. SAFETY The most common adverse events were related to local irritation; these were burning sensation, pruritus, and skin erythema (Table 2).
Table 2. Incidence of the Most Common Application Site Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>Application Site Only</th>
<th>Application Site and Nonapplication Site</th>
<th>Total†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin burning</td>
<td>138 (43.7)</td>
<td>12 (3.8)</td>
<td>148 (46.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>60 (19.0)</td>
<td>19 (6.0)</td>
<td>80 (25.3)</td>
</tr>
<tr>
<td>Skin erythema</td>
<td>28 (8.9)</td>
<td>10 (3.2)</td>
<td>39 (12.3)</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>21 (6.6)</td>
<td>7 (2.2)</td>
<td>34 (10.6)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>18 (5.7)</td>
<td>8 (2.5)</td>
<td>41 (13.0)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>18 (5.7)</td>
<td>19 (6.0)</td>
<td>37 (11.1)</td>
</tr>
<tr>
<td>Lack of drug effect</td>
<td>14 (4.4)</td>
<td>20 (6.3)</td>
<td>34 (9.5)</td>
</tr>
<tr>
<td>Alcohol intolerance</td>
<td>12 (3.8)</td>
<td>3 (0.9)</td>
<td>15 (4.6)</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>11 (3.5)</td>
<td>3 (0.9)</td>
<td>13 (4.1)</td>
</tr>
<tr>
<td>Pustular rash</td>
<td>10 (3.2)</td>
<td>3 (0.9)</td>
<td>13 (4.0)</td>
</tr>
</tbody>
</table>

*Based on COSTART (coding symbols for thesaurus of adverse reaction terms).
†Overall incidence of events that occurred exclusively at a treated site, at a treated site and a nontreated site, or exclusively at a nontreated site.

In practice, pruritus seemed related to burning; patients reported these events in the context of local discomfort. The incidence and intensity of these adverse events, particularly skin burning, decreased with time. For example, the incidence of skin burning at the application site was 45.3% of patients during days 1 to 4, 22.8% during days 5 to 8, and 7.9% during days 23 to 30. During months 10 to 12, only 2.1% of patients experienced this event. The higher incidence of events that occurred exclusively at a treated site compared with the incidence of those that occurred in a patient at both a treated and nontreated site (Table 2) suggests that skin burning, pruritus, skin erythema, folliculitis, herpes simplex, alcohol intolerance, and maculopapular rash were specific for the area of application. More than 90% of all patients treated the face, and herpes simplex (mostly labial) and alcohol intolerance ("facial flushing") were, by nature, localized on the face; thus, their relation to localized treatment is not clear. Folliculitis, maculopapular rash, and pustular rash are suspected to be related to the occlusive properties of the ointment. Because lack of drug effect and skin infection were not localized to the treated area (Table 2), these events probably represent a generalized flare-up of the disease. The most common nonapplication site events (irrespective of causality) during the 12-month study were flu syndrome (69/316, 21.8%); allergic reaction (66/316, 20.9%); infection
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(45/316, 14.2%); headache (32/316, 10.1%); herpes simplex (20/316, 6.3%); and asthma, pharyngitis, and rhinitis (each 15/316, 4.7%). Flu syndrome was reported most frequently during the winter months. There was otherwise no increase in the prevalence of any infection over time. In total, 6 patients (1.9%) experienced eczema herpeticum. There were 5 serious adverse events for which a causal relation with the study drug was unknown or considered possible; all were associated with hospitalization. These constituted 1 patient who experienced a severe flare-up of atopic dermatitis, 1 who experienced a Staphylococcus superinfection of the skin, 1 with eczema herpeticum (the patient had a long history of relapses), 1 with varicella, and 1 with cellulitis. All but cellulitis were present on the application site. Cox regression analyses were performed to assess the effect of cumulative ointment use on the time to first occurrence of skin infection, nonskin infection, adverse events of the digestive system, adverse events of the nervous system, and severe related adverse events that required medical intervention. No significant increase in the risk of these types of adverse events was found with increased cumulative ointment use. Laboratory measurements showed mean eosinophil counts and lactate dehydrogenase concentrations greater than the reference range at baseline and all study visits, as expected for this study population. All other mean laboratory values were within the reference range during the study and showed no marked changes over time. One patient experienced an increase in transaminase levels that resolved before treatment discontinuation. Median whole blood concentrations of tacrolimus were minimal during the study: 0.32 ng/mL at 1 week, 0.30 ng/mL at 2 weeks, 0.26 ng/mL at 1 month, 0.18 ng/mL at 3 months, 0.14 ng/mL at 6 months, and 0.13 ng/mL at 12 months. Throughout the study, a maximum concentration of less than 1 ng/mL was observed in 74.7% of patients (236/316), of 1 to less than 2 ng/mL in 16.8% of patients (53/316), and of 2 to less than 5 ng/mL in 5.4% of patients (17/316). Only 1 patient had a maximum concentration of 5 ng/mL or greater (5.75 ng/mL); all other blood concentrations for this patient were less than 1 ng/mL. All tacrolimus blood concentrations within the limit of quantification (0.025 ng/mL) were transient. Results of the Recall Antigen Test showed a patient population with depressed cell-mediated immunity at baseline, but no notable changes were observed with prolonged treatment. Mean Mérieux scores are shown in Figure 1. The mean + SD number of positive antigens was 1.3 + 1.2 at 1 day, 1.5 + 1.3 at 6 months, and 1.8 + 1.4 at 12 months. The proportion of patients with no positive reactions was also similar over time: 28 patients (33.3%) at 1 day, 16 (26.2%) at 6 months, and 5 (25.0%) at 12 months.
Figure 1. Results of the Recall Antigen Test. The Mérieux score is the sum of the diameters from positive reactions of 2 mm or greater after skin testing with an 8-pronged applicator containing 7 preloaded antigens and 1 vehicle control. Error bars represent SD.

Efficacy
The greatest decrease in symptoms, as measured by the mEASI, was seen during the first week of treatment (Figure 2). The mEASI continued to decrease until month 3, and maximal improvement was maintained during the rest of the study. Decreases in affected body surface area showed the same trend over time (Figure 2). The size of the treated area over time was nearly identical to the size of the affected area (data not shown). Ointment use also decreased; median daily ointment use was 3.9, 2.5, 2.0, and 2.3 g during months 1, 3, 6, and 12, respectively. The investigator's assessment of global improvement (Figure 3) shows that a substantial proportion of patients experienced at least marked (75%-100%) improvement by the end of the first week of treatment. As the study progressed, more patients experienced at least excellent (90%-100%) improvement. In terms of overall improvement, Figure 4 shows photographs of the face and neck of a woman before and after 8 days of treatment with 0.1% tacrolimus ointment. Figure 5 shows clinical improvement of atopic lesions on the legs after 6 months of treatment in a woman who had skin atrophy at baseline.
Figure 2. Mean modified Eczema Area and Severity Index score (A) and mean affected body surface area (B). The modified Eczema Area and Severity Index considers the affected body surface area and the severity of erythema, edema, excoriations, lichenification, and itch. Error bars represent SD.
Figure 3. Investigator's global assessment of clinical improvement.
Figure 4. Atopic dermatitis of the face and neck in an 18-year-old woman before treatment (A and B) and after 8 days of treatment with 0.1% tacrolimus ointment (C and D).
**Figure 5.** Atopic dermatitis and skin atrophy of the leg flexure regions before treatment (A) and after 6 months of treatment with 0.1% tacrolimus ointment (B).

**COMMENT**

This is the first study to assess the long-term safety and efficacy of tacrolimus ointment in adults with atopic dermatitis. The long-term (up to 1 year) safety profile of tacrolimus ointment observed in this study was similar to that of short-term trials. We surmise that the heightened local irritation at the start of treatment can be accounted for by the baseline disease severity and that the skin becomes more tolerant to the application of any agent as it heals during treatment. Apart from adverse events related to local irritation, the safety data collected in this study reflect concomitant illnesses and complications generally associated with atopic dermatitis. Adverse events not indicative of local irritation were mostly related to atopic dermatitis, atopy in general, infections associated with atopic dermatitis, and seasonal infections such as influenza. Given that there was no increase in any type of infection with prolonged treatment, and the overall incidence of infections was consistent with that anticipated for this patient population and follow-up period, it seems unlikely that tacrolimus ointment use contributes to an increased risk of infection. The skin of patients with atopic dermatitis is prone to colonization with aerobic bacteria and skin infection.19 In a pediatric study,20 with a mean follow-up of 13 months, 40% of patients experienced skin infection compared with 11% of patients in the present study. Patients with atopic dermatitis are also at high risk
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for recurrent herpes simplex infections. More than 5 episodes of cold sores per year were noted in approximately 8% of adult patients who had been hospitalized at least once during their childhood for atopic dermatitis compared with less than 1% in a control population.21 Relative to these data, the incidence of herpes simplex in the present study was consistent with that expected for this patient population and duration of observation. Eczema herpeticum is a complication of atopic dermatitis arising from herpes simplex infection that resembles varicella.22 Because cell-mediated immunity is critical for protection against recurrent viral infections, it has been proposed that the compromised cell-mediated immunity in patients with atopic dermatitis is responsible for their increased susceptibility to viral superinfections of the skin and the frequent recurrence of lower-grade viral skin infections.23 Compared with the incidence of eczema herpeticum demonstrated in a survey24 conducted at a single university clinic, which showed an incidence of approximately 12 patients per year from 1982 to 1986, the incidence observed in the present study (6 patients) is not remarkable. Findings from the Recall Antigen Test suggest that long-term treatment with tacrolimus ointment had no effect on circulating cell-mediated immunity. Consistent with results of previously published studies,23 a depressed cell-mediated immunity was observed at baseline. No change with long-term treatment was observed. Thus, any systemic immunosuppression seems unlikely. Systemic absorption of tacrolimus was minimal. The lack of a skin atrophogenic effect is a major advantage of tacrolimus ointment compared with conventional treatment with topical corticosteroids.12 Although it was not assessed systematically in this study, we suspect that the reversal of skin atrophy associated with long-term tacrolimus ointment use (Figure 5) was a result of the discontinuation of topical corticosteroid use. This is the first study, to our knowledge, in which topical corticosteroids were withheld from patients with atopic dermatitis for a prolonged period. To further evaluate this, it would be useful to assess collagen synthesis and skin thickness during long-term tacrolimus treatment. The results of this study are consistent with the time to improvement of atopic dermatitis observed previously in short-term, vehicle-controlled efficacy trials,7-10 ie, improvement was apparent by the first week of treatment. All efficacy parameters—the mEASI, the investigator's global assessment, and the investigator's assessment of the affected areas—showed greatest improvement after 1 week of treatment, continued increases in improvement until approximately month 3 of treatment, and maintenance of maximal improvement during prolonged treatment. However, these findings are limited in the context of a noncomparative, open-label design. In conclusion, the results of this study demonstrate that long-term treatment with tacrolimus ointment is safe and well tolerated in patients with moderate to severe atopic dermatitis. Local irritation
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seemed to be the only adverse event clearly related to the use of tacrolimus ointment; no systemic toxic effects were apparent. Clinical improvement was apparent after 1 week of treatment, and maximal improvement was maintained with prolonged treatment. This agent represents a promising new treatment for atopic dermatitis.

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