A topic dermatitis (AD), which can produce extreme itching, is an inflammatory skin disorder with childhood onset and a chronically relapsing course. A variety of treatment methods have been used, but no entirely satisfactory treatment exists for AD. Topical agents for treating AD, directed at controlling the predominant symptoms (e.g., erythema and pruritus), include the liberal use of emollients, corticosteroids, coal tar preparations, antibiotics, and antihistamines. Topical corticosteroid treatment has been the mainstay in AD therapy and has generally been well tolerated. However, long-term use of potent topical steroids is known to cause a variety of side effects, including skin atrophy, atrophic striae, purpura, rosacea-like eruptions, exacerbation of acne, glaucoma, and dermatophyte infections at the
application site, especially in the facial area where the skin tends to be more permeable.\(^3\) In addition, a rebound phenomenon with exacerbation of the AD and facial swelling frequently occurs after abrupt discontinuation of corticosteroid ointment after prolonged use.\(^5\) Nonsteroid alternatives have been sought which can safely suppress the aberrant immune activity associated with AD while avoiding the side effects of steroids.

The most important pathogenesis of AD is immunologic abnormalities, among others.\(^1\) Increased levels of circulating immunoglobulin E (IgE) antibodies reactive against airborne or ingested protein antigens are found in most patients.\(^1,6\) At the level of cellular immunity, both type 1 and type 2 populations of helper T cells appear to undergo proliferation; activation of these T-cell subsets leads to the overproduction of cytokines which initiates and sustains the dermal inflammation.\(^10\) In view of the emphasis on the immunopathogenesis, new inflammatory cytokine inhibitors have been under investigation.

Tacrolimus (FK506) is a nonsteroid inhibitor of T-cell activation, used to prevent organ transplant rejection through immunosuppression. It is a 23-member macrolide produced by Streptomyces tsukubaensis, and is the active ingredient of tacrolimus ointment.\(^7\) The molecular target of tacrolimus is calcineurin, a calcium-dependent phosphatase, which plays an essential role in the intracellular signal transduction pathway leading to the transcriptional activation of genes that encode various cytokines and which is necessary for the induction of IL-2 and subsequent T-cell activation.\(^8,9\) It is the first in a new class of topical immunomodulators. Topically applied tacrolimus acts locally via multiple cell types, including T cells, mast cells, basophils, and dendritic cells.\(^10\) It is active topically and has shown success in clinical trials as a treatment for AD.\(^11-13\) The purpose of this study was to evaluate the efficacy and safety of topically applied tacrolimus ointment (Protopic\(^8\)) in treating patients with AD at Chang Gung Memorial Hospital, Taipei, between March 12 and June 29, 2002. The enrolled patients were divided into pediatric (2-15 years old) and adult (16 and above) groups. The adult patients were treated with 0.1% tacrolimus ointment, while the pediatric patients were treated with 0.03% tacrolimus ointment at a usual dose of twice daily for up to 4 weeks. Patients who had received at least 3 consecutive days (a minimum of 5 applications) of the tacrolimus ointment beginning at baseline without protocol violation were included in the efficacy evaluable population. Patients who had received at least 1 application of tacrolimus ointment were included in the safety population. The protocol was approved by the Medical Ethics and Human Research Committee of Chang Gung Memorial Hospital (IRB # 90-176). The patients (and their parents/guardians) gave written informed consent before enrollment.

**Patient selection**

Male and female patients were enrolled in the study if they were diagnosed with AD using the Hanifin and Rajka criteria\(^14\) which was rated as moderate to severe using the Rajka and Langeland criteria\(^15\) and involved at least 10% of the body surface area. Patients were required to meet the inclusion criteria and follow specific pre-study and concomitant therapy restrictions (Table 1).

**Treatment plans**

A thin layer of 0.03% (for the pediatric group) or 0.1% (for the adult group) tacrolimus ointment was applied twice daily to active disease. Treatment of AD continued for 4 weeks or until approximately 1 week after complete clearance. Patients were evaluated at the baseline, and at weeks 1, 2, 3, and 4 (or at the end of treatment).

Efficacy was evaluated on the basis of the physician’s global evaluation of the clinical response (PG) at the end of treatment. Success was defined as a rating of better than moderate improvement (≥ 50% improvement). Other evaluations included the Eczema Area and Severity Index (EASI),\(^16\) the percent of body surface area (%BSA) affected, patient assessment of pruritus (visual analog scale), and a total score for the clinical signs. The EASI is a composite score calculated from the scores of individual

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**METHODS**

**Study design**

This was an open-labeled, non-comparative, single-center study to evaluate the efficacy and safety of topical tacrolimus ointment (Protopic\(^8\)) in treating patients with AD at Chang Gung Memorial Hospital, Taipei, between March 12 and June 29, 2002. The enrolled patients were divided into pediatric (2-15 years old) and adult (16 and above) groups. The adult patients were treated with 0.1% tacrolimus ointment, while the pediatric patients were treated with 0.03% tacrolimus ointment at a usual dose of twice daily for up to 4 weeks. Patients who had received at least 3 consecutive days (a minimum of 5 applications) of the tacrolimus ointment beginning at baseline without protocol violation were included in the efficacy evaluable population. Patients who had received at least 1 application of tacrolimus ointment were included in the safety population. The protocol was approved by the Medical Ethics and Human Research Committee of Chang Gung Memorial Hospital (IRB # 90-176). The patients (and their parents/guardians) gave written informed consent before enrollment.

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**METHODS**

**Study design**

This was an open-labeled, non-comparative, single-center study to evaluate the efficacy and safety of
signs of AD combined with the %BSA affected in each of the 4 body regions; it has a maximum score of 72. Patients assessed pruritus by means of a 10-cm visual analog scale (0 cm, no itching; 10 cm, worst itching imaginable). Clinical signs of AD included erythema, edema/induration/papulation, excoriation, oozing/weeping/crusting, scaling, and lichenification in each of the 4 body regions (head and neck, trunk, upper limbs, and lower limbs). A standard severity grading scale (0, absent; 1, mild; 2, moderate; 3, severe) was used to rate each sign/symptom. The clinical score for each of the clinical signs was the average value for each clinical parameter for all body regions being treated. The total score for the clinical signs was the sum of the clinical scores for each of the 6 clinical signs plus the pruritus score (analog scale converted to a 4-point score).

For the safety evaluation, patients were assessed at the baseline, and at weeks 1, 2, 3, and 4 (or at the end of treatment). Blood was collected at the baseline, week 1, and week 4 (or at the end of treatment) for hematology and chemistry profiles and tacrolimus concentrations. The blood concentration of tacrolimus was determined at least 2 hours after ointment application by a validated IMX® method, with the lower limit of quantitation (LOQ) of 1.5 ng/ml (IMX® tacrolimus II assay; Abbott Diagnostics, Abbott Park, IL, USA). The IMX system is an automated analyzer designed to perform a microparticle enzyme immunoassay, a fluorescence polarization immunoassay, and ion capture technologies. Other laboratory parameters, including complete blood cell count with differential count (CBC/DC), IgE, and blood chemistry, were also evaluated. The incidence of adverse events and changes from the baseline of clinical laboratory values were also recorded.

Statistical methods

The statistical analysis of the pediatric and adult groups was performed separately on the same set of parameters. All statistical tests were 2-sided with a significance level of \( \alpha < 0.05 \) unless otherwise specified. Descriptive statistics such as the number of observations, mean, standard deviation, minimum, and maximum, were used to summarize the continuous variables. Frequency and proportion were used to summarize the categorical variables. The last observation carried forward (LOCF) approach was used to evaluate missing data for all populations.

Demographics and other baseline information were tabulated. For efficacy end point-repeated measures, repeated measures ANOVA followed by contrast was used to evaluate the effects before and after treatment. Adverse events and concomitant medication were tabulated for each group.

RESULTS

Demographics and baseline characteristics

In total, 30 patients were enrolled, including 16 pediatric and 14 adult patients. Five patients withdrew due to adverse events, poor compliance, or

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Table 1. Pre-study and Concomitant Therapy Restrictions and Conditions Excluding Patients from Study Participation

<table>
<thead>
<tr>
<th>Restricted therapy</th>
<th>Washout period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Terfenadine, other non-sedating antihistamines</td>
<td>7 days</td>
</tr>
<tr>
<td>Other investigated drugs, nonsteroid immunosuppressants, light treatments (UVA, UVB), systemic corticosteroids</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Intranasal and/or inhaled corticosteroids, if &gt; 2 mg of prednisone equivalent required per day</td>
<td>14 days</td>
</tr>
<tr>
<td>Topical corticosteroids, topical H1 and H2 antihistamines, topical antimicrobials, other medicated topical agents</td>
<td>7 days</td>
</tr>
<tr>
<td>Non-medicated topical agents (including creams, lotions, and emollients) in areas to be treated with study medication</td>
<td>1 day</td>
</tr>
</tbody>
</table>

Exclusion criteria

Other serious skin disorder, pigmentation, or extensive scarring in affected areas
Clinically infected atopic dermatitis
Any systemic disease that would contraindicate the use of tacrolimus ointment
Any chronic condition that was not well controlled
Pregnancy or lactation
reluctance to give blood samples. In the pediatric group, 13 patients (7 with moderate AD and 6 with severe AD) were enrolled in the efficacy evaluation, and 16 patients were included in the safety evaluation. In the adult group, 12 patients (3 with moderate AD and 9 with severe AD) were enrolled in the efficacy evaluation, and 14 patients were included in the safety evaluation.

The baseline demographic information of the pediatric and adult patients (including age, gender, severity, and %BSA affected) is summarized in Table 2. It was also found within the enrolled patients that 68.8% (11/16) of pediatric patients and 71.4% (10/14) of adult patients had a personal history of 1 of the following: asthma, allergic rhinitis, or other allergies. And 12.5% (2/16) and 43.8% (7/16) of pediatric patients had currently active asthma and allergic rhinitis, respectively. The majority of pediatric (93.8%, 15/16) and adult patients (85.7%, 12/14) had a family history of asthma or allergic rhinitis. The average lengths of time afflicted with AD in pediatric and adult patients were 2.69 and 8.86 years, respectively.

### Efficacy parameters

#### Physician’s global evaluation of clinical response

There were 13 patients in the pediatric group and 12 patients in the adult group for the efficacy analysis. Since no patient obtained complete clearance by the end of the 4-week study period, all patients were treated with tacrolimus ointment for 4 weeks. The primary efficacy outcome was PG at week 4. Success was defined as ≥ 50% improvement (defined as "success", including cleared, and excellent, marked, or moderate improvement). The success rate at week 1 was 30.8% for the pediatric and 50% for the adult group. The success rate at week 4 was 92.3% for the pediatric and 100% for the adult group. According to the protocol, patients were evaluated on a predetermined schedule, i.e., every week after enrollment. The success rates of both the pediatric and adult groups by different severities at each time point are presented in Fig. 1 and Table 3.

The secondary efficacy outcomes were the EASI score, changes from baseline in %BSA affected, the patient assessment of pruritus, and the total score for clinical signs.

### Table 2. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Pediatric (N = 16)</th>
<th>Adult (N = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year) (mean±std)</td>
<td>7.9±4.24</td>
<td>22.1±5.97</td>
</tr>
<tr>
<td>Range</td>
<td>2-14</td>
<td>16-36</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 9 (56.25%)</td>
<td>7 (50.0%)</td>
</tr>
<tr>
<td></td>
<td>Female 7 (43.75%)</td>
<td>7 (50.0%)</td>
</tr>
<tr>
<td>Severity</td>
<td>Moderate 8 (50.0%)</td>
<td>4 (28.6%)</td>
</tr>
<tr>
<td></td>
<td>Severe 8 (50.0%)</td>
<td>10 (71.4%)</td>
</tr>
<tr>
<td>%BSA affected</td>
<td>(mean±std) 35.1±20.64</td>
<td>65.9±22.52</td>
</tr>
<tr>
<td>Range (min-max)</td>
<td>12-77.8</td>
<td>21.2-94</td>
</tr>
</tbody>
</table>

### Fig. 1 Success rate (≥ 50% improvement) at week 1 (open bar) and week 4 (solid bar) for moderate and severe AD of the pediatric and adult groups.

### Table 3. Response Rate

<table>
<thead>
<tr>
<th>Efficacy evaluation population</th>
<th>Pediatric (N = 13)</th>
<th>Adult (N = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Response at week 1</td>
<td>4/7 (57.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Response at week 2</td>
<td>4/7 (57.1%)</td>
<td>5/6 (83.3%)</td>
</tr>
<tr>
<td>Response at week 3</td>
<td>6/7 (85.7%)</td>
<td>5/6 (83.3%)</td>
</tr>
<tr>
<td>Response at week 4/ (end of treatment)</td>
<td>6/7 (85.7%)</td>
<td>6/6 (100%)</td>
</tr>
</tbody>
</table>
EASI and %BSA affected

At baseline the EASI score was 15.2 for the pediatric and 26.8 for the adult group, whereas at week 4, it was 7.8 for the pediatric and 9.3 for the adult group. The EASI score at the end of treatment had improved by 48.0% and 63.4%, respectively, for the pediatric and adult groups (Fig. 2). The change in the EASI score from baseline to the end of treatment was significant ($p \leq 0.01$) in both groups. A significant change in the %BSA affected from the baseline to the end of treatment was also observed ($p \leq 0.01$ for both the pediatric and adult groups). The %BSA affected at the baseline was 34.6% for the pediatric and 63.4% for the adult groups, whereas it was 22.5% and 39.5%, respectively, at week 4. The %BSA affected at the end of treatment had improved by 35.0% in the pediatric and 37.7% in the adult group (Fig. 3).

Patient assessment of pruritus and total score of clinical signs

Both pediatric and adult groups showed a statistically significant decline ($p \leq 0.01$) in pruritus as assessed by patients using a visual analog scale. The itching score declined by 41.5% in the pediatric and by 54.2% in the adult group.

The total score for clinical signs was the sum of the clinical scores for each of the 6 clinical signs plus the pruritus score. Change in the total score from the baseline to the end of treatment are shown in Fig. 4. A significant improvement ($p \leq 0.01$) was observed in both groups.

Figures 5-9 illustrate selected lesions over time in various patients.

Safety

Tacrolimus blood concentrations were monitored at baseline, week 1, and week 4. None of the patients who had blood samples collected during treatment had a quantifiable tacrolimus blood concentration (i.e., concentrations were below the limit of quantitation (LOQ): 1.5 ng/ml) at the baseline. Four patients had a detectable blood tacrolimus concentration (all below 5 ng/ml) at the week 1 visit.
but it had dropped to below the LOQ by week 4. Another 2 cases had detectable blood tacrolimus concentrations of 2.9 and 1.8 ng/ml, respectively, at week 4. This indicates that minimal absorption of tacrolimus occurred through affected skin.

**Adverse events**

Adverse events were recorded based on the spontaneous reports by patients or on being detected by the investigator. Nine pediatric patients and 11 adult patients reported at least 1 adverse event, regardless of whether or not the causality was related to the study medication. All adverse events were mild to moderate in severity and were transient. The incidence rate of treatment-related adverse events (excluding those events rated as "not related" and "unknown") was 56.25% (9/16) for pediatric and 78.6% (11/14) for adult patients. A summary of

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Fig. 5 Neck and upper chest of a 17-year-old man with severe atopic dermatitis at the baseline (A) and at week 4, (B) with excellent improvement at the end of 0.1% tacrolimus ointment treatment.

Fig. 6 Face of a 23-year-old woman with severe atopic dermatitis at the baseline (A) and at week 4, (B) with great improvement at the end of 0.1% tacrolimus ointment treatment.
treatment-related adverse events separated into moderate and severe groups of both pediatric and adult patients is presented in Table 4.
Laboratory parameters

The laboratory tests were performed at the baseline and week 4. No consistent changes or notable differences in laboratory profiles of either age group were observed. As can be expected in patients with AD, eosinophil count, IgE, and lactate dehydrogenase (LDH) were elevated in some patients at the baseline and remained so throughout the study. All other parameters remained within normal ranges throughout the study.

**DISCUSSION**

In previous studies, tacrolimus ointment had been proven to be significantly more effective than the vehicle$^{(12,13)}$ and to have a comparable efficacy with mid-potent to potent topical corticosteroids, such as 0.1% hydrocortisone butyrate ointment$^{(18)}$ or hydrocortisone acetate ointment.$^{(19)}$ In our study, most patients treated with tacrolimus ointment demonstrated moderate improvement (>$50\%$ PG) or better by the end of treatment (4 weeks). Improvement was apparent even only 1 week after starting treatment for patients with moderate AD ($57.1\%$ for the pediatric and $100\%$ for the adult group). Patients with severe AD responded more slowly ($0\%$ for pediatric and $33\%$ for adult patients at week 1) but still showed a good response by week

**Fig. 9** Anterior trunk of an 8-year-old boy with severe atopic dermatitis at the baseline (A) and at week 4, (B) with great improvement at the end of $0.03\%$ tacrolimus ointment treatment.

<table>
<thead>
<tr>
<th>Table 4. Treatment-related Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
</tr>
<tr>
<td>Severity at baseline</td>
</tr>
<tr>
<td>Skin burning</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Folliculitis</td>
</tr>
<tr>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
</tr>
</tbody>
</table>
4 (Fig. 1). The secondary end-point for the efficacy assessment, including the EASI score, the %BSA affected, patient assessment of pruritus (using a visual analog scale), and the total score for the clinical signs, demonstrated satisfactory improvement. Improvement was apparent even 1 week after starting treatment for most patients (Figs. 5-9).

The majority of adverse events associated with tacrolimus ointment occurred at the site of drug application. The most common adverse events were 'skin burning' and pruritus (Table 3), which tended to decrease after the first few days of treatment as disease status improved and lesions healed. The complications occurred randomly and were not related to the severity of AD or age of patients. Complications appeared to have been tolerable by most patients. However, 2 of our patients decided to drop out of the study due to moderate burning with ointment application. No serious adverse event was observed in any patient in this study. In other studies of tacrolimus, a low incidence of infectious events was reported, but they were of clinical interest, including herpes simplex, molluscum contagiosum, verruca vulgaris, and influenza. Since AD patients are predisposed to superficial skin infections and extracutaneous infection such as upper respiratory tract infections, the infection conditions are related to the atopic diathesis of these patients instead of being drug-related. In the pediatric group of our study, 1 patient experienced a herpes simplex virus infection, and 1 patient suffered from a flu-like syndrome. Folliculitis was found in 2 adult group patients; and it is possible that the occlusive properties of the ointment vehicle contributed to its development. No changes in laboratory profiles that would indicate a safety concern were observed.

Topical steroids have been the standard treatment for AD, but they are also known to decrease collagen synthesis and inhibit proliferation of cultured human skin fibroblasts. Because AD is a chronic disease, long-term treatment with topical corticosteroids is inappropriate due to the unacceptable risk of local and systemic side effects. The efficacy and safety of tacrolimus ointment monotherapy are of particular benefit for AD patients with persistent disease. The results of the study suggest that Protopic® ointment may be a safe and effective therapy in treating patients at least 2 years of age with moderate to severe atopic dermatitis. Tacrolimus ointment provides an alternative to conventional therapies, in particular topical corticosteroids, for which there are safety concerns with chronic use and many reported adverse events (e.g., atrophy, hypopigmentation, telangiectasia, etc.). With a selective and specific mechanism of action, rapid onset, and minimal side effects, tacrolimus ointment offers significant advantages in the management of AD. This study was conducted for only 4 weeks. Because AD is a chronic disease, there is a need for long-term assessment of patients treated with tacrolimus ointment in Taiwan. The long-term safety profile of tacrolimus ointment is still under investigation.

REFERENCES


Tacrolimus藥膏對中至嚴重程度之異位性皮膚炎患者之有效性及安全性

翁韻柔 蔡翔如 洪宏翔

背景：Tacrolimus可選擇性抑制T細胞。局部塗敷劑型（普特皮®）可用於包括異位性皮膚炎的一些發炎性的皮膚疾病。此研究的目的在於評估普特皮®對於治療台灣中重度異位性皮膚炎患者的有效性及安全性。

方法：為開放性、無對照組單一中心之臨床研究。患者按常用藥量，每日塗敷2次普特皮®達4週。療效評估是依據醫師整體評估 (PG)，濕疹面積與嚴重度指標 (EASI)、治療後患部之體表面積 (%BSA) 改變、以及整體分數之評估。本藥品之安全性則是由病患的tacrolimus血中濃度以及所經歷之不良反應來評估。

結果：共納入30位中至嚴重程度之異位性皮膚炎患者。包含16位病患之孩童組 (2至15歲者)及14位病患之成人組 (大於16歲者)。結果顯示當4周治療結束時，有療效反應之病患比例在孩童組為92.3%，在成人組為100%。另外，所有患者的療效評估亦指出，普特皮®可改善異位性皮膚炎之症狀。除了2例病患，所有病患之tacrolimus血中濃度均低於偵測值下限。常見之不良反應為皮膚灼熱感與癢，這些通常是輕微且短暫的。

結論：試驗結果建議普特皮®軟膏對兩歲以上之異位性皮膚炎病患，為一兼具有有效性與安全性的治療藥物。

(長庚醫誌 2003;26:485-95)

關鍵字：異位性皮膚炎，普特皮®。