

Pharmacology and therapeutics

Overview of efficacy and safety of tacrolimus ointment in patients with atopic dermatitis in Asia and other areasKyu-Han Kim^{1,2}, MD, and Takeshi Kono^{1,2}, MD

¹Department of Dermatology, Seoul National University Hospital, Seoul, Korea, and ²Department of Dermatology, Nippon Medical School, Tokyo, Japan

Correspondence

Dr. Kyu-Han Kim, MD
Seoul National University Hospital
101 Daehang-ro, Jongno-gu
Seoul 110-744
Korea
E-mail: kyuhkim@snu.ac.kr

Conflict of interest: None.

Abstract

Objective To assess the efficacy and safety of tacrolimus ointment in a large population of patients with atopic dermatitis (AD) by pooling data from individual Asian studies, and to compare the results of this study with those in the United States, Europe, and Japan.

Materials and methods We analyzed the pooled data from individual studies conducted in the eight Asian areas. The efficacy assessments included success rate based on Physician's Global Evaluation of Clinical Response, Eczema Area Severity Index (EASI), Percent Body Surface Area (%BSA) affected, Patient's Assessment of Itch (Itch), Dermatology Life Quality Index (DLQI) and children's DLQI (CDLQI). The results that were published in the United States, Europe, and Japan were cited.

Results A total of 860 patients were included in this study. The success rates were more than 80% in both adult and pediatric patients. Similar success rates were shown in the United States, European, and Japanese studies. There were no differences in the improvements in %BSA affected, EASI, and Itch between this study and the United States study. In both Asia and the United States, tacrolimus therapy improved total quality of life and all subscales in DLQI and CDLQI. Skin burning and pruritus were common adverse events among the Asian, United States and European studies.

Conclusions Tacrolimus ointment is an effective and well-tolerated treatment option in patients with AD in Asia. In this study, the efficacy and safety of tacrolimus are similar to those in the United States, European, and Japan studies.

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease with severe pruritus and eczematous lesions. The condition significantly affects quality of life (QOL) in both adult and pediatric patients with AD. Particularly, patients have an impaired QOL, such as sleep disorder affected by itch.¹

Tacrolimus is a calcineurin inhibitor that suppresses T-lymphocyte activation.² Tacrolimus ointment has been approved to treat adult and pediatric patients with AD worldwide, and many reports of tacrolimus ointment therapy have been published in Europe, North America and Japan.^{1,3-13} Tacrolimus ointment (0.03 and 0.1%) has been shown to be effective and safe for treatment of AD in the above studies. In European studies, patients who received tacrolimus ointment had low systemic exposure to tacrolimus, and there was no report of systemic accumulation.^{14,15}

Recently, clinical studies on the efficacy and safety of tacrolimus have been conducted in different parts of Asia.¹⁶⁻²⁰ There have been few studies reported on the

efficacy and safety in a large population of Asian patients with AD. In eight Asian areas, single-arm open-label multi-center studies were conducted to assess the efficacy and safety of tacrolimus ointment in patients. Each of the studies was conducted based on the same study protocol. The main objectives of this pooled analysis were:

- 1 to describe the efficacy and safety of tacrolimus ointment in patients with AD in individual Asian studies;
- 2 to assess the efficacy and safety of tacrolimus ointment in a large population of Asian patients with AD by pooling the data from individual Asian areas; and
- 3 to compare the results in the Asian study with those in USA, Europe, as well as Japan.

Materials and methods**Study design**

The data of individual studies in eight Asian areas were included in the pooled analysis. These open-label, single-arm, multi-center studies were conducted in Asian areas (China, Indonesia, Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand). The tacrolimus arms of the Chinese study

were also included in the analysis associated with the other Asian studies, which was conducted by randomized, double-blind, vehicle-controlled, multicenter. The study protocol was approved by the institutional review board and performed in accordance with the standards of the Declaration of Helsinki.

Patient selection

Adult and pediatric patients were required to have a diagnosis of AD on the basis of Hanifin and Rajka criteria,²¹ an AD severity grading of moderate to severe based on Rajka and Langeland criteria,²² and more than 10% of the body surface area (BSA). Baseline disease severity of the patients included in the analysis is shown in Table 1. The exclusion criteria were as follows: any serious skin disorders, pigmentation or extensive scarring in affected areas that would interfere with efficacy parameters; clinically infected AD at baseline; any systemic disease; pregnancy or lactation; and any chronic condition that was not well controlled. The prohibited therapies prior to the study were Astemizole, other investigational drugs, non-steroidal immunosuppressants, phototherapy, systemic corticosteroids, intranasal and/or inhaled corticosteroids, topical corticosteroids, topical H₁ and H₂ antihistamines, terfenadine, and other non-sedating systemic antihistamines.

Treatment plan

Adult patients applied 0.1 or 0.03% tacrolimus ointment, and pediatric patients applied 0.03% tacrolimus ointment twice daily to the areas of active disease for 3–4 weeks. Patients were prohibited systemic or topical corticosteroids and immunosuppressive drugs during the study. They were permitted to take sedating antihistamines if on a stable dose at baseline and allowed to use emollients as needed to non-treatment areas of the body throughout the study.

Assessment

The primary efficacy endpoint was Physician's Global Evaluation of Clinical Response. Physician's Global Evaluation of Clinical Response was performed at the end of treatment (week 3 or 4). The overall change of improvement of the lesions of AD was graded by a physician only in affected areas at baseline, using the following scales: "Cleared" = 100%; "Excellent Improvement" = 90–99%; "Marked Improvement" = 75–89%; "Moderate Improvement" = 50–74%; "Slight Improvement" = 30–49%; "No Appreciable Improvement" = 0–29%; and "Worse" = <0%. The success of treatment was defined as a rating of at "Moderate Improvement" and above (≥50% improvement).

Other evaluations included Eczema Area Severity Index (EASI), %BSA Affected, Patient's Assessment of Itch, Patient's Assessment of Overall Response, and each subscale of Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI).

Patient's Assessment of Overall Response was recorded at the end of treatment. This evaluation was defined as follows: "Much Better;" "Better;" "Slightly Better;" "Same;" "Slightly Worse;" "Worse;" and "Much Worse." Success was defined as a rating of at least "Slightly Better."

The percentage of BSA affected was evaluated for each of the four body regions (head and neck; upper limbs; trunk; and lower limbs) at baseline/day 1, and at weeks 1 and 2 and at the end of treatment.

The EASI was calculated from scores assigned to the four individual signs of AD (erythema; edema/induration/population; excoriations; and lichenification), and area score in head and neck, upper limbs, trunk, and lower limbs at baseline/day 1, and at weeks 1 and 2 and at the end of treatment.²³ The maximum EASI score possible was 72.

The Patient's Assessment of Itch was assessed by a 10-cm visual analog scale (0 cm = no itch; 10 cm = worst itch imaginable) at baseline/day 1, and at weeks 1, 2 and at the end of treatment.

DLQI²⁴ for adults and CDLQI²⁵ for children were evaluated by the questionnaire to measure how much a patient's disease had affected their lives over the last weeks. The response to each questionnaire was defined as 0–3 (0 = not at all affected; 3 = very much affected). DLQI was summarized under six subscales: "Symptoms and feelings;" "Leisure;" "Personal relationships;" "Treatment;" "Work and school;" and "Daily activities." The CDLQI was summarized under six subscales: "Symptoms and feelings;" "Leisure;" "Personal relationships;" "Treatment;" "School or holidays;" and "Sleep." Total QOL score was calculated by summing the score of each question. Total QOL score and the six subscales were expressed as a percentage of the respective maximum scores. The reliability and validity of DLQI were assured in the review, which included data from the Asian population.²⁶ Safety was assessed by adverse events reported by patients or observed by physicians.

Statistical analysis

Comparison for the incidence of adverse events between adult patients and pediatric patients was carried out using a Chi-square test. To measure the relationships between the improvements in the efficacy assessments and QOL scores, Pearson's product-moment correlation coefficients were calculated in the available data from Korean and Taiwanese studies. The tests for Pearson's product-moment correlation coefficients were carried out, and *P*-values of <0.05 were regarded as significantly correlated.

Results

Study demographics and baseline disease severity

A total of 860 patients were included in this Asian study. Of these patients, 811 were included in the efficacy analysis. There were 58 (6.7%) patients who did not complete

Table 1 Efficacy and safety results in each Asian study

Dose (%)	Age group	Withdrawn from study			Baseline disease severity			Efficacy evaluation					Safety evaluation	
		N	Total (%)	Adverse events (%)	Lack of efficacy (%)	Severe (%)	Moderate (%)	Success rate evaluated by physicians ^a (%)	Success rate evaluated by patients ^b (%)	%BSA affected	EASI	Patient's assessment of itch	Skin burning ^c (%)	Pruritus ^d (%)
Malaysia	0.1/0.03	Adult	36	2.8	0.0	36	64	97.1	97.1	-23.6 ^e	-13.5 ^e	-3.8 ^e	91.7	77.8
	0.03	Pediatric	37	8.1	0.0	76	24	91.2	97.1	-35.5 ^e	-15.6 ^e	-4.4 ^e	48.6	67.6
Thailand	0.1	Adult	49	4.1	0.0	24	76	97.6	93.0	-	-	-3.8 ^e	57.1	20.4
	0.03	Pediatric	61	4.9	0.0	52	48	94.7	94.8	-	-	-4.1 ^e	23.0	16.4
Indonesia	0.1	Adult	34	3.0	0.0	21	79	73.3 ^f	80.0 ^f	-	-9.8 ^e	-	14.7	17.6
	0.03	Pediatric						83.3 ^f	83.3 ^f	-	-10.4 ^e	-		
Singapore	0.1/0.03	Adult	19	10.5	0.0	68	32	70.6	70.6	-37.2 ^e	-	-2.5 ^e	47.4	42.1
Philippines	0.1/0.03	Adult and pediatric	100 ^g	0.0	0.0	16	70	94.6	100.0	-14.4 ^e	-	-	10.0	7.0
Taiwan	0.1	Adult	42	7.1	0.0	71	29	84.2	100.0	-20.3 ^e	-18.7 ^e	-3.5 ^e	81.0	40.5
	0.03	Pediatric	26	0.0	0.0	73	27	80.8	88.5	-26.3 ^e	-18.8 ^e	-2.8 ^e	34.6	23.1
Korea	0.1	Adult and pediatric	57	7.0	1.8	30	70	-	-	-	-13.3 ^e	-3.3 ^e	31.6	12.3
	0.03	Adult	180 ^h	11.1	1.7	-	-	64.8	83.6	-	-11.6 ^e	-	47.2	43.3
China	0.1	Adult	74	8.1	2.7	31	69	92.6 ^f	94.1 ^f	-24.1 ^{ef}	-15.4 ^{ef}	-3.0 ^{ef}	39.2	36.5
	0.03	Adult	75	8.0	0.0	27	73	75.4 ^f	89.9 ^f	-15.9 ^{ef}	-11.5 ^{ef}	-2.4 ^{ef}	28.0	32.0
		Pediatric	70	10.0	1.4	41	59	90.5 ^f	95.2 ^f	-25.5 ^{ef}	-15.2 ^{ef}	-3.1 ^{ef}	20.0	30.0
Total	0.1/0.03	Adult	295	6.8	1.0	38	62	80.0	90.3	-21.9 ^e	-13.1 ^e	-2.8 ^e	51.1	36.8
	0.03	Pediatric	194	6.7	2.1	56	44	85.3	90.5	-28.3 ^e	-14.6 ^e	-3.2 ^e	28.0	28.9
	0.1/0.03	Adult and pediatric	860 ⁱ	6.7	1.3	30	47	83.6	91.6	-22.2 ^e	-13.7 ^e	-3.0 ^e	38.0	31.9

^aSuccess rate based on physician's global evaluation of clinical response. Success was defined as a rating of better than moderate improvement ($\geq 50\%$ improvement).^bSuccess rate based on patient's assessment of overall response. Success was defined as a rating of slightly better and above.^cIncidence rates of skin burning include stinging, pain and soreness.^dIncidence rates of pruritus include itch and worsening of pruritus.^eMean changes from baseline to the end of treatment.^fThe end of treatment was week 3.^gTwenty patients were mild, and two patients were moderate to severe.^hTwenty patients were mild, and 180 patients were moderate to severe.ⁱTwenty patients were mild, two patients were moderate to severe, and 180 patients were moderate to severe.

the study ("Withdrawn from Study" in Table 1). The most common reasons for the withdrawals were for administrative reasons, such as follow-up loss, withdrawal of consent, and non-compliance. Other reasons for the withdrawals were adverse events (1.3% of patients) and lack of efficacy (1.4% of patients). At baseline, 30.1% of patients had severe, 47.3% had moderate, and 1.4% had mild AD ("Baseline disease severity" in Table 1). In the remaining 21.2%, disease severity of individual patients was reported to be moderate to severe. Reasons for withdrawal were similar among the studies included in this Asian study. In each study, withdrawals due to adverse events or lack of efficacy occurred less frequently.

Success rate based on physician's global evaluation of clinical response and patient's assessment of overall response

Success of treatment based on physician's global evaluation of clinical response was observed in 83.6% of total patients ("Efficacy evaluation" in Table 1). The success rates in adult and pediatric patients were 80 and 85.3%. In each study, most adult and pediatric patients were rated as success based on physician's global evaluation of clinical response at the end of treatment.

Success of treatment based on patient's assessment of overall response was observed in 91.6% of total patients ("Efficacy evaluation" in Table 1). At least "slightly better" was obtained in 90.3% of adult patients and 90.5% of pediatric patients. In each study, most adult and pediatric patients were rated as success based on patient's assessment of overall response at the end of treatment.

Percent BSA affected, EASI and patient's assessment of itch

In total patients, the change from baseline in %BSA affected was -22.2% at the end of treatment ("Efficacy

evaluation" in Table 1). The changes in %BSA affected in adult and pediatric patients were observed to be -21.9 and -28.3%, respectively. Topical tacrolimus therapy showed the improvements in %BSA affected in each of the Asian studies.

In total patients, the change from baseline in EASI was -13.7 at the end of treatment ("Efficacy evaluation" in Table 1). The changes in EASI were observed to be -13.1 and -14.6 in adult and pediatric patients, respectively. Topical tacrolimus therapy showed the improvement in EASI in each of the Asian studies.

In total patients, the change in patient's assessment of itch measured by VAS score from baseline was -3 cm at the end of treatment ("Efficacy evaluation" in Table 1). The changes in patient's assessment of itch were observed to be -2.8 and -3.2 cm in adult and pediatric patients, respectively. Tacrolimus therapy showed the improvements in patient's assessment of itch in each of the Asian studies.

DLQI and CDLQI

A decrease in the scores of DLQI and CDLQI indicates improvement in patient's QOL. The improvements in total QOL score from baseline to the end of treatment were observed in adults and children.

In the analysis of each DLQI subscale for adults, all DLQI subscales were improved by tacrolimus therapy (Fig. 1a). The subscale "Symptoms and feelings" had the greatest improvement in all DLQI subscales. Tacrolimus therapy showed the marked improvement in "Leisure" and "Daily activities" during the treatment period. The other three subscales ("Work and school," "Treatment" and "Personal relationship") also had improvements during the treatment period.

Tacrolimus therapy showed improvements in all the CDLQI subscales for children (Fig. 1b). "Symptoms and feelings" had the greatest improvement compared with

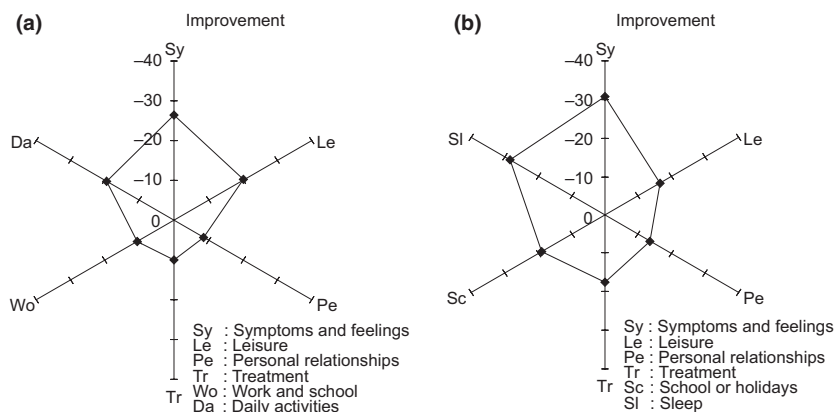


Figure 1 Changes in QOL from baseline to the end of treatment in the Asian adults (a) and children (b)

other CDLQI subscales. The improvement in "Sleep" was nearly equal to that in "Symptoms and feelings." In the other four subscales ("Leisure," "School or holiday," "Treatment," and "Personal relationship"), the improvements from baseline were observed during the treatment period.

The analysis in detail was made on the relationship between improvements in efficacy assessments and QOL scores in children from Korean and Taiwanese studies ($N = 73$). Itch, "Symptoms and feelings," and "Sleep" are considered to be the main symptoms in AD and, in this Asian study, markedly improved by topical tacrolimus therapy. A relationship was found between the patient's assessment of itch and the two CDLQI subscales (i.e. "Symptoms and feelings" and "Sleep;" Fig. 2). The improvement in patient's assessment of itch correlated with the improvement in "Sleep" ($r = 0.35$, $P < 0.01$). Such a relationship was also seen between patient's assessment of itch and "Symptoms and feelings" ($r = 0.41$, $P < 0.01$). "Sleep" and "Symptoms and feelings" correlated with each other ($r = 0.40$, $P < 0.01$).

Safety results

The most common adverse events were skin burning and pruritus in both adult and pediatric patients ("Safety evaluations" in Table 1). Skin burning was observed in 38% of patients. The incidences of skin burning were 51.1 and 28% in adult and pediatric patients, respectively ($P < 0.05$). Pruritus was reported in 31.9% of patients. The incidences of pruritus were 36.8 and 28.9% in adult and pediatric patients, respectively (no significant difference). In a total of 860 patients, skin infection (6.2%) and skin erythema (2.8%) also occurred. Less frequently reported

adverse events were rash (0.7%), papules (0.6%), greasy (0.5%), heat sensation (0.5%), and infection (0.5%).

Discussion

This Asian study evaluated the efficacy and safety of tacrolimus ointment in a large population of Asian patients with AD and described a brief overview of the results in the included studies. It is of interest to consider the results of Asian studies by contrast with those of similar United States, European, and Japanese studies. Therefore, we cited the results of such studies (data are shown in Tables 2 and 3).

Similar to the Asian studies, the withdrawals due to adverse events and lack of efficacy were infrequent in the United States and European studies ("Withdrawn from study" in Table 2).^{6,8-10} In the United States studies, the higher frequency of withdrawals compared with these Asian studies seemed to be because of a longer period of treatment than the other studies. The data of withdrawal in the Japanese studies were not available.³⁻⁵

In this Asian study, most of the adult and pediatric patients had success with tacrolimus therapy based on the physician's global evaluation of clinical response ("Efficacy evaluation" in Table 2). The Japanese studies used physician's global improvement rating that is graded as "Cured," "Markedly Improved," "Moderately Improved," "Mildly Improved," "Unchanged," and "Aggravated." In the Japanese adult and pediatric studies, the success ("Moderately Improved" and above) rates were similar to those in this Asian study.³⁻⁵ The similar success rates based on physician's global evaluation of clinical response compared with this Asian study were also shown in the United States and European studies.^{6,8-10} There was not much difference in the success rates of physician's global evaluation of clinical response between this Asian study, and the United States, European, and Japanese studies.

Topical tacrolimus therapy improved the %BSA affected in both adult and pediatric patients in this Asian study. %BSA affected was not evaluated in the Japanese studies.³⁻⁵ The improvements in %BSA affected similar to this Asian study were shown in the United States adult and pediatric studies.^{6,8} The data of %BSA affected in the European studies were not available. In the European studies, Reitamo *et al.*^{9,10} described that adult and pediatric patients had improvements in %BSA affected, and these improvements were apparent three days after starting treatment.

Tacrolimus therapy improved the EASI in both adult and pediatric patients in this Asian study. EASI was not evaluated in the Japanese studies.³⁻⁵ The improvements in EASI similar to this Asian study were shown in the United States adult and pediatric studies.^{6,8} The data of

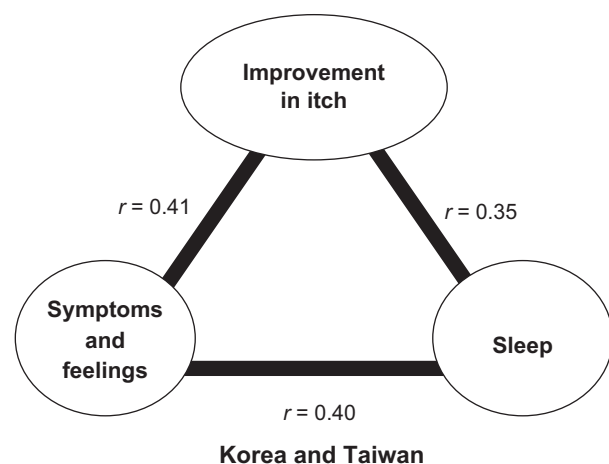


Figure 2 Pearson's product-moment correlation coefficients in improvements between patient's assessment of itch and the two CDLQI subscales, "Symptoms and feelings" and "Sleep"

Table 2 Efficacy and safety results in Asian study and other studies

	Baseline disease severity										Safety evaluation			
	Withdrawn from study					Efficacy evaluation					Patient's assessment of itch			
	Adverse events					Success					VAS			
	Age group	Evaluation timing (week)	Dose (%)	N	Total (%)	Lack of efficacy (%)	Severe (%)	Moderate (%)	Success rate ^a (%)	%BSA affected	EASI	Rating scale	Skin burning ^b (%)	Pruritus ^c (%)
Asian study	Adult	3-4	0.1/0.03	295	6.8	1.0	1.0	38	80.0	-21.9 ^d	-13.1 ^e	-2.8 ^d	51.1	36.8
	Pediatric	3-4	0.03	194	6.7	2.1	1.5	56	85.3	-28.3 ^d	-14.6 ^e	-3.2 ^d	28.0	28.9
	Adult and pediatric	3-4	0.1/0.03	860 ^e	6.7	1.3	1.4	30	83.6	-22.2 ^d	-13.7 ^e	-3.0 ^d	38.0	31.9
Japanese study	Adult	3	0.1	78 ^f	-	-	-	49	95.5	-	-	-	-	-
K506 ointment study group ³ (1997)	Adult	1	0.1	73 ^f	-	-	-	37	97.2	-	-	-	-	-
FK506 ointment study group ⁴ (1997)	Pediatric	3	0.1	70 ^f	-	-	-	51	91.3	-	-	-	-	-
Otsuki <i>et al.</i> ⁵ (2003)	Adult	12	0.03	72 ^f	-	-	-	40	88.9	-	-	-	-	-
United States study	Adult	12	0.1	209	24.9	5.3	8.6	59	72.7	-24.0 ^{d,g}	-14.9 ^{d,g}	-3.5 ^{d,g}	57.7	46.1
Hanifin <i>et al.</i> ⁶ (2001)	Pediatric	12	0.03	211	28.9	6.2	12.3	56	61.6	-19.0 ^{d,g}	-11.7 ^{d,g}	-3.3 ^{d,g}	45.6	46.1
Soler <i>et al.</i> ⁷ (2001)	Adult	12	0.1	118	14.4	2.5	4.2	64	78.0	-27.5 ^{d,g}	-15.0 ^{d,g}	-3.9 ^{d,g}	33.7	32.2
Paller <i>et al.</i> ⁸ (2001)	Pediatric	12	0.03	117	19.7	5.1	3.4	62	72.6	-26.0 ^{d,g}	-14.0 ^{d,g}	-3.9 ^{d,g}	42.7	41.2
European study	Adult	3	0.1	191	11.5	4.2	0.5	49	85.0	-	-	-	59.2	15.2
Reitamo <i>et al.</i> ⁹ (2002)	Pediatric	3	0.03	193	11.4	3.6	0.1	54	79.9	-	-	-	45.1	20.2
Reitamo <i>et al.</i> ¹⁰ (2002)	Adult	3	0.1	186	7.0	1.6	0.5	46	85.3	-	-	-	20.4	11.3
	Pediatric	3	0.03	189	11.1	1.6	1.6	39	80.2	-	-	-	18.5	13.2

^aSuccess rate based on physician's global evaluation of clinical response. Success was defined as a rating of better than moderate improvement ($\geq 50\%$ improvement).

^bIncidence rates of skin burning include stinging, pain and soreness.

^cIncidence rates of pruritus include itch and worsening of pruritus.

^dMean changes from baseline to the end of treatment.

^eTwenty patients were mild, two patients were moderate to severe, and 180 patients were moderate to severe.

^fPatients from efficacy analysis.

^gValues estimated from a graph.

^hSeverity score of itch was assessed according to the following six-point rating scale (0: none; 1: slight; 2: mild; 3: moderate; 4: severe; 5: aggravation from severe) by physicians.

Table 3 Changes in QOL from baseline to the end of treatment in Asian and United States patients

QOL measures	Asian study ^a	United States study ^b	
		(0.1%)	(0.03%)
Adults			
Symptoms and feelings	-26.5	-41.1	-33.7
Leisure	-20.3	-28.6	-21.9
Personal relationships	-8.8	-15.1	-10.2
Treatment	-9.9	-14.8	-13.3
Work and school	-10.7	-31.8	-22.0
Daily activities	-19.4	-28.4	-20.9
Total QOL score	-18.7	-27.1	-21.1
Children			
Symptoms and feelings	-30.8	-35.9	-36.4
Leisure	-16.3	-17.8	-18.2
Personal relationships	-13.6	-15.8	-11.3
Treatment	-17.6	-34.7	-35.0
School or holidays	-19.1	-21.9	-17.5
Sleep	-28.4	-32.5	-37.6
Total QOL score	-19.8	-24.1	-24.4

^aEvaluation timing was week 3–4.^bDrake *et al.*¹; evaluation timing was week 12.

EASI in the European studies were not available. In the European studies, Reitamo *et al.*^{9,10} described that adult and pediatric patients had improvements in modified EASI (mEASI), and the finding for improvements in EASI was similar to those in the mEASI and %BSA affected in both adult and pediatric patients.

Tacrolimus therapy improved the patient's assessment of itch measured by VAS score in both adult and pediatric patients in this Asian study. The improvements in itch evaluated by physicians on a five-point rating scale were observed in the Japanese studies.^{3–5} The improvements in patient's assessment of itch similar to this Asian study were shown in the United States adult and pediatric studies.^{6,8} The data of patient's assessment of itch in the European studies were not available. In the European studies, Reitamo *et al.*^{9,10} described that the finding for improvements in the patient's assessment of itch was similar to those in the mEASI and %BSA affected in both adult and pediatric patients.

The improvement of the patient's assessment of itch suggests tacrolimus ointment is effective in the improvement of itch in patients with AD. Toyoda and Nakagawa showed the mechanism for antipruritic effects of tacrolimus ointment. Indeed, these reports demonstrated that the mechanism for antipruritic effects involves neuropeptides such as substance P and nerve growth factor in the skin of patients with atopic eczema.^{27,28} The improvement of the patient's assessment of itch may be caused by the mechanism for antipruritic effects of tacrolimus.

In this Asian study, tacrolimus therapy improved Total QOL score and all subscales in DLQI and CDLQI (Table 3). The United States studies also reported the improvements in Total QOL score and all DLQI and CDLQI subscales.¹ Except for "Work and school," the improvements in DLQI subscales were not so different between this Asian study and the United States studies. Similar improvements were seen in the CDLQI subscales, except "Treatment," between this Asian study and the United States studies. In adults, "Symptoms and feelings" showed marked improvements in this Asian and the United States studies. In children, "Symptoms and feelings" and "Sleep" had marked improvements in this Asian and the United States studies. The large improved subscales, such as "Symptoms and feelings" and "Sleep," seemed to be the subscales affected by itch. This Asian study has shown that there were positive correlations between patient's assessment of itch and two CDLQI subscales (i.e. "Symptoms and feelings" and "Sleep"). The result in this Asian study suggested that tacrolimus therapy improved itch, and the improvements of "Symptoms and feelings" and "Sleep" were induced by the improvement of itch.

In the Asian study, as well as the United States and European studies,^{7–10} common adverse events were skin burning and pruritus in both adult and pediatric patients ("Safety evaluation" in Table 2). The adverse events in the Japanese studies were not available.

In the Asian study, the incidence rates of skin burning were 51.1% in adult patients and 28% in pediatric patients. Skin burning was the most common adverse event in total of adult and pediatric patients, and it was similar to those reported in the United States and European studies.^{7–10} The Asian studies showed that the incidence of skin burning was significantly lower in pediatric patients than in adult patients. In the United States and European studies, the incidence of skin burning tended to be lower in pediatric patients than in adult patients. Also, this result is similar to those reported in the Canadian open-label, non-comparative, multicenter, 6-month study reported by Tan and Langley²⁹ (date not shown). It may be speculated that the difference in the incidence of skin burning may be caused by the difference in the thickness of the skin between adult and pediatric patients.

The incidence rates of pruritus were 36.8 and 28.9% in adult and pediatric patients in the Asian study. In pruritus, there was no statistically significant difference in incidence rates between adult and pediatric patients in this Asian study. Unlike the incidence of skin burning, an age-related difference in the incidence of pruritus was not shown in this Asian study. This result is similar to those reported in the United States and European studies.^{7–10}

Skin burning and pruritus were local and transient. These events were brief and resolved during the first few days of treatment. This feature of common adverse events was similar to the United States and European studies.⁷⁻¹⁰

In this Asian study, the incidence of skin infection in total of adult and pediatric patients was 6.2%. It seemed that there was no difference in the incidence of skin infection between this Asian study and the United States and European studies, as well as Japan.^{3-5,7-10,13} In this Asian study, cancer was not reported. In the United States studies, there is no indication of an increased risk of skin cancer and lymphoma in tacrolimus-treated patients in comparison with the general population of United States.^{11,30-33}

In the studies included in this Asian study, there were no reports of skin atrophy, striae, and telangiectasia associated with topical corticosteroid. This feature of tacrolimus ointment therapy is an advantage over topical corticosteroid treatment.^{7-10,34}

In conclusion, tacrolimus ointment is an effective and well-tolerated treatment option in adult and pediatric patients with AD in Asia. In this Asian study, the efficacy and safety of tacrolimus assessed are similar to those in the USA and European studies, as well as Japan. This study may indicate that tacrolimus ointment has possibilities of recommendation as a first-line therapy, although it controls the active AD lesion with another treatment.

Acknowledgments

The authors express gratitude to Dr. Finlay for the use of the DLQI and CDLQI. The authors thank Astellas Pharma Inc. for their support in data collection.

References

- 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.
- Hanifin JM, Chan S. Biochemical and immunologic mechanisms in atopic dermatitis: new targets for emerging therapies. *J Am Acad Dermatol* 1999; **41**: 72-77.
- FK506 Ointment Study Group. Phase III comparative study of FK506 ointment vs betamethasone valerate ointment in atopic dermatitis (trunk/extremities) [in Japanese]. *Nishinibon J Derm* 1997; **59**: 870-879.
- FK506 Ointment Study Group. Phase III comparative study of FK506 ointment vs alclometasone dipropionate ointment in atopic dermatitis (face and neck) [in Japanese]. *Acta Derm (Kyoto)* 1997; **92**: 277-288.
- Otsuki M, Nakagawa H, Kawashima M, *et al.* Efficacy and safety of FK506 (tacrolimus) ointment in children with atopic dermatitis: phase III double-blinded comparison with vehicle ointment. *J Clin Ther Med* 2003; **19**: 569-595.
- Hanifin JM, Ling MR, Langley R, *et al.* Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. *J Am Acad Dermatol* 2001; **44**: S28-S38.
- Soter NA, Fleischer AB, Webster GF, *et al.* Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. *J Am Acad Dermatol* 2001; **44**: S39-S46.
- Paller A, Eichenfield LF, Leung DY, *et al.* A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol* 2001; **44**(1 Suppl): S47-S57.
- Reitamo S, Rustin M, Ruzicka T, *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109**: 547-555.
- Reitamo S, Van Leent EJ, 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.
- Hanifin JM, Paller AS, Eichenfield L, *et al.* Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis. *J Am Acad Dermatol* 2005; **53**: S186-S194.
- Koo JY, Fleischer AB, Abramovits W, *et al.* Tacrolimus ointment is safe and effective in the treatment of atopic dermatitis: results in 8000 patients. *J Am Acad Dermatol* 2005; **53**: S195-S205.
- Fleischer AB, Ling M, Eichenfield L, *et al.* Tacrolimus ointment for the treatment of atopic dermatitis is not associated with an increase in cutaneous infections. *J Am Acad Dermatol* 2002; **47**: 562-570.
- 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.
- Rubins A, Gutman R, Valdmann N, *et al.* 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.
- Lan CC, Huang CC, Chen YT, *et al.* Tacrolimus ointment for the treatment of atopic dermatitis: report of first clinical experience in Taiwan. *Kaohsiung J Med Sci* 2003; **19**: 296-304.
- Won CH, Seo PG, Park YM, *et al.* A multicenter trial of the efficacy and safety of 0.03% tacrolimus ointment for atopic dermatitis in Korea. *J Dermatolog Treat* 2004; **15**: 30-34.
- Kim HO, Park CW, Lee CH, *et al.* Efficacy of 0.1% tacrolimus ointment in Korean patients with atopic dermatitis. *Korean J Dermatol* 2005; **43**: 312-318.
- Yeung CK, Ma KC, Chan HH. Efficacy and safety of tacrolimus ointment monotherapy in Chinese children with atopic dermatitis. *Skinmed* 2006; **5**: 12-17.
- Singalavanija S, Noppakun N, Limpongsanuruk W, *et al.* Efficacy and safety of tacrolimus ointment in pediatric

- patients with moderate to severe atopic dermatitis. *J Med Assoc Thai* 2006; 89: 1915-1922.
- 21 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1980; 92: 44-47.
- 22 Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1989; 144: 13-14.
- 23 Hanifin JM, Thurston M, Omoto M, *et al.* The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol* 2001; 10: 11-18.
- 24 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; 19: 210-216.
- 25 Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995; 132: 942-949.
- 26 Basra MK, Fenech R, Gatt RM, *et al.* The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; 159: 997-1035.
- 27 Toyoda M, Nakagawa H. Antipruritic mechanism of tacrolimus ointment for atopic eczema: 2. the role of neuropeptide, substance P [poster]. 16th EADV Congress, 16-20 May 2007. Vienna, Austria.
- 28 Toyoda M. Antipruritic mechanism of tacrolimus ointment for atopic dermatitis: consideration of dermatoneuronal factors. *Clin Dermatol* 2003; 57: 45-50.
- 29 Tan J, Langley R. Safety and efficacy of tacrolimus ointment 0.1% (Protopic) in atopic dermatitis: a Canadian open-label multicenter study. *J Cutan Med Surg* 2004; 8: 213-219.
- 30 Naylor M, Elmets C, Jaracz E, Rico JM. Non-melanoma skin cancer in patients with atopic dermatitis treated with topical tacrolimus. *J Dermatolog Treat* 2005; 16: 149-153.
- 31 Spergel JM, Leung DY. Safety of topical calcineurin inhibitors in atopic dermatitis: evaluation of the evidence. *Curr Allergy Asthma Rep* 2006; 6: 270-274.
- 32 Munzenberger PJ, Montejo JM. Safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. *Pharmacotherapy* 2007; 27: 1020-1028.
- 33 Fonacier L, Spergel J, Charlesworth EN, *et al.* Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2005; 115: 1249-1253.
- 34 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.