

Blood Level of Tacrolimus in Patients with Severe Allergic Conjunctivitis Treated by 0.1% Tacrolimus Ophthalmic Suspension

Nobuyuki Ebihara¹, Yuichi Ohashi², Hiroshi Fujishima³, Atsuki Fukushima⁴, Yayoi Nakagawa⁵, Kenichi Namba⁶, Shigeki Okamoto⁷, Jun Shoji⁸, Etsuko Takamura⁹, Eiichi Uchio¹⁰ and Dai Miyazaki¹¹

ABSTRACT

Background: To estimate the efficacy and safety of 0.1% tacrolimus ophthalmic suspension based on the blood level of tacrolimus in patients with severe allergic conjunctivitis.

Methods: Fifty-two patients in whom topical anti-allergic agents had been ineffective were treated with 0.1% tacrolimus ophthalmic suspension twice daily for 12 weeks. Adverse drug reactions were monitored, as well as ocular symptoms and signs. The blood concentration of tacrolimus was measured before the initiation of treatment and 4 and 12 weeks later.

Results: About 75% of the patients without concomitant using of tacrolimus ointment had blood levels of tacrolimus below the detection limit of the assay (0.5 ng/mL). On the other hand, 71% (week 4) and 57% (week 12) of patients with concomitant using of tacrolimus ointment had blood levels above the detection limit of the assay. However, the maximum blood concentration was less than 2 ng/mL. Adverse drug reactions occurred in 16 patients. These were disorders of the eye such as warmth, irritation, and a burning sensation. However, all of the patients could continue treatment with tacrolimus for 12 weeks. There were no serious adverse events such as increased intraocular pressure or ocular infection during the study. All symptoms and signs improved over time.

Conclusions: The good safety profile of 0.1% tacrolimus ophthalmic suspension based on the low blood concentration of tacrolimus, coupled with demonstrated efficacy, make it an important tool for treating severe allergic conjunctivitis.

KEY WORDS

allergic conjunctivitis, blood level, efficacy, safety evaluation, tacrolimus

¹Department of Ophthalmology, Juntendo University School of Medicine, ⁸Department of Ophthalmology, Division of Visual Sciences, Nihon University School of Medicine, ⁹Department of Ophthalmology, Tokyo Women's Medical University School of Medicine, Tokyo, ²Department of Ophthalmology, Ehime University School of Medicine, ⁷Okamoto Eye Clinic, Ehime, ³Department of Ophthalmology, Tsurumi University School of Dental Medicine, Kanagawa, ⁴Department of Ophthalmology, Kochi Medical School, Kochi, ⁵Nakagawa Eye Clinic, Osaka, ⁶Department of Ophthalmology and Visual Science, Hokkaido University Graduate School of Medicine, Hokkaido, ¹⁰Department of Ophthalmology, Fukuoka University, School of Medicine, Fukuoka and ¹¹Department of Ophthalmology, Tottori University, School of Medicine, Tottori, Japan.

Authors' Contributions: Design of the study, interpretation of the data and review of the manuscript were done by all the authors. YO conducted the study. The data were collected by YO, EU, NE,

SO, JS, YN, KN, AF, HF, and DM. Management of the data was carried out by YO. YO and NE made analysis of the data and prepared the manuscript. All the authors approved the final manuscript.

Conflict of interest: This study was sponsored by Senju Pharmaceutical Co., Ltd., Osaka, Japan. YO conducted with Senju Pharmaceutical as medical adviser for the clinical trial, and received advisory fees from this company. Other authors have no commercial or proprietary interest in the products or the company mentioned in this article.

Correspondence: Nobuyuki Ebihara, MD, PhD, Department of Ophthalmology, Juntendo University School of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan.

Email: ebihara@juntendo.ac.jp

Received 28 June 2011. Accepted for publication 19 October 2011.

©2012 Japanese Society of Allergology

INTRODUCTION

Topical anti-allergy agents and steroids are the first-line treatments for severe allergic conjunctivitis, such as vernal keratoconjunctivitis (VKC) or atopic keratoconjunctivitis (AKC). However, these diseases require long-term treatment in many cases, and steroids cannot be administered because long-term steroid therapy often results in significant adverse reactions such as increased intraocular pressure,¹ especially in children under the age of 10 years,² as well as infections.³ It is also true, however, that there are few effective treatment options for severe allergic conjunctivitis that provide as an alternative to topical steroids.⁴

Tacrolimus is a macrolide antibiotic produced by *Streptomyces tsukubaensis*.⁵ Due to its potent immunosuppressive effect, oral and parenteral tacrolimus preparations were developed for preventing rejection after organ transplantation. Subsequently, tacrolimus ointment was released for atopic dermatitis and autoimmune skin diseases, and it is now available all over the world. In recent years, there have been several reports about the usefulness of cyclosporin ophthalmic solution and tacrolimus ointment for the treatment of VKC and AKC.⁶⁻¹⁰ Both of these drugs are calcineurin inhibitors that block the activation of T cells and their production of cytokines involved in the development of VKC and AKC. Based on the fact that the inhibitory effect of tacrolimus on cytokine production by T cells is about 100 times greater than that of cyclosporin,¹¹ an ophthalmic tacrolimus preparation is expected to be effective for severe VKC and AKC. Previously, we examined the efficacy of a 0.1% tacrolimus ophthalmic suspension (TALYMUS®, Senju Pharmaceutical Co., Ltd., Osaka, Japan) for severe allergic conjunctivitis in a multicenter, randomized, double-blinded, placebo-controlled clinical trial.¹² Fifty-six patients were treated either with tacrolimus or placebo twice daily for 4 weeks. As a result, both objective findings and subjective symptoms were significantly better in the tacrolimus group than in the placebo group.

Although tacrolimus is a very useful immunosuppressant, it is known from previous experience with oral preparations that a persistently high blood concentration of the drug (trough level ≥ 10 -20 ng/mL) is associated with renal impairment.¹³ On the other hand, after topical application of tacrolimus ointment for treatment of atopic dermatitis, the blood concentration is usually low or undetectable.¹⁴ However, Rita L *et al.* recently reported that there may be an increased risk of T cell lymphoma in atopic dermatitis patients treated with tacrolimus ointment.¹⁵ The theoretical risk of cancer from exposure is low because no evidence of systemic accumulation has been observed after repeated application of tacrolimus ointment. However, younger patients with a higher body

surface area per weight and subjects with abnormalities of the epidermis can display considerable percutaneous absorption of tacrolimus ointment that may result in blood concentrations corresponding to the levels known to cause immunosuppression. The risk of severe systemic reactions to tacrolimus may depend on its blood level. Therefore, this study was conducted to clarify the blood level of tacrolimus after ocular instillation of a 0.1% ophthalmic suspension in patients with severe allergic conjunctivitis and to examine adverse drug reactions.

METHODS

This multicentre, prospective, open-label, non-comparative clinical study of patients with severe allergic conjunctivitis (VKC and AKC) was conducted at 11 institutions. We diagnosed VKC patients for characteristic appearances such as giant papillae in upper tarsal conjunctivae, Trantas dot in limbal conjunctivae. A various corneal disorders such as superficial punctate keratitis, shield ulcer and corneal plaque were observed in corneas of VKC patients. 15 VKC patients were enrolled in this study. On the other hand, chronic AKC patients had fibrosis of upper tarsal conjunctivae and neovascularization of corneas. However, acute AKC patients had severe papillae in upper tarsal conjunctivae and various corneal disorders. In this study, among AKC patients, we chose patients with severe papillae in upper tarsal conjunctivae. 37 AKC patients were enrolled in this study. The study was performed from May 2008 to September 2009 and its protocol was approved by the Institutional Review Boards of all participating institutions. In addition, the study was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice, and Good Post-marketing Study Practice (Japan). All patients who participated in this study gave written consent after the details had been explained to them. The study was registered with the Japanese University Hospital Medical Information Network (<https://center.umin.ac.jp>) and was assigned the ID code UMIN000001262.

Patients who had been diagnosed as having severe allergic conjunctivitis and for whom topical anti-allergic agents were ineffective were eligible for this study. The following patients were excluded from the study: (1) those who had known hypersensitivity to tacrolimus hydrate or to any component of this drug; (2) those with infectious eye diseases; (3) women who were pregnant or possibly pregnant; (4) patients who had already used an ophthalmic preparation of tacrolimus hydrate (including in clinical trials); (5) patients using tacrolimus capsules, granules and/or injections; (6) patients who wore contact lenses; and (7) patients who had participated in any other clinical trial within 3 months prior to enrollment.

Patients were instructed to instill one drop of 0.1% tacrolimus ophthalmic suspension into both eyes

Table 1 Baseline characteristics of the patients

		AKC (<i>n</i> = 37)	VKC (<i>n</i> = 15)
Age (yrs): mean $\pm$ SD (range)		17.4 $\pm$ 11.02 (5-41)	14.1 $\pm$ 8.4 (6-36)
Sex	Male (%)	30 (81.1%)	12 (80.0%)
	Female	7	3
Concomitant medications:			
Topical steroids		18	6
Oral steroids		3	0
Tacrolimus ointment		7	0
Total symptom score		6.9 $\pm$ 4.44	5.9 $\pm$ 3.35
Total clinical sign score		15.6 $\pm$ 4.8	16.4 $\pm$ 4.97

AKC, Atopic keratoconjunctivitis; VKC, Vernal keratoconjunctivitis.

twice a day for 12 weeks. Patient's compliances with the administration of the drug were confirmed at each observational time point during the study. Almost patients were in compliance with the rule of prescriptions in this study. Concomitant administration of tacrolimus ointment for severe atopic dermatitis was allowed without any dose change from 4 weeks prior to and during the study.

Safety was assessed from ocular findings, visual acuity, intraocular pressure, adverse events, and laboratory test results. All adverse events observed by the investigators or reported by patients in weeks 2, 4, 8, and 12 were recorded. Each event was graded as mild, moderate, or severe, and the potential relationship to the study drug was assessed. For laboratory tests, blood samples were obtained from a cubital vein in weeks 4 and 12.

To evaluate systemic absorption after topical instillation of 0.1% tacrolimus ophthalmic suspension, approximately 1 mL of whole venous blood was collected before the initiation of administration and after 4 and 12 weeks of treatment. We collected blood samples at three-four hours after the last administration of tacrolimus suspension. The blood concentration of tacrolimus was measured by using liquid chromatography tandem mass spectrometry (LC-MS²) at the Osaka laboratory of JCL Bioassay Corp. (Osaka, Japan). LC-MS² is widely used for quantitative determination of immunosuppressive drugs in biological fluids, because of the features such as selectivity and lower cost of analysis.¹⁶

Ten ocular findings were assessed, including 5 for the tarsal conjunctiva (hyperemia, swelling, follicles, papillae, and giant papillae), 2 for the bulbar conjunctiva (hyperemia and edema), and limbal edema, Trantas' dots, and corneal lesions. Six ocular symptoms were also assessed, including itching, eye discharge, lacrimation, eye pain, foreign body sensation, and photophobia. Each of these signs/symptoms was graded on a 4-point scale (0 = none, 1 = mild, 2 = mod-

erate, or 3 = severe). The primary efficacy outcome measure was the mean change of the total score for the 10 ocular findings.

Statistical analysis was performed using JMP statistical software (version 8 for Windows, SAS Institute Inc., Cary, NC, USA). Significance was accepted at a two-sided level of $P < 0.05$. Efficacy assessments were based on the worse eye (the eye with a higher total score for ocular findings), with the total scores being compared between baseline and post-treatment by the Wilcoxon signed rank test.

RESULTS

PATIENT PROFILE

The baseline characteristics and clinical scores of the subjects are shown in Table 1. A total of 52 patients (42 males and 10 females) were enrolled. The mean age was 17.4 years for those with AKC and 14.1 years for those with VKC. In 18 of the 37 AKC patients and 6 of the 15 VKC patients, corticosteroid eye drops and/or ointment were being used at study initiation. However, only 5 patients with AKC were still using steroids at the completion of the study. Tacrolimus ointment was used by 7 patients for treatment of severe atopic dermatitis.

BLOOD LEVEL OF TACROLIMUS

Table 2A, B show the blood levels of tacrolimus in various subsets of patients without or with concomitant using of tacrolimus ointment at all the three points (Initial/week4 and week12). About 75% of the patients without concomitant using of tacrolimus ointment had blood levels below the detection limit of the assay (0.5 ng/mL). In the other hand, 71% (week 4) and 57% (week12) of patients with concomitant using of tacrolimus ointment had blood levels above the detection limit of the assay (0.5 ng/mL). However, the maximum blood concentrations of both groups were always less than 2 ng/mL. In the others, the mean blood level was not affected by sex, age, steroid ther-

Table 2A Systemic exposure to tacrolimus without concomitant using of tacrolimus ointment

Blood level of tacrolimus (ng/mL)			Time Point			P value*
			Initial	Week4	Week12	
Sex	Male	Mean $\pm$ SD	N.D.	0.27 $\pm$ 0.462	0.3 $\pm$ 0.498	0.0832
		Max	—	1.47	1.78	
		N [†]	(0/36)	(10/34)	(12/36)	
	Female	Mean $\pm$ SD	N.D.	N.D.	N.D.	
		Max	—	—	—	
		N [†]	(0/9)	(0/9)	(0/8)	
Age	<10	Mean $\pm$ SD	N.D.	0.15 $\pm$ 0.295	0.16 $\pm$ 0.263	0.1622
		Max	—	0.82	0.59	
		N [†]	(0/14)	(3/14)	(4/14)	
	10-15	Mean $\pm$ SD	N.D.	0.13 $\pm$ 0.385	0.15 $\pm$ 0.455	
		Max	—	1.47	1.78	
		N [†]	(0/18)	(2/16)	(2/17)	
	>15	Mean $\pm$ SD	N.D.	0.39 $\pm$ 0.549	0.47 $\pm$ 0.587	
		Max	—	1.43	1.64	
		N [†]	(0/13)	(5/13)	(6/13)	
Steroid therapy	Yes	Mean $\pm$ SD	N.D.	0.18 $\pm$ 0.427	0.20 $\pm$ 0.442	0.4887
		Max	—	1.43	1.64	
		N [†]	(0/25)	(4/24)	(5/24)	
	No	Mean $\pm$ SD	N.D.	0.26 $\pm$ 0.427	0.31 $\pm$ 0.494	
		Max	—	1.47	1.78	
		N [†]	(0/20)	(6/19)	(7/20)	
Severity (corneal involvement)	Mild	Mean $\pm$ SD	N.D.	0.33 $\pm$ 0.586	0.35 $\pm$ 0.655	0.4391
		Max	—	1.47	1.78	
		N [†]	(0/15)	(4/15)	(4/15)	
	Moderate	Mean $\pm$ SD	N.D.	0.17 $\pm$ 0.312	0.26 $\pm$ 0.379	
		Max	—	0.91	1.09	
		N [†]	(0/17)	(4/16)	(6/17)	
	Severe	Mean $\pm$ SD	N.D.	0.13 $\pm$ 0.299	0.09 $\pm$ 0.211	
		Max	—	0.82	0.57	
		N [†]	(0/13)	(2/12)	(2/12)	

[†]No. of detected/total patients.

*P value were calculated with the use of MANOVA test.

apy and severity.

SAFETY

Adverse drug reactions were reported in 16 patients. The incidence of adverse drug reactions among the 20 patients who had detectable blood levels of tacrolimus was 30.0%, which was very close to the 31.3% for patients without detectable levels (below the lower limit of quantification). All of the adverse drug reactions are listed in Table 3. No serious adverse events or ocular infections occurred during the treatment with the study drug. Although laboratory abnormalities occurred in 8 cases, no clinically relevant problems were observed.

The changes from baseline of visual acuity and intraocular pressure after 12 weeks are shown in Table 4. Baseline of visual acuities of patients was im-

proved. As for the mean intraocular pressure, elevation was not recognized in patients with or without concomitant steroid use.

EFFICACY

At the start of treatment, the mean symptom score was 7.7 $\pm$ 4.46 in the steroid group and 5.5 $\pm$ 3.54 in the non-steroid group. These scores showed a significant decrease to 2.5 $\pm$ 3.01 (P < 0.001) and 2.0 $\pm$ 2.04 (P < 0.001), respectively, in week 2 (Fig. 1). The scores decreased further to 1.2 $\pm$ 1.93 for the steroid group and 0.9 $\pm$ 1.42 for the non-steroid group by week 12. As for ocular findings, the mean score at the start of treatment was 16.0 $\pm$ 5.26 for the steroid group and 15.8 $\pm$ 4.42 for the non-steroid group. These scores decreased significantly to 10.8 $\pm$ 4.66 (P < 0.001) and 9.9 $\pm$ 3.36 (P < 0.001), respectively, in

Table 2B Systemic exposure to tacrolimus with concomitant using of tacrolimus ointment

Blood level of tacrolimus (ng/mL)			Time Point			P value*
			Initial	Week4	Week12	
Sex	Male	Mean $\pm$ SD	N.D.	0.75 $\pm$ 0.754	0.79 $\pm$ 0.758	0.5599
		Max	—	1.69	1.83	
		N [†]	(0/6)	(4/6)	(4/6)	
	Female	Mean $\pm$ SD	N.D.	0.64	N.D.	
		Max	—	0.64	—	
		N [†]	(0/1)	(1/1)	(0/1)	
Age	<10	Mean $\pm$ SD	N.D.	0.52 $\pm$ 0.485	0.28 $\pm$ 0.479	0.3049
		Max	—	0.96	0.83	
		N [†]	(0/3)	(2/3)	(1/3)	
	10-15	Mean $\pm$ SD	—	—	—	
		Max	—	—	—	
		N [†]	(0)	(0)	(0)	
	>15	Mean $\pm$ SD	N.D.	0.90 $\pm$ 0.737	0.98 $\pm$ 0.836	
		Max	—	1.69	1.83	
		N [†]	(0/4)	(3/4)	(3/4)	
Steroid therapy	Yes	Mean $\pm$ SD	N.D.	1.26	1.50	0.2921
		Max	—	1.26	1.50	
		N [†]	(0/1)	(1/1)	(1/1)	
	No	Mean $\pm$ SD	N.D.	0.65 $\pm$ 0.636	0.54 $\pm$ 0.725	
		Max	—	1.69	1.83	
		N [†]	(0/6)	(4/6)	(3/6)	
Severity (corneal involvement)	Mild	Mean $\pm$ SD	N.D.	0.64	N.D.	0.8503
		Max	—	0.64	—	
		N [†]	(0/1)	(1/1)	(0/1)	
	Moderate	Mean $\pm$ SD	N.D.	0.81 $\pm$ 0.706	0.67 $\pm$ 0.870	
		Max	—	1.69	1.83	
		N [†]	(0/4)	(3/4)	(2/4)	
	Severe	Mean $\pm$ SD	N.D.	0.63 $\pm$ 0.891	1.05 $\pm$ 0.636	
		Max	—	1.26	1.50	
		N [†]	(0/2)	(1/2)	(2/2)	

[†]No. of detected / total patients.

*P value were calculated with the use of MANOVA test.

week 2, and then decreased further to 6.5 ± 3.44 and 4.5 ± 3.15 , respectively, by week 12.

DISCUSSION

The 0.1% ophthalmic suspension of tacrolimus is a topical preparation of calcineurin inhibitor that was developed specifically for the treatment of severe allergic conjunctivitis, including VKC and AKC. Tacrolimus inhibits calcineurin activity, leading to marked suppression of the production of various cytokines by activated T cells (including IL-2, IL-4, IL-5, and interferon-gamma).¹⁷ On account of its potent immunosuppressive activity, tacrolimus was considered to show promise for application to intractable allergic eye diseases. After studies conducted in Japan proved the usefulness of 0.1% tacrolimus ophthalmic suspension,¹² it was released in 2008.

On the other hand, it is known that adverse drug reactions to tacrolimus, such as renal dysfunction, tend to occur with systemic use when a whole blood concentration of about 10 ng/mL (trough level) persists for a long time.¹³ Furthermore, a recent review focused on the potential risk of T cell lymphoma in patients using tacrolimus ointment.¹⁵ The age- and sex-adjusted hazard ratio for T cell lymphoma was 5.44 (95% CI: 2.51-11.79; $P < 0.001$) for patients exposed to tacrolimus versus those not exposed. However, no data on the blood levels of tacrolimus were reported for the patients who developed T cell lymphoma. Because systemic immunosuppression is associated with an increased risk of lymphoma, there is a theoretical possibility that tacrolimus ointment could increase the risk of lymphoma. However, there is no evidence of a causal link between cancer and

Table 3 Adverse drug reactions and laboratory abnormalities

	Number (%) of patients or events			
	Not detected [†] (N = 32)		Detected [†] (N = 20)	
Adverse drug reactions	10	(31.25)	6	(30.00)
Warmness in eye	7	(21.88)	1	(5.00)
Eye irritation	1	(3.13)	3	(15.00)
Burning sensation in eye	1	(3.13)	1	(5.00)
Dysgeusia	1	(3.13)	0	
Acute bronchitis	0		1	(5.00)
Throat irritation	0		1	(5.00)
Overall events	10	(31.25)	7	(35.00)
Clinical laboratory abnormalities	6	(18.75)	2	(10.00)
Neutrophil count decreased	0		1	(5.00)
White blood cell count increased	0		1	(5.00)
Eosinophil count decreased	0		1	(5.00)
Blood sugar decreased	0		1	(5.00)
Haemoglobin decreased	1	(3.13)	0	
Haematocrit decreased	1	(3.13)	0	
White blood cell count increased	2	(6.25)	1	(5.00)
Atypical lymphocytes	0		1	(5.00)
Aspartate aminotransferase increased	1	(3.13)	0	
Alanine aminotransferase increased	1	(3.13)	1	(5.00)
Blood lactate dehydrogenase increased	2	(6.25)	0	
Blood urea increased	1	(3.13)	0	
Amylase increased	1	(3.13)	0	
Overall events	10	(31.25)	7	(35.00)

[†] Blood level of tacrolimus during the study period.

Table 4 Visual acuity and intraocular pressure (IOP)

	Baseline (N)	Week 12 (N)	P value*
Best visual acuity (mean ± SD)	0.99 ± 0.45 (52)	1.20 ± 0.37 (52)	<i>P</i> < 0.001
IOP (mmHg) (mean ± SD)			
Not-combined with steroids	12.6 ± 2.86 (26)	12.5 ± 2.45 (26)	<i>P</i> = 0.469
Combined with steroids temporarily and/or throughout study period	14.2 ± 2.34 (25)	14.6 ± 2.65 (24)	<i>P</i> = 0.830

**P* value were calculated with the use of the Wilcoxon signed rank test compared with baseline value.

tacrolimus.¹⁸⁻²⁵ Many pharmacokinetic studies have shown that systemic exposure to tacrolimus is low in patients using the ointment, with blood concentrations being below the limit of quantification (0.5 ng/mL) in the majority of patients.²⁶⁻³¹ In this study, to evaluate the safety of 0.1% tacrolimus ophthalmic suspension, we investigated the blood level of tacrolimus in patients using the suspension.

Blood levels of tacrolimus were monitored in all 52 patients during the study period. About 75% of the pa-

tients without concomitant using tacrolimus ointment had blood levels below the detection limit of the assay (0.5 ng/mL). On the other hand, 71% (week 4) and 57% (week 12) of patients with concomitant using of tacrolimus ointment had blood levels above the detection limit of the assay (0.5 ng/mL). However, the maximum blood concentration was lower than 2 ng/mL, which was less than high risk level (10 ng/mL) at which systemic adverse drug reactions might occur. Therefore, the theoretical risk of adverse effects

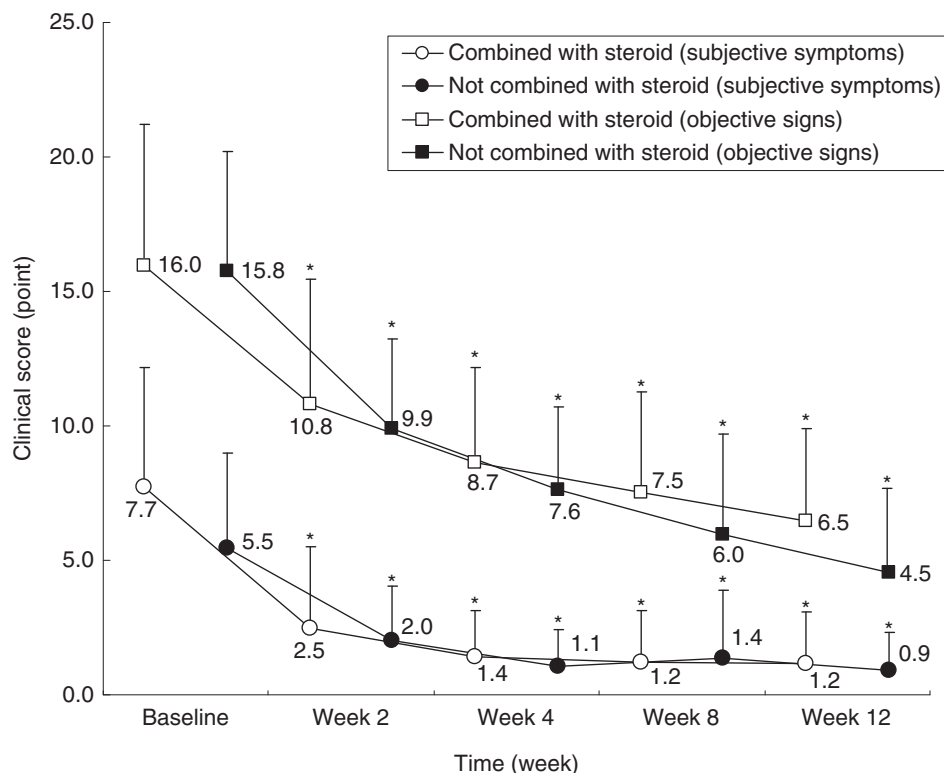


Fig. 1 Changes of the total scores for symptoms and signs during the 12-week study period. Error bars represent the standard deviation. The significance of differences was evaluated by using the Wilcoxon signed rank test to assess the change of each score in comparison with the baseline value. * $P < 0.0001$.

due to exposure to tacrolimus is very low because no evidence of accumulation was observed after repeated use of 0.1% tacrolimus ophthalmic suspension with or without concomitant using of tacrolimus ointment. Despite this finding, especially for patients with concomitant using of tacrolimus ointment, caution may be required to monitor the blood level of tacrolimus.

Among the 52 patients, adverse drug reactions occurred in 16. The most common adverse events associated with 0.1% tacrolimus ophthalmic suspension treatment were transient application-site reactions, such as warmth, irritation, and a burning sensation. However, all of the patients could continue treatment with tacrolimus for 12 weeks. These complications were related to their ocular diseases and decreased in frequency over time as allergic conjunctivitis showed improvement. Because tacrolimus modulates the local immune response at the ocular surface, treatment with 0.1% tacrolimus ophthalmic suspension could theoretically increase the risk of infections. However, there was no increase in the incidence of infections among adults or children in the present study. Despite this finding, especially for patients with a history of herpes simplex infection, caution may be required to prevent recurrence during

long-term treatment.³²

During this study, when 0.1% tacrolimus ophthalmic suspension was used for 12 weeks, giant papillae and corneal disorders showed marked improvement. The effect was significant after only 2 weeks of treatment, and both symptoms and objective findings responded quickly to 0.1% tacrolimus ophthalmic suspension.

In conclusion, we evaluated the safety and efficacy of 0.1% tacrolimus ophthalmic suspension in patients with severe allergic conjunctivitis. On the basis of the blood concentration profile of tacrolimus, systemic exposure was minimal and transient after topical application of the ocular preparation. The safety of 0.1% tacrolimus ophthalmic suspension and its demonstrated efficacy make it an important option for the treatment of severe allergic conjunctivitis.

REFERENCES

1. Lewis JM, Priddy T, Judd J *et al*. Intraocular pressure response to topical dexamethasone as a predictor for the development of primary open-angle glaucoma. *Am J Ophthalmol* 1988;**106**:607-12.
2. Ohji M, Kinoshita S, Ohmi E, Kuwayama Y. Marked intraocular pressure response to instillation of corticosteroids in children. *Am J Ophthalmol* 1991;**112**:450-4.

3. Wilhelmus KR. Indecision about corticosteroids for bacterial keratitis: an evidence-based update. *Ophthalmology* 2002;**109**:835-42.
4. Uchio E. Possibility of non-steroidal treatment in allergic conjunctival diseases. *Allergol Int* 2004;**53**:315-9.
5. Kino T, Hatanaka H, Hashimoto M *et al.* FK-506, a novel immunosuppressant isolated from a *Sterptomyces* I. fermentation, isolation, and physico-chemical and biological characteristics. *J Antibiot* 1987;**40**:1249-55.
6. Ozcan AA, Ersoz TR, Dulger E. Management of severe allergic conjunctivitis with topical cyclosporine A 0.05% eyedrops. *Cornea* 2007;**26**:1035-8.
7. Ebihara N, Ohashi Y, Uchio E *et al.* A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2009;**25**:365-72.
8. Vichyanond P, Tantimongkolsuk C, Dumronbkigchaiporn P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P. Vernal keratoconjunctivitis: Result of a novel therapy with 0.1% topical ophthalmic FK-506 ointment. *J Allergy Clin Immunol* 2004;**113**:355-8.
9. Attas-Fox L, Barkana Y, Iskhakov V *et al.* Topical tacrolimus 0.03% ointment for intractable allergic conjunctivitis: an open-label pilot study. *Curr Eye Res* 2008;**33**:545-9.
10. Miyazaki D, Tominaga T, Kakimaru-Hasegawa A, Nagata Y, Hasegawa J, Inoue Y. Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. *Ophthalmology* 2008;**115**:988-92.
11. Anderson J, Nagy S, Groth CG, Andersson U. Effect of FK506 and cyclosporine A on cytokine production studied in vitro at a single-cell level. *Immunology* 1992;**75**:136-42.
12. Ohashi Y, Ebihara N, Fujishima H *et al.* A randomized, placebo-controlled clinical trial of tacrolimus ophthalmic suspension 0.1% in severe allergic conjunctivitis. *J Ocul Pharmacol Ther* 2010;**26**:165-74.
13. Przepiorka D, Nash RA, Wingard JR *et al.* Relationship of tacrolimus whole blood levels to efficacy and safety outcomes after unrelated donor marrow transplantation. *Biol Blood Marrow Transplant* 1999;**5**:94-7.
14. Sakari R, Andreas W, Erwin S *et al.* Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. *Arch Dermatol* 2000;**136**:999-1006.
15. Rita L, William L, James C, Schottinger J, Yoshinaga M, Millares M. Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother* 2009;**43**:1956-63.
16. Taylor PJ, Jones A, Balderson GA, Lynch SV, Norris RL, Pond SM. Sensitive, specific quantitative analysis of tacrolimus (FK506) in blood by liquid chromatography-electrospray tandem mass spectrometry. *Clin Chem* 1996;**42**:279-85.
17. Sakuma S, Higashi Y, Sato N *et al.* Tacrolimus suppressed the production of cytokines involved in atopic dermatitis by direct stimulation of human PBMC system. (Comparison with steroids). *Int Immunopharmacol* 2001;**1**:1219-26.
18. Beck LA. The efficacy and safety of tacrolimus ointment: a clinical review. *J Am Acad Dermatol* 2005;**53**:S165-70.
19. Carroll CL, Fleischer AB Jr. Tacrolimus: focusing on atopic dermatitis. *Drugs Today (Barc)* 2006;**42**:431-9.
20. Bieber T, Cork M, Ellis C *et al.* Consensus statement on the safety profile of topical calcineurin inhibitors. *Dermatology* 2005;**211**:77-8.
21. Richardson K. Topical pimecrolimus, tacrolimus, and the risk for cancer: an expert interview with Lawrence Eichenfield, MD. *Medscape Dermatol* 2005;**6**. Available at: <http://www.medscape.com/viewarticle/502337>. Accessed September 1, 2007.
22. 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**:1249-53.
23. Ormerod AD. Topical tacrolimus and pimecrolimus and the risk of cancer: how much cause for concern? *Br J Dermatol* 2005;**153**:701-5.
24. Berger TG, Duvic M, van Voorhees AS, VanBeek MJ, Frieden IJ; American Academy of Dermatology Association Task Force. The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol* 2006;**54**:818-23.
25. Fleischer AB Jr. Show me the signal, FDA. *Skin Allergy News* 2005;**36**:10.
26. Patel RR, Vander Straten MR, Korman NJ. The safety and efficacy of tacrolimus therapy in patients younger than 2 years with atopic dermatitis. *Arch Dermatol* 2003;**139**:1184-6.
27. Alaiti S, Kang S, Fiedler VC *et al.* Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. *J Am Acad Dermatol* 1998;**38**:69-76.
28. 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**:695-9.
29. Rubins A, Gutmane R, Valdmann N, Stevenson P, Foster C, Undre N. Pharmacokinetics of 0.1% tacrolimus ointment after first and repeated application to adults with moderate to severe atopic dermatitis. *J Invest Dermatol* 2005;**125**:68-71.
30. Tonin E, Varagnolo C, Pigozzi B *et al.* Tacrolimus blood levels after 3 months repeated application to children with atopic dermatitis [abstract]. *J Eur Acad Dermatol Venereol* 2005;**19** (Suppl 2):150.
31. Tonin E, Pigozzi B, Fortina AB. Does prolonged topical application of tacrolimus in children result in systemic accumulation? *J Invest Dermatol* 2005;**125**:613.
32. Joseph MA, Kaufman HE, Insler M. Topical tacrolimus ointment for treatment of refractory anterior segment inflammatory disorders. *Cornea* 2005;**4**:417-20.