

Evaluation of Clinical Efficacy and Safety of Prolonged Treatment of Vernal and Atopic Keratoconjunctivitis Using Topical Tacrolimus

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Purpose: To evaluate the clinical improvement and safety of prolonged treatment of vernal (VKC) and atopic keratoconjunctivitis (AKC) using topical tacrolimus.

Methods: We included 36 eyes of 36 patients who had VKC and AKC and were treated with topical tacrolimus ophthalmic suspension (0.1%) for 24 months. The demographic data of the enrolled patients were collected from their medical files. Clinical scores, remission rates, number of relapses, concomitant use of steroids, and refractory indices were assessed. Clinical outcomes were determined using papillae–limbus–cornea (PLC) scores and 5-5-5 exacerbation grading scale scores. Clinical characteristics associated with the need for concomitant steroid eye drops administration were determined using logistic regression analysis. All patients were classified into 3 subgroups using cluster analysis.

Results: PLC scores recorded in the sixth month were significantly improved compared with those recorded at baseline. PLC scores recorded in the 18th, 21st, and 24th months were significantly improved compared with those recorded in the sixth month. The remission rates increased diachronically and significantly, reaching 92% in the 24th month. Logistic regression analysis showed that, for every 10-year increase in patient age, the risk for requiring concomitant administration of steroid eye drops was reduced by half (odds ratio, 0.53; 95% confidence interval, 0.29–0.96). Using cluster analysis, the patients were divided into 3 clusters: adolescent type, pediatric type, and adult type.

Conclusions: Two years of treatment with topical tacrolimus ophthalmic suspension is an effective method for inducing and maintaining the stable stages of VKC and AKC.

Key Words: atopic keratoconjunctivitis, clinical score, tacrolimus, prolonged use, vernal keratoconjunctivitis

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Vernal keratoconjunctivitis (VKC) is a severe form of allergic conjunctival disease (ACD) that mainly affects children and young adults living in a region with a warm climate. Characteristic clinical findings of VKC are proliferative conjunctival lesions, such as giant papillae and gelatinous limbal infiltration. The signs and symptoms of VKC worsen in the spring.¹ Atopic keratoconjunctivitis (AKC), first reported by Hogan in 1953,² is a refractive and chronic form of ACD that is characterized by atopic dermatitis on the face and eyelid skin; it is associated with atopic ocular complications, such as keratoconus, atopic cataract, and retinal detachment, at varying frequencies.³ Patients with severe VKC and AKC commonly develop giant papillae, gelatinous limbal infiltration, and corneal epitheliopathy, including punctate corneal keratitis; rarely, they present with corneal shield ulcers in the active and acute exacerbation phases of VKC and AKC. They often have poor responses to medical treatment. Therefore, VKC and AKC are recognized as severe and refractive forms of ACDs.

Conventional topical therapies for severe ACDs include antiallergy and corticosteroid eye drops. However, long-term use of steroid eye drops may result in various adverse events such as steroid-induced glaucoma, steroid-induced cataracts, and infectious keratitis including herpes simplex virus keratitis. Therefore, topical therapies that induce clinical remission without causing significant adverse events are required for the treatment of severe ACDs. Immunosuppressants are being considered as possible alternatives to steroid eye drops as first-line treatment of VKC.

Tacrolimus, which is a macrolide antibiotic drug isolated from the fermentation of *Streptomyces tsukubaensis*, has immunosuppressive effects.⁴ Tacrolimus is known to inhibit calcineurin after binding to FK506-binding proteins in T-lymphocytes. Therefore, tacrolimus suppresses the production of helper T-cell type 1 cytokines, including interleukin (IL)-2 and interferon- γ , and helper T-cell type 2

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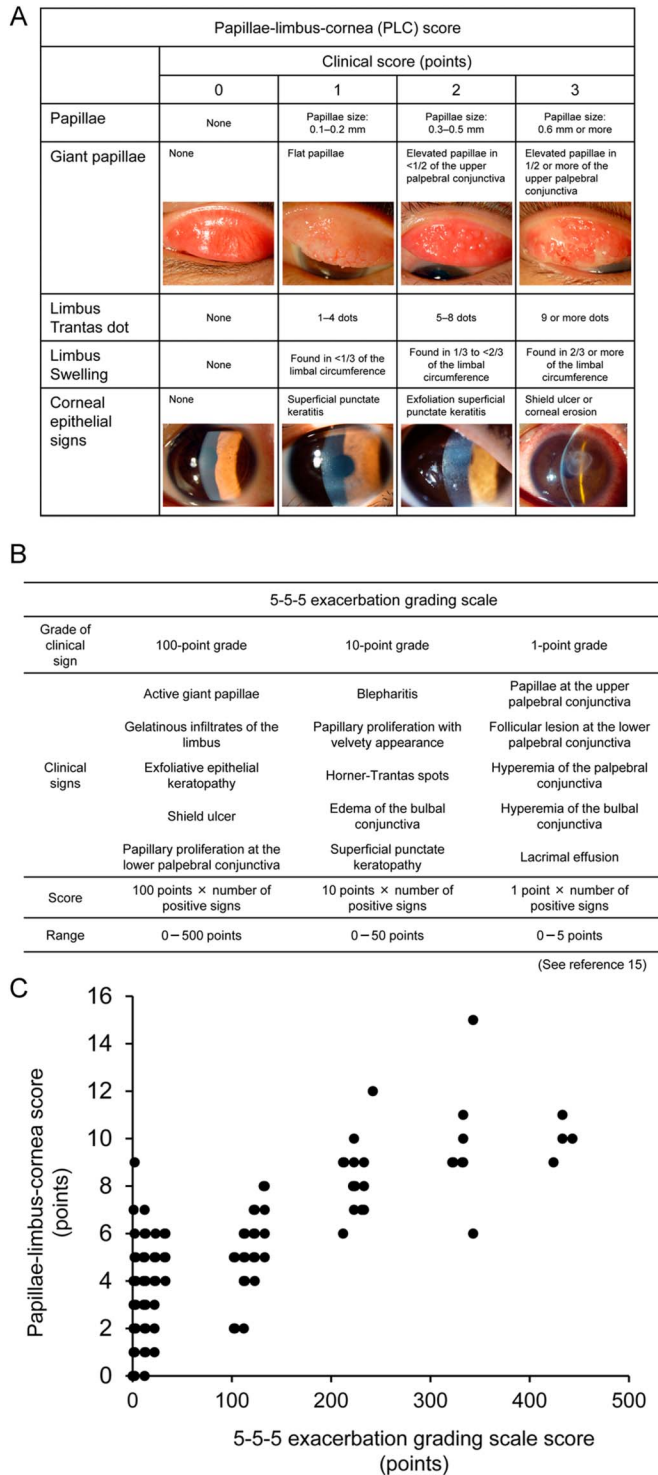


FIGURE 1. PLC scores and 5-5-5 exacerbation grading scale scores. Clinical findings of the patients were evaluated using both the PLC score and the 5-5-5 exacerbation grading scale score. **A**, Evaluation criteria for PLC scores. **B**, Evaluation criteria for 5-5-5 exacerbation grading scale scores. **C**, Correlation between PLC scores and 5-5-5 exacerbation grading scale scores. Both clinical scores indicated a statistically significant correlation ($\rho = 0.692$; $P < 0.001$; Spearman correlation coefficient). (The full color version of this figure is available at www.corneajrnl.com.)

cytokines, such as IL-4 and IL-5.⁵ Tacrolimus is used in systemic therapy, mainly for the management of organ transplant rejection and the treatment of systemic immune-mediated conditions (eg, rheumatoid arthritis); tacrolimus ointment is used for the treatment of atopic dermatitis.⁶ The efficacy and safety of using various concentrations (0.003%, 0.005%, 0.01%, and 0.1%) of tacrolimus eye drops and 0.03% ointment for treating VKC have been reported.^{7–11} Among the different preparations of tacrolimus ophthalmic suspensions, the most common concentration is 0.1%.

Tacrolimus ophthalmic suspension 0.1% was launched in May 2008 in Japan. A nationwide survey of patients with chronic ACD who used tacrolimus ophthalmic suspension 0.1% was conducted in Japan between May 2008 and November 2011.^{11–13} In this survey, clinical investigations were conducted to evaluate the efficacy and safety of tacrolimus ophthalmic suspension for the treatment of VKC and AKC. This was performed by clarifying and assessing improvement in clinical scores, increase in clinical remission rates, and decrease in the concomitant use of steroid eye drops during 6 months of observation. Regarding adverse events due to treatment with tacrolimus ophthalmic suspension, glaucoma and cataract were not reported; however, a transient burning sensation on instillation and ocular herpes simplex viral infection were reported as major adverse events.^{12,13}

Although the observation period of the nationwide survey in Japan was 6 months, VKC and AKC are chronic diseases and affected patients require long-term treatment over several years. However, the effects of the prolonged use of tacrolimus ophthalmic suspension for the treatment of VKC and AKC are not fully understood. Therefore, we conducted this study to clarify the clinical improvement with and safety of the use of tacrolimus ophthalmic suspension 0.1% over a 24-month follow-up period in patients with VKC and AKC.

MATERIALS AND METHODS

This 2-year retrospective observational study was approved by the institutional review board of the Nihon University School of Medicine (approval number: RK-171212-09) and adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective study design.

The primary objective was to evaluate the clinical improvement in patients with VKC and AKC after treatment with tacrolimus ophthalmic suspension 0.1%. The secondary objective was to analyze the representative clinical characteristics of the patient subgroups using cluster analysis.

Eligibility Criteria and Diagnosis

This study included 36 eyes of 36 consecutive patients who were diagnosed with AKC or VKC at Nihon University Itabashi Hospital, according to the clinical guidelines for ACDs.¹⁴ All patients were followed up for 24 months after starting treatment with tacrolimus ophthalmic suspension. If the disease severity was different between the left and right eyes, we included the eye with more severe disease; the right

eye was selected if the left and right eyes had similar disease severity. Patients were excluded from participation for any of the following reasons: 1) patients were not treated in our hospital for 24 months; 2) patients had eye diseases other than ACDs; and 3) patients had systemic diseases other than allergic diseases.

Observation Period and Methods

The demographic data and clinical findings of the enrolled patients were collected from their medical files. The collated data were as follows: age, sex, complications of allergic disease, clinical score, concomitant use of topical drugs including steroids and antiallergy eye drops, frequency of relapses, and adverse events. Clinical findings were evaluated using the papillae–limbus–cornea score (PLC score) and the 5-5-5 exacerbation grading scale.^{13,15} Clinical scores and concomitant drugs used were recorded at baseline and at each follow-up visit (1st, 3rd, 6th, 9th, 12th, 15th, 18th, 21st, and 24th months).

Treatment Protocol

At our hospital, patients with AKC and VKC were switched to a combination therapy after the discontinuation of their existing medications. The combination therapy initially comprised tacrolimus ophthalmic suspension 0.1% and anti-allergy eye drops; however, 1 patient was treated with the antiallergic, steroid, and tacrolimus eye drops, and another patient was only treated with tacrolimus eye drops. If the effect of the combination therapy was inadequate or if acute exacerbation occurred during the course of the combination therapy, a steroid was concurrently administered in the form of an eye drop or a subconjunctival injection. Eighteen of the 36 patients required the addition of steroids to their treatment regimen due to a relapse or an acute exacerbation. When the symptoms and clinical findings improved, the combination therapy was continued without steroids.

Outcome Measures

PLC Score

PLC scores were used to evaluate clinical improvement (Fig. 1A). Objective evaluations were made by scoring clinical photographs according to established guidelines.¹⁴ The PLC score was obtained by evaluating the following objective signs of AKC/VKC: palpebral conjunctival papillae, giant papillae, limbal Trantas dots, limbal swelling, and corneal epithelial lesions.¹³ These 5 objective signs were chosen from the clinical evaluation criteria for ACDs described in previously established guidelines in Japan,¹⁴ because they are the most important signs of AKC/VKC. Each objective sign is evaluated using a 4-point scale (none, mild, moderate, and severe), and the PLC score is determined by summing the scores of the 5 objective signs. The range of the PLC score is 0 to 15 points, and AKC/VKC patients with scores of 5 points or less are considered to be in remission.

TABLE 1. Demographic and Clinical Characteristics of the Patients Included in the Study

	Patients (eyes)	36
	Age (yr) (mean ± SD)	20 ± 12.4
	Sex (male:female)	32 : 4
Clinical from of ACD	AKC	19
Eyes	VKC	17
	Allergic rhinitis	13
Allergic complications	Atopic dermatitis	34
Cases	Bronchial asthma	16
Concomitant use of eye	Antiallergic eye drops	35
Drops at baseline (eyes)	Steroid eye drops	1

Remission Rate

The remission threshold was set at a PLC score of 5 points.¹³ The remission rate of each patient was determined using this threshold, with a score ≤5 points indicating the remission stage and a score >5 points indicating an active disease stage.

5-5-5 Exacerbation Grading Scale

The clinical severity of AKC/VKC was determined using the 5-5-5 exacerbation grading scale for ACDs (Fig. 1B).¹⁵ In this method, 100 points are assigned to each of the 5 severe clinical findings (active giant papillae, gelatinous infiltrates of the limbus, exfoliative epithelial keratopathy, shield ulcer, and papillary proliferation at the lower palpebral conjunctiva); 10 points are assigned to each of the 5 moderate clinical findings (blepharitis, papillary proliferation with velvety appearance, Horner–Trantas spots, edema of the bulbar conjunctiva, and superficial punctate keratopathy); and 1 point is given for each of the 5 mild clinical findings (papillae at the upper palpebral conjunctiva, follicular lesion at the lower palpebral conjunctiva, hyperemia of the palpebral conjunctiva, hyperemia of the bulbar conjunctiva, and lacrimal effusion). The sum of the total points in each severity grade determines the severity score on the 5-5-5 exacerbation grading scale. A total score of less than 100 points indicates a stable stage of VKC and AKC. The 5-5-5 exacerbation grading scale was used to determine the refractory index and to perform cluster analysis.

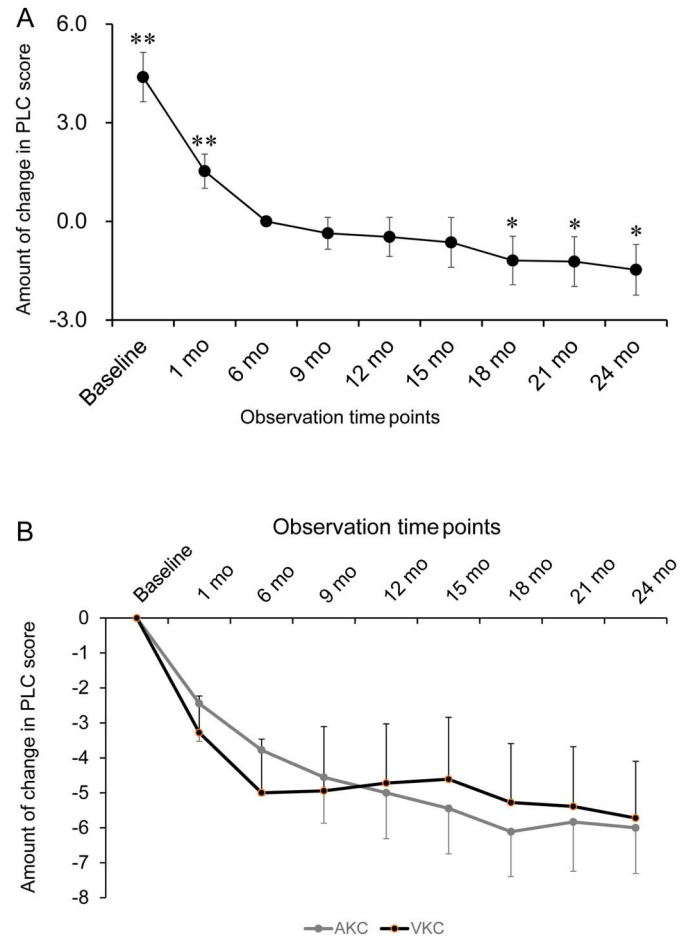
Refractory Index

The refractory index was determined using the 5-5-5 exacerbation grading scale. The 4 classes of the refractory index are class 3 (severe stage), class 2 (moderate stage), class 1 (mild stage), and class 0 (complete remission). Patients who had clinical scores that were more than 100, between 10 and 99, less than 10, and 0, were categorized as having refractory index classes 3, 2, 1, and 0, respectively.

Relapses

The number of relapses was recorded in each patient. A relapse was defined as an increase of 5 or more points in the PLC scores of patients who were in the remission stage of VKC and AKC during the observation period.

FIGURE 2. Improvement of PLC scores over 24 months. **A,** Improvement of PLC scores in all patients. The changes in PLC scores for all patients recorded at baseline ($P < 0.0001$) and in the first month ($P < 0.0001$) were significantly higher than that recorded in the sixth month (linear mixed-effects model). The changes recorded in the 18th month ($P = 0.0017$), 21st month ($P = 0.0016$), and 24th month ($P = 0.0002$) were significantly lower than that recorded in the 6th month (linear mixed-effects model). **B,** Individual improvement of PLC scores in patients with VKC and AKC. The efficacy of tacrolimus ophthalmic suspension over the time course (observation period \times clinical form) was different between the AKC and VKC groups. ($P = 0.011$, linear mixed-effects model). However, there was no difference in the final degree of change after 24 months ($P = 0.610$, Mann-Whitney U test) between the VKC and AKC groups. The points and the error bars of the graph indicate the mean values and 95% confidence intervals, respectively. * $P < 0.005$; ** $P < 0.001$. (The full color version of this figure is available at www.corneajrnl.com.)



Safety of Tacrolimus Treatment

Adverse events reported during the observation period were recorded for all registered patients.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Advanced Statistics 22 (IBM Japan, Tokyo, Japan), and MAC Toukei-Kaiseki v.2 software (Esumi, Tokyo, Japan). A linear mixed-effects model was used to analyze the clinical improvement of the patients and the outcome of treatment with tacrolimus ophthalmic suspension. Remission rates and refractory indices recorded at each follow-up visit were compared with those recorded at baseline using the Steel test. Furthermore, we analyzed the correlation between the PLC and 5-5-5 exacerbation grading scale scores. A logistic regression analysis was used to assess potential associations between patient clinical characteristics and the need for concomitant steroid eye drop administration. All patients were classified into 3 subgroups using cluster analysis.

RESULTS

Patient Backgrounds

The baseline characteristics of the 36 enrolled patients are summarized in Table 1. The percentage of male patients in

the study population was 88.9%, and the mean age of the patients was 20.0 ± 12.4 (SD) years at the time of enrolment. Of all enrolled patients, 97% had an allergic complication. Thirty-five patients who concomitantly used anti-allergy ophthalmic solutions (eg, antihistamines and mast cell stabilizers) and 1 patient who concomitantly used a steroid ophthalmic solution were included.

Clinical Improvement of VKC and AKC after Topical Tacrolimus Treatment

The clinical improvements in the enrolled patients, which were evaluated using the PLC and 5-5-5 exacerbation grading scale scores over a period of 24 months, are shown in Figures 2A, 3, respectively. We used the sixth month as a reference point to assess the effects of longer-term tacrolimus treatment. In addition, both clinical scores indicated a statistically significant correlation ($\rho = 0.692$, $P < 0.001$, Spearman correlation coefficient) (Fig. 1C).

Improvement of Clinical Scores in Patients with VKC and AKC

The PLC scores recorded at baseline and at the 6th month, 12th month, and the 24th month were 8.4 (7.6–9.3)

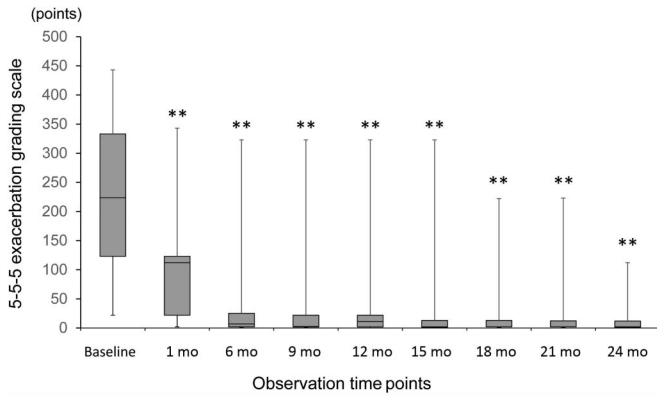


FIGURE 3. Improvement of 5-5-5 exacerbation grading scale scores over 2 years. The 5-5-5 exacerbation grading scale scores significantly decreased from the 1st month to the 24th month ($P < 0.01$ at each observation time point, Steel test) compared with the baseline scores. A score of less than 100 points indicates a stable stage of VKC and AKC. At each observation time point after the sixth month, the median value was less than 100 points. $**P < 0.001$.

[mean (95% confidence interval)], 4.0 (3.4–4.6), 3.6 (3.0–4.1), and 2.6 (2.2–3.0), respectively. The changes in PLC scores at each time point were calculated based on the PLC score recorded in the sixth month (Fig. 2A). The changes in the PLC scores recorded at baseline ($P < 0.0001$) and in the first month ($P < 0.0001$) were significantly higher than that recorded in the sixth month (linear mixed-effects model). The changes recorded in the 18th ($P = 0.0017$), 21st ($P = 0.0016$), and 24th month ($P = 0.0002$) were significantly lower than that recorded in the 6th month (linear mixed-effects model).

The course of topical tacrolimus treatment was examined for each clinical form. In VKC with seasonal exacerbations, clinical scores showed an increasing trend at the 12th–15th months, whereas in AKC with a perennial course, gradual improvement was observed consistently. The efficacy

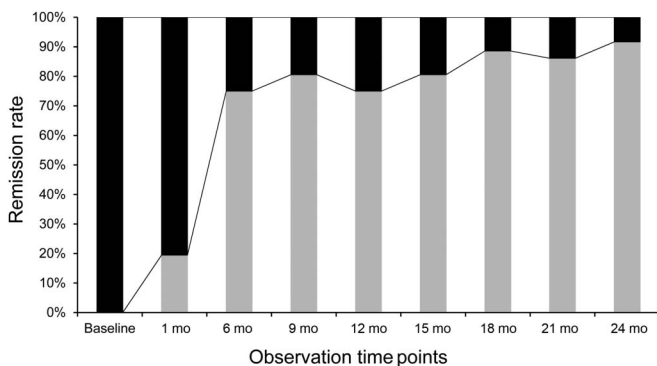


FIGURE 4. Alterations in the remission rates of patients treated with topical tacrolimus treatment over 24 months. The remission rate of each patient was determined using a PLC threshold of ≤ 5 points. The remission rate was 19% in the 1st month; it increased over time, reaching 92% in the 24th month. active; remission.

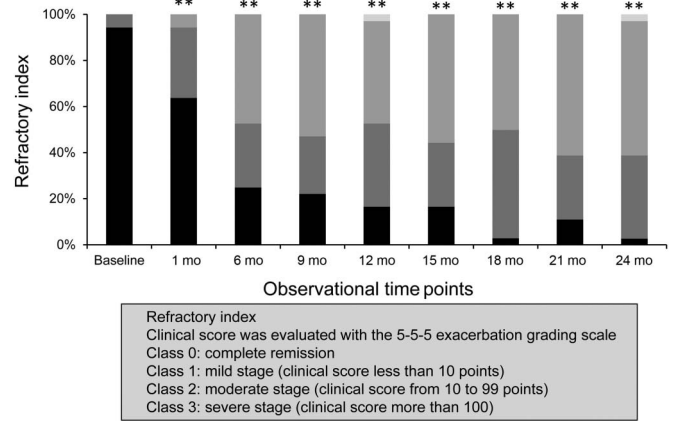


FIGURE 5. Alterations in the refractory indices of patients treated with topical tacrolimus over 24 months. Refractory indices were classified from zero to 3 depending on the 5-5-5 exacerbation grading scale score of the patients. The classification criteria are shown in a panel within the figure. The ratio of patients who had a class 3 (severe stage) index was reduced to 16% and 2.8% in the 12th and 24th month, respectively. Refractory indices recorded at each observation time point were significantly improved compared with those at recorded at baseline (Steel test). ■, class 0; ■, class 1; ■, class 2; ■, class 3. *, $P < 0.01$.

of tacrolimus ophthalmic suspension over the time course (observation period \times clinical form) was different between the AKC and VKC groups ($P = 0.011$, linear mixed-effects model). However, there was no difference in the final degree of change after 24 months ($P = 0.610$, Mann–Whitney U test) between the VKC and AKC groups (Fig. 2B).

The changes in remission rates over time are shown in Figure 4. The remission rate was 19% in the first month. The remission rate then increased over time, reaching 75.0% in the 6th and 12th months and 92% in the 24th month.

Seventeen of the 36 patients (47.2%) had relapses. Seven patients had a single relapse, and 6 patients had 2 relapses. Three patients had 3 relapses. One refractory case was observed, which had an exacerbation frequency ≥ 5 . Thirteen of the 36 patients (36.1%) had exacerbations less than once a year.

The clinical severity of VKC and AKC was evaluated using the 5-5-5 exacerbation grading scale. The scores of the patients at each observation time point are shown in the box-and-whisker plots in Figure 3. The scores of the 5-5-5 exacerbation grading scale recorded at each observation time point significantly improved compared with scores recorded at baseline ($P < 0.01$ for all observation time points, Steel test). The median values of the 5-5-5 exacerbation grading scale scores after the sixth month were almost less than 100 points: 2.5, 11, 2, 2, 2, and 2 points at 9, 12, 15, 18, 21, and 24 months, respectively.

The refractory index was used to convert the refractory degree of each patient’s disease into a clinical classification. The ratio of enrolled patients who had a class 3 index gradually decreased over time: 34 (94.4%), 9 (25.0%), and 6 (16.7%) patients had a class 3 index at baseline, 6th month,

TABLE 4. Incidence of Adverse Drug Reactions Over the 24-Mo Period

Observational Period	Adverse Reactions	No. of Patients
Less than 1 mo	Chickenpox	1
1–5 mo	Infectious impetigo	1
6–11 mo	Bacterial conjunctivitis	2
	External hordeolum	1
12–24 mo	Cold	1
	Pneumonia	1
	None	0

DISCUSSION

We evaluated the clinical outcomes and safety of treating patients with VKC and AKC with tacrolimus ophthalmic suspension 0.1% over a 24-month period. Our study had 3 important findings. First, continuous therapy with tacrolimus ophthalmic suspension showed that the clinical scores recorded in the 24th month were significantly improved compared with those recorded in the 6th month. Second, increased age was significantly associated with a decreased requirement for steroid eye drops on logistic regression analysis. Third, cluster analysis showed that, based on background characteristics, the patients could be divided into 3 clusters: adolescent type, pediatric type, and adult type.

VKC is a severe allergic disorder that is characterized by seasonal exacerbation in the spring. In this study, we were able to assess the clinical improvement of the patients over 2 seasons by conducting a 24-month follow-up. A previous nationwide survey in Japan has evaluated the effectiveness and safety of administering tacrolimus ophthalmic suspension 0.1% in more than 1000 patients with VKC and AKC, over a 6-month period.^{12,13} Clinical scores, including PLC scores, significantly improved from the first to the sixth month, and the remission rate at the sixth month was 85.2%; the ratio of patients who concomitantly used steroids gradually decreased as well.¹² In a recent study published in 2019, Yazu et al¹⁶ reported that tacrolimus ophthalmic suspension 0.1% had a significant effect on clinical scores during a 1-year follow-up and was safe for the treatment of AKC.

Nevertheless, the effectiveness and safety of tacrolimus treatment of patients with VKC and AKC who require prolonged treatment are not yet fully understood. To help clarify this, we assessed the clinical scores of the patients at several observation time points, using the clinical score recorded in the sixth month as a basis to assess effectiveness and safety of tacrolimus ophthalmic suspension 0.1% in the subsequent months. To determine the clinical score, we used 2 evaluation methods: the PLC score and the 5-5-5 exacerbation grading scale. The PLC score is an index that permits easy understanding of the amount of change in clinical findings that occurs over time, and the 5-5-5 exacerbation grading scale is an index that allows for easy assessment of disease severity.^{13,15} The clinical scores determined with these evaluation criteria are significantly correlated, and it is considered that objective findings can be appropriately evaluated using these 2 types of clinical scores. In this study,

PLC scores recorded in the 24th month were significantly improved compared with those recorded in the sixth month. In addition, the remission rate recorded in the 24th month was 92%, whereas that recorded in the 6th month was 75%, a value that is moderately lower than that of a previous report (85.2%).¹³ One of the reasons for the differences in the remission rates recorded in the sixth month may be that patients in this study who required prolonged medical treatment had severe clinical findings, which included giant papillae, limbal gelatinous infiltration, and shield ulcer. Therefore, the increased remission rate in the 24th month with prolonged use of tacrolimus ophthalmic suspension 0.1% suggests that patients who have severe symptoms likely require treatment over 2 consecutive seasons. Subsequently, further research is required on proactive therapy with immunosuppressant eye drops in patients who have stable VKC and AKC. Proactive therapy entails instillation of low doses of drugs to prevent recurrences; this is similar to the medical treatment of atopic dermatitis using tacrolimus ointment.¹⁷ Appropriate dosing in proactive therapy is a crucial issue in the medical treatment of VKC and AKC.

In this study, logistic regression analysis showed that there was an almost 50% reduction in the risk for concomitant use of steroid eye drops for every 10-year increase in patient age. Because the 5-5-5 scale is an excellent tool for determining the disease severity in patients with AKC/VKC, it was used as a clinical scale to include patient severity in the classification data used in cluster analysis. For these reasons, the patients were divided into 3 subgroups (adolescent type, pediatric type, and adult type) depending on characteristics including patient age, clinical score measured with the 5-5-5 exacerbation grading scale, refractory index, concomitant use of steroids, and number of relapses, and cluster analysis was performed. Patients in the adolescent type subgroup included those who used tacrolimus ophthalmic suspension 0.1% alone and did not have relapses or use steroids concomitantly. Patients in the pediatric type subgroup included those who occasionally developed acute exacerbation and required concomitant use of steroids. The adult type subgroup consisted mostly of patients with AKC who had persistent mild inflammation with a moderate refractory index and did not have relapses or use steroids. These results indicate that the severity of VKC and AKC may vary depending on the age group of the patient, which may modify the effectiveness of treatment with tacrolimus ophthalmic suspension 0.1%. Furthermore, these results suggest that, when acute exacerbations of AKC and VKC make topical tacrolimus treatment inadequate, treatment of allergic inflammation needs to be augmented with a steroid regimen. Notably, Miyazaki et al reported on the significant effects of topical tacrolimus alone on shield ulcers and corneal epitheliopathy. Patients with severe VKC who had giant papillae in the upper tarsal conjunctiva required prolonged treatment with tacrolimus ophthalmic suspension 0.1%; therefore, it was suggested that severe palpebral conjunctival symptoms, such as giant papillae, may be a risk factor for treatment resistance. In addition, topical steroids did not have a significant additive effect in this scenario.¹⁸ These previously reported results and the results of this study indicate that,

when a reset effect on allergic inflammation in acute exacerbation of VKC and AKC is expected, subconjunctival injection of topical steroids may be better than instillation.

There is considerable concern about the adverse effects of the prolonged use of tacrolimus ophthalmic suspension 0.1%; however, the details are unclear. The adverse reactions recorded in this study are comparable with those previously reported,^{12,13} indicating that there are no specific adverse reactions associated with the prolonged use of tacrolimus ophthalmic suspension 0.1%.

This study had some limitations. First, this was a retrospective study that did not include a control group. Moreover, the course of VKC and AKC in patients who were untreated after the sixth month of topical tacrolimus treatment was not known. A selection bias was evident because evaluations were limited to patients who could be followed up for 2 years. Therefore, a prospective intervention study would be required to confirm whether continuing treatment with tacrolimus ophthalmic suspension after 2 years is necessary. Second, the sample size was small, and the study was conducted at a single institution. In the future, collaborative multicenter research that includes large sample sizes will be required to consolidate the results of this study. In conclusion, we demonstrated that 2-year medical treatment for VKC and AKC using tacrolimus ophthalmic suspension 0.1% is more effective for improving clinical scores and reducing adverse reactions than 6-month treatment.

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REFERENCES

- Singhal D, Sahay P, Maharana PK, et al. Vernal keratoconjunctivitis. *Surv Ophthalmol*. 2019;64:289–311.
- Hogan MJ. Atopic keratoconjunctivitis. *Am J Ophthalmol*. 1953;36:937–947.
- Tuft SJ, Kemeny DM, Dart JK, et al. Clinical features of atopic keratoconjunctivitis. *Ophthalmology*. 1991;98:150–158.
- Kino T, Hatanaka H, Miyata S, et al. FK-506, a novel immunosuppressant isolated from a Streptomyces. *J Antibiot (Tokyo)*. 1987;40:1256–1265.
- 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;1:1219–1226.
- Ohtsuki M, Morimoto H, Nakagawa H. Tacrolimus ointment for the treatment of adult and pediatric atopic dermatitis: review on safety and benefits. *J Dermatol*. 2018;45:936–942.
- Al-Amri AM, Fiorentini SF, Albarry MA, et al. Long-term use of 0.003% tacrolimus suspension for treatment of vernal keratoconjunctivitis. *Oman J Ophthalmol*. 2017;10:145–149.
- Zanjani H, Aminifard MN, Ghafourian A, et al. Comparative evaluation of tacrolimus versus interferon alpha-2b eye drops in the treatment of vernal keratoconjunctivitis: a randomized, double-masked study. *Cornea*. 2017;36:675–678.
- Shoughy SS, Jaroudi MO, Tabbara KF. Efficacy and safety of low-dose topical tacrolimus in vernal keratoconjunctivitis. *Clin Ophthalmol*. 2016;10:643–647.
- Chatterjee S, Agrawal D. Tacrolimus in corticosteroid-refractory vernal keratoconjunctivitis. *Cornea*. 2016;35:1444–1448.
- 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;26:165–173.
- Fukushima A, Ohashi Y, Ebihara N, et al. Therapeutic effects of 0.1% tacrolimus eye drops for refractory allergic ocular diseases with proliferative lesion or corneal involvement. *Br J Ophthalmol*. 2014;98:1023–1027.
- Shoji J, Ohashi Y, Fukushima A, et al. Topical tacrolimus for chronic allergic conjunctival disease with and without atopic dermatitis. *Curr Eye Res*. 2019;44:796–805.
- Takamura E, Uchio E, Ebihara N, et al. Japanese guidelines for allergic conjunctival diseases 2017. *Allergol Int*. 2017;66:220–229.
- Shoji J, Inada N, Sawa M. Evaluation of novel scoring system named 5-5-5 exacerbation grading scale for allergic conjunctivitis disease. *Allergol Int*. 2009;58:591–597.
- Yazu H, Shimizu E, Aketa N, et al. The efficacy of 0.1% tacrolimus ophthalmic suspension in the treatment of severe atopic keratoconjunctivitis. *Ann Allergy Asthma Immunol*. 2019;122:387–392.e1.
- Wollenberg A, Reitamo S, Girolomoni G, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy*. 2008;63:742–750.
- Miyazaki D, Fukushima A, Ohashi Y, et al. Steroid-sparing effect of 0.1% tacrolimus eye drop for treatment of shield ulcer and corneal epitheliopathy in refractory allergic ocular diseases. *Ophthalmology*. 2017;124:287–294.