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To cite this article: Jun Shoji, Yuichi Ohashi, Atsuki Fukushima, Dai Miyazaki, Eiichi Uchio, Etsuko Takamura, Hiroshi Fujishima, Kenichi Namba, Naoki Kumagai, Nobuyuki Ebihara & Shigeki Okamoto (2019): Topical Tacrolimus for Chronic Allergic Conjunctival Disease with and without Atopic Dermatitis, Current Eye Research, DOI: [10.1080/02713683.2019.1600197](https://doi.org/10.1080/02713683.2019.1600197)

To link to this article: <https://doi.org/10.1080/02713683.2019.1600197>



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Published online: 05 Apr 2019.



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Topical Tacrolimus for Chronic Allergic Conjunctival Disease with and without Atopic Dermatitis

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ABSTRACT

Purpose/Aim: This study evaluated the efficacy of topical 0.1% tacrolimus ophthalmic suspension for treating chronic allergic conjunctival disease with and without atopic dermatitis.

Materials and Methods: This study was conducted as a prospective observational post-market survey. Our large-scale study protocol was accepted by the Pharmaceuticals and Medical Devices Agency in Japan and included patients who were prescribed topical tacrolimus for the treatment of chronic allergic conjunctival disease from May 2008 to Aug 2010 in Japan. Topical tacrolimus was instilled 2 times daily for 6 months. The primary endpoint was the change from baseline in papillae-limbus-cornea clinical signs score (based on the presence of papillae, giant papillae, Trantas' dots, limbal swelling, and corneal epithelial signs). Remission rate following topical tacrolimus treatment was investigated using generalized estimating equations.

Results: A total of 1821 subjects were included in the analyses. Six months into treatment, 83.0% and 87.7% of subjects with and without atopic dermatitis, respectively, were in remission (based on the papillae-limbus-cornea grading score). Topical tacrolimus treatment was equally effective in improving papillae-limbus-cornea grading scores from baseline in both study groups after 6 months of treatment. Additionally, the odds ratio for remission increased over time. The concomitant use of topical steroids improved papillae-limbus-cornea grading scores, including papillary signs with a statistically significant, but low odds ratio.

Conclusion: Tacrolimus ophthalmic suspension is useful for treating chronic allergic conjunctival disease with and without atopic dermatitis. Clinical response to local tacrolimus therapy is dependent upon treatment duration.

ARTICLE HISTORY

Received 31 August 2018
Revised Vxx xxx xxxx
Accepted 10 March 2019

KEYWORDS

Allergic conjunctivitis; atopic dermatitis; atopic keratoconjunctivitis; tacrolimus ophthalmic suspension; vernal keratoconjunctivitis

Introduction

Allergic conjunctival disease (ACD), including seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC), is caused by an ocular surface allergy.¹ Most ACDs related to SAC and PAC have mild-to-moderate clinical manifestations which coincide with seasonal and perennial responses, respectively. Both disease forms involve an immunoglobulin E-mediated type 1 hypersensitivity caused by pollen, pets, or house dust allergens.¹ Severe and refractory forms of ACD include AKC and VKC, which are characterized by their chronic nature, the presence of conjunctival proliferative lesions (e.g., giant papillae and gelatinous limbus infiltration), and visual impairment caused by corneal lesions (e.g., shield ulcers). Disease severity is dependent upon allergic disease complications; patients are said to have chronic

ACD when severe ACD with or without allergic rhinitis, atopic dermatitis and/or bronchial asthma is present.^{2,3}

Topical therapies are often used to treat ACD, but their complicating effects on allergic disease is not fully understood in chronic ACD patients. Mild ACD, including allergic conjunctivitis, is generally treated with topical anti-allergic drugs that have antihistaminic and mast cell-stabilizing properties. Chronic ACD patients are often treated with topical, oral, or subconjunctival corticosteroids in addition to topical anti-allergic agents. However, corticosteroid use is associated with serious adverse reactions, including elevated intraocular pressure, glaucoma,^{4,5} posterior subcapsular cataract formation,⁶ and secondary infection.³ Therefore, other medications have been investigated, including topical immunosuppressants. Both cyclosporine ophthalmic solution and tacrolimus ophthalmic suspension have been shown to be effective nonsteroidal

therapies for treating chronic ACD.^{7,8} Furthermore, both topical medications have been approved in Japan to treat VKC because they are well tolerated and effectively manage VKC with and without atopic dermatitis.^{9,10}

Tacrolimus ophthalmic suspension 0.1% was launched in May 2008 in Japan. Tacrolimus is a 23-member cyclic macrolide lactone that was isolated from *Streptomyces tsukubaensis* in 1984.¹¹ In T cells, tacrolimus inhibits calcineurin (via binding to FK506-binding proteins) and cytokine secretion.¹² Cytokine secretion inhibition of tacrolimus is approximately 100-times that of cyclosporine,¹³ which is important because managing T cell cytokine secretion is of primary importance for managing severe allergic eye diseases.^{14,15} As a result, topical tacrolimus is more effective than topical cyclosporine for managing most allergic eye disease and is better tolerated by patients.⁹

A nationwide survey of chronic ACD patients who used tacrolimus ophthalmic suspension was conducted between May 2008 and November 2011 in Japan to evaluate the efficacy and safety of 0.1% tacrolimus ophthalmic suspension. The survey registered 1821 chronic ACD patients. We previously examined the benefits of tacrolimus in 1436 patients younger than 40 years of age because chronic ACD occurs most frequently in this age group.^{1,16} In this sample of younger patients, both subjective symptoms and objective clinical findings were significantly improved by 1 month of tacrolimus therapy, even in patients who had responded poorly to cyclosporine.¹⁷ Chronic ACD accompanied by AD may be harder to treat than chronic ACD without AD, but it is unknown if the presence of AD affects the ability of tacrolimus to successfully treat chronic ACD. The current study examines tacrolimus efficacy in chronic ACD patients with and without AD. All 1821 chronic ACD patients registered in the Japanese nationwide survey were included.

Materials and methods

This study was conducted under the drug re-examination system in compliance with the Japanese Good Post-Marketing Study Practice. The study protocol, including patient registration procedures and case report form modules, was reviewed by the Pharmaceuticals and Medical Devices Agency in Japan. The study protocol and results were registered in the Japanese University Hospital Medical Information Network (UMIN000008640).

Registered patients

This observational study included patients in Japan with chronic ACD who began topical 0.1% tacrolimus ophthalmic suspension (TALYMUS®, Senju Pharmaceutical Co., Ltd., Osaka, Japan) therapy between May 2008 and August 2010. All data were obtained from a post-marketing survey that examined 0.1% tacrolimus ophthalmic suspension safety and efficacy in Japan.

Chronic ACD diagnoses were made using the Japanese Ophthalmological Society guidelines for ACDs.¹ Patients who were diagnosed with chronic ACD were registered in the study if they had conjunctival proliferative changes (giant papillae or limbal gelatinous infiltration) and responded

poorly to anti-allergic drugs, steroids, and cyclosporine. Patients were excluded from the study if they had a history of hypersensitivity to any tacrolimus ophthalmic suspension component, had an eye infection, or were pregnant or might be pregnant. Patients were formally registered into the study by faxing the completed site/patient information form to the central registration center.

Data collection

Patient demographics at the time of registration were collected, including age at tacrolimus therapy initiation, sex, allergic complications (e.g., atopic dermatitis, bronchial asthma, and allergic rhinitis), and eye drop use (e.g., anti-allergic drops, corticosteroids, and cyclosporine) immediately before and during tacrolimus therapy.

Subjective symptoms

Six subjective symptoms were examined in this study, including itching, discharge, lacrimation, photophobia, foreign body sensation, and eye pain. Each subjective symptom category was scored using the following four-point scale: 0 = asymptomatic, 1 = mild, 2 = moderate, and 3 = severe. The change in the sum of symptom scores was evaluated over time.

Papillae-limbus-cornea grading scores

Several objective evaluations were also made by scoring clinical photographs according to established guidelines.^{1,16} Papillae-limbus-cornea (PLC) grading score definitions and two representative examples are shown in Figure 1a–c. The PLC score was obtained by evaluating the following objective signs of chronic ACD: palpebral conjunctival papillae, giant papillae, limbal Trantas' dots, limbal swelling, and corneal epithelial lesions. These five items were chosen because they are the most important signs of chronic ACD.¹ The papillary (palpebral conjunctival papillae and giant papillae scores), limbal (limbal Trantas' dots and swelling scores), and corneal epithelial sign subscores were also examined. The PLC score and subscores were used in clinical efficacy evaluations.¹⁰

Outcome measures

This study examined baseline chronic ACD patient characteristics and changes in subjective symptoms and objective findings after initiating treatment with 0.1% tacrolimus ophthalmic suspension. Tacrolimus was administered twice a day for a period of 6 months. Subjective symptoms and objective PLC grading scores were determined before and 1, 2, 3, and 6 months after beginning tacrolimus therapy. Patients were divided into “with-AD” and “without-AD” groups and changes in symptom and PLC grading scores from baseline were examined and compared. Tacrolimus safety was evaluated using the incidences of adverse reactions reported during the 6-month study period.

Statistical analyses

Categorical data are presented as mean (95% confidence interval [CI]) and continuous data are presented as mean $\pm$ standard

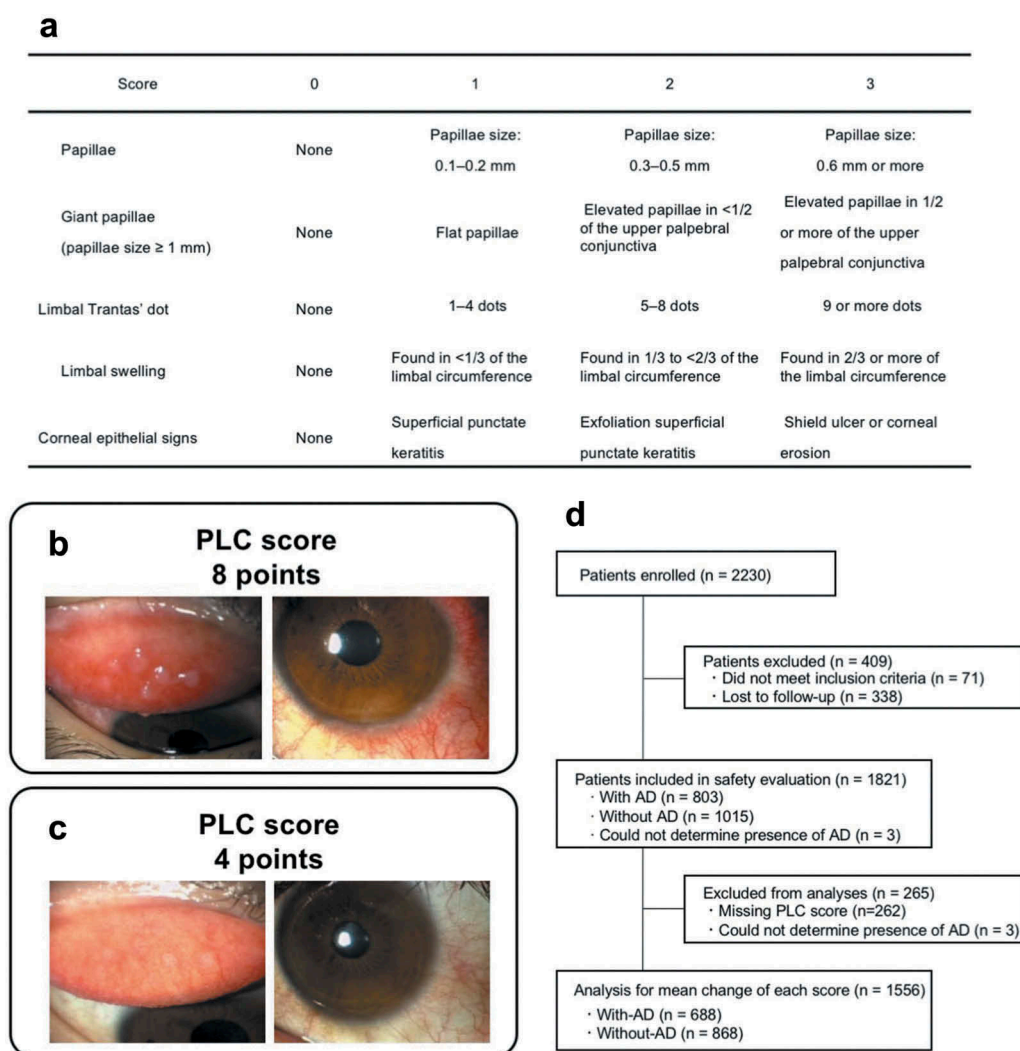


Figure 1. (a) Grading scales used to determine the papillae-limbal-corneal epithelial (PLC) score, which was defined as the sum of the papillae (papillae size, giant papillae appearance), limbal (number of Trantas' dots and limbal swelling extent), and corneal epithelial sign subscores. (b) Representative case of 12-year-old patient with vernal keratoconjunctivitis (VKC). The PLC score was 8 points (papillae subscore = 5, limbal subscore = 2 [1 point for Trantas' dots, 1 point for limbal swelling], corneal epithelial subscore = 0). (c) The same patient after 2 months of treatment with topical 0.1% tacrolimus ophthalmic suspension. The clinical signs of VKC had markedly improved and the PLC score was 4 points (papillae subscore = 4, limbal subscore = 0, corneal epithelial subscore = 0). (d) Flow diagram for this study. A tacrolimus study committee was established to assess eligibility of ophthalmologists in Japan.

deviation. The Wilcoxon rank sum test was used to examine differences in objective baseline PLC scores between AD subgroups and among age subgroups. Two-sided *P* values were examined. Generalized estimating equation (GEE) analyses¹⁸ with the Logit Link function were used to analyze the impact of AD on tacrolimus treatment outcomes. Associations between PLC and symptoms scores and the following factors were examined at each time point (baseline and 1, 2, 3, and 6 months): age, sex, concomitant anti-allergic drug use, and concomitant corticosteroid use. In our analyses, dependent (response) variables were binary (e.g., remission of subjective score and yes or no for objective sign score), with remission thresholds set at ≤ 5 points for the overall PLC grading score, ≤ 4 points for the papillary sign subscore, 0 points for the limbal sign subscore, ≤ 1 point for the corneal epithelial sign subscore, and 0 points for the subjective symptom score.^{16,19} The remission rate of chronic ACD patients treated with topical tacrolimus was also evaluated and compared

between study groups. Incidence rates of adverse reactions in patients with- and without-AD were analyzed using Fisher's exact test. All statistical analyses were performed using SAS statistical software (version 9.3 for Windows, SAS Institute Inc., Cary, NC) and statistical significance was defined as $P < 0.05$.

Results

The CONSORT flow diagram for this study is shown in Figure 1d. Baseline characteristics of the 1821 chronic ACD patients (1350 men, 471 women) included in this study are summarized in Table 1. Briefly, subjects had an average age of 19.3 ± 14.2 years and 44.1% of patients had AD. The records of 1559 patients contained scores for all objective clinical and subjective symptom measures. This included 688 patients with AD and 868 patients without AD. Three patients were

Table 1. Baseline characteristics of included patients.

	With AD (n = 803)	Without AD (n = 1015)	Unknown (n = 3)	All patients (n = 1821)
Sex				
Male (%)	642 (80.0%)	706 (69.6%)	2	1350 (74.1%)
Female (%)	161 (20.0%)	309 (30.4%)	1	471 (25.9%)
Age (years)	19.5 ± 11.7	19.3 ± 15.9	17.7 ± 9.3	19.3 ± 14.2
Allergic complications				
Allergic rhinitis	181 (22.6%)	220 (21.7%)	0	401 (22.1%)
Asthma	197 (24.6%)	101 (9.9%)	0	298 (16.4%)
Pretreatment				
Anti-allergic eye drops	482 (60.1%)	543 (53.4%)	1	1026 (57.3%)
Topical steroids	467 (58.2%)	524 (51.6%)	1	992 (55.4%)
Topical cyclosporine	294 (36.7%)	279 (27.5%)	0	573 (31.5%)

Data presented as n (%) and mean ± standard deviation. AD, atopic dermatitis.

excluded from analyses because it was not possible to determine whether or not AD was present.

Effect of tacrolimus on objective allergic conjunctival disease measures

Overall papillae-limbus-cornea grading score

The baseline PLC grading score was significantly higher for the with-AD group (7.50 [7.31–7.70]) (mean [95% confidence interval]) than the without-AD group (6.72 [6.55–6.88], $P < 0.0001$; Table 2). Tacrolimus therapy decreased the overall PLC grading score and all clinical subscores in both groups at each time point examined (Figure 2a). Furthermore, the 6-month PLC grading score and subscores indicated that topical tacrolimus therapy was equally effective for improving clinical signs of chronic ACD. At this time, the overall PLC grading score was 3.31 ([3.03–3.59], mean change from baseline = −4.19) in the with-AD group and 2.75 ([2.44–3.06],

mean change from baseline = −3.97) in the without-AD group ($P = 0.6863$; Figure 2a).

Each patient was divided into four subgroups depending on the season when medical treatment started; spring (March to May), summer (June to August), autumn (September to November), and winter (December to February), and effect of treatment with 0.1% tacrolimus ophthalmic suspension for PLC grading score of chronic ACD patients in each season was evaluated. In both with- and without AD groups, the effects of medical treatment were not different among the seasonal subgroups (Figure 3a–b).

Papillae, limbus, and corneal epithelium sign subscores

The baseline papillary subscore was 4.82 (4.73–4.92) in the with-AD group and 4.38 (4.27–4.48) in the without-AD group ($P < 0.0001$; Table 2). After 6 months of tacrolimus therapy, the papillary subscore was 2.77 ([2.56–2.99], mean change from baseline = −2.05) in the with-AD group and 2.28 ([2.04–2.52], mean change from baseline = −2.10) in the without-AD group. The difference between groups was not statistically significant ($P = 0.6363$; Figure 2b).

Baseline total limbal subscore was significantly higher in the without-AD group (1.33 [1.23–1.44]) than in the with-AD group (1.13 [1.01–1.25], $P = 0.0015$; Table 2). Six months of tacrolimus therapy decreased this subscore to 0.19 ([0.10–0.27], mean change from baseline = −1.14) in the without-AD group and 0.10 ([0.05–0.16], mean change from baseline = −1.03) in the with-AD group. The difference between groups in limbal subscore at 6 months was not statistically significant ($P = 0.1541$; Figure 2c).

The baseline corneal epithelial sign score was 1.55 (1.46–1.63) in the with-AD group and 1.00 (0.94–1.07) in the without-AD group (Table 2, $P < 0.0001$). The corneal subscore

Table 2. Papillae-limbus-cornea grading scores and symptom scores in chronic allergic conjunctival disease patients with and without atopic dermatitis.

Age (years)	AD	n (patients)	% with AD	PLC score		Papillary subscore		Limbal subscore		Corneal subscore	
				Mean (95% CI)	P	Mean (95% CI)	P	Mean (95% CI)	P	Mean (95% CI)	P
Overall	With	688	44.2	7.50 (7.31–7.70)	< 0.0001	4.82 (4.73–4.92)	< 0.0001	1.13 (1.01–1.25)	0.0015	1.55 (1.46–1.63)	< 0.0001
	Without	868		6.72 (6.55–6.88)		4.38 (4.27–4.48)		1.33 (1.23–1.44)		1.00 (0.94–1.07)	
< 10	With	157	39.2	8.45 (8.04–8.85)	< 0.0001	4.88 (4.63–5.12)	< 0.0001	1.74 (1.44–2.03)	0.6207	1.83 (1.65–2.00)	< 0.0001
	Without	244		7.14 (6.80–7.48)		4.19 (3.96–4.42)		1.75 (1.54–1.97)		1.20 (1.07–1.33)	
10–19	With	274	42.0	7.39 (7.10–7.69)	0.0024	4.94 (4.80–5.08)	0.0002	1.00 (0.82–1.19)	0.0226	1.45 (1.32–1.58)	< 0.0001
	Without	379		6.81 (6.56–7.06)		4.49 (4.34–4.65)		1.27 (1.10–1.43)		1.05 (0.94–1.16)	
20–29	With	108	52.7	7.25 (6.76–7.74)	0.1189	4.89 (4.68–5.10)	0.8857	1.00 (0.70–1.30)	0.9152	1.36 (1.14–1.58)	0.0009
	Without	97		6.65 (6.20–7.10)		4.86 (4.63–5.08)		0.96 (0.68–1.24)		0.84 (0.64–1.03)	
30–39	With	113	64.9	7.02 (6.56–7.47)	0.0187	4.62 (4.39–4.85)	0.0697	0.77 (0.53–1.01)	0.1113	1.63 (1.40–1.85)	< 0.0001
	Without	61		6.15 (5.57–6.72)		4.16 (3.80–4.53)		1.13 (0.73–1.53)		0.85 (0.61–1.09)	
≥ 40	With	36	29.3	6.53 (5.69–7.36)	0.0539	4.17 (3.66–4.67)	0.6914	0.97 (0.50–1.45)	0.4688	1.39 (1.01–1.77)	< 0.0001
	Without	87		5.56 (5.15–5.98)		4.00 (3.65–4.35)		1.01 (0.76–1.26)		0.55 (0.38–0.72)	

P-values calculated using Wilcoxon rank sum tests. PLC, papillae-limbus-conjunctival; AD, atopic dermatitis; 95% CI, 95% confidence interval.

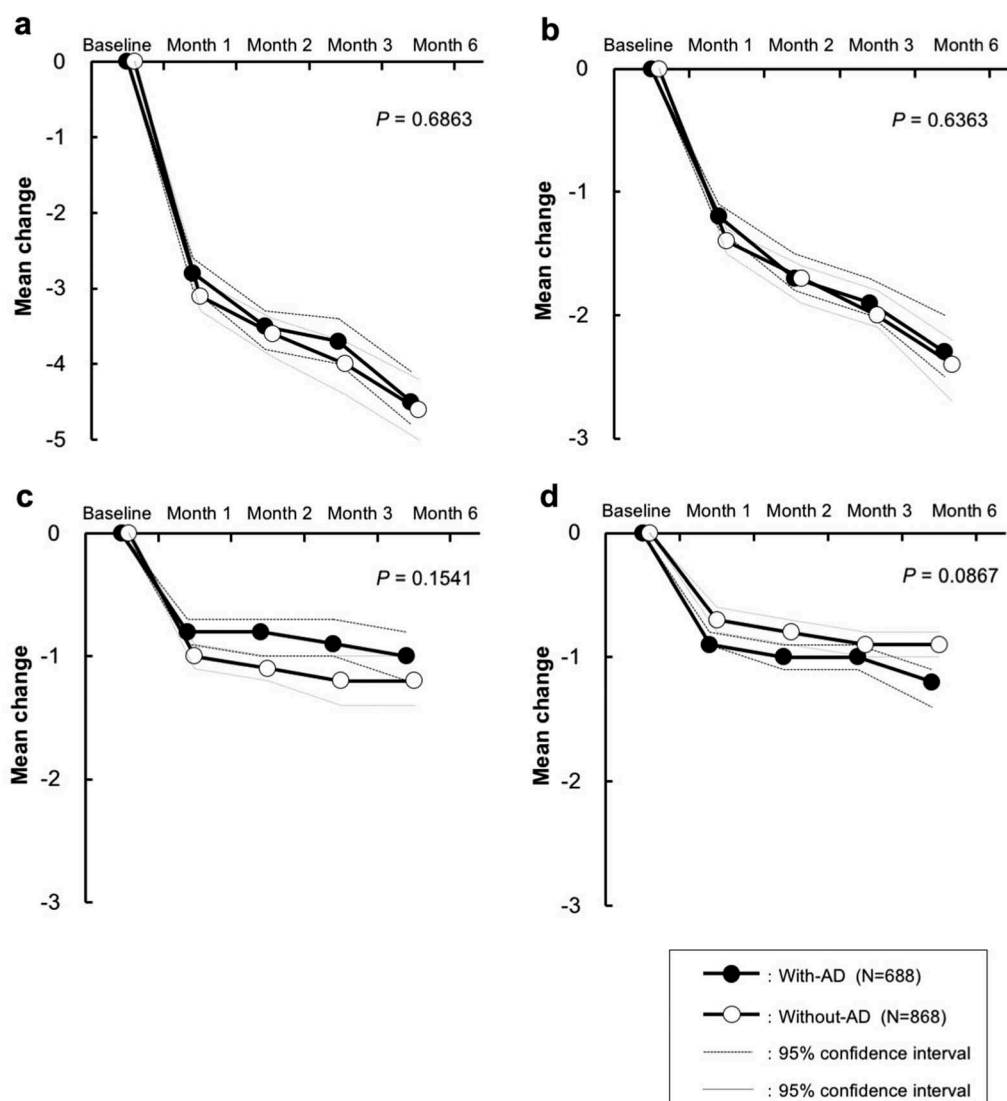


Figure 2. Clinical effect of topical 0.1% tacrolimus ophthalmic suspension treatment over time in patients with chronic allergic conjunctival disease (ACD). Mean change from baseline in papillae-limbus-corneal (PLC) score (a) and papillary sign (b), limbal sign (c), and corneal epithelial sign (d) subscores are shown for the 6-month study period for patients with and without atopic dermatitis (AD). Each data point represents the mean value and dotted lines represent the 95% confidence interval. There were no statistically significant treatment efficacy differences between patients with and without AD (generalized estimating equation [GEE] analysis).

was significantly higher in the with-AD group than the without-AD group in all age subgroups (all $P < 0.0001$). As with the papillary and limbus subscores, 6 months of tacrolimus therapy decreased the corneal epithelial sign score at 6 months, which was 0.43 ([0.34–0.53], mean change from baseline = -1.12) in the with-AD group and 0.28 ([0.20–0.36], mean change from baseline = -0.72) in the without-AD group. The 6-month corneal subscore was not significantly different between the with-AD and without-AD groups ($P = 0.0867$; Figure 2d).

Allergic conjunctival disease remission rates

Remission rates increased as tacrolimus treatment duration increased for patients with and without AD when remission was determined using objective (PLC grading scores) and subjective (symptom scores) measures (Figure 4a–d, respectively). This was also true when all included patients were examined as one group. At 6 months, the PLC grading score remission rate

was 83.0%, 87.7%, and 85.2% in the with-AD group (Figure 4a), the without-AD group (Figure 4b), and in all patients, respectively. The symptom score remission rate was 46.3%, 52.0%, and 49.2% in the with-AD group (Figure 4c), the without-AD group (Figure 4d), and in all patients, respectively.

Proportion of patients on combined local medical treatment

The proportions of patients on combined local medical treatment are shown in Figure 4e, and 4f. In the baseline observation, the percentage of patients with concomitant use of steroid ophthalmic solutions was 48.7% in the with-AD group, and 46.5% in the without-AD group. The percentage of patients using steroid eye drops progressively decreased during the 6-month observational period in both the with- and without-AD groups (Figure 4e, and 4f, respectively).

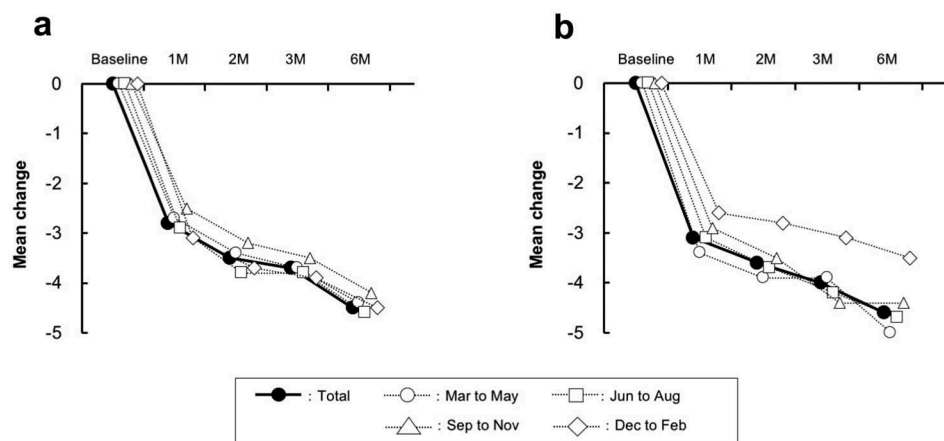


Figure 3. (a) Mean change from baseline in papillae-limbus-corneal (PLC) grading score in with-AD patients. (b) Mean change from baseline in PLC score in without-AD patients. The solid line shows the mean value of PLC grading scores in total patients with-AD (a) or without-AD (b). Each dotted line shows dose initiation season.

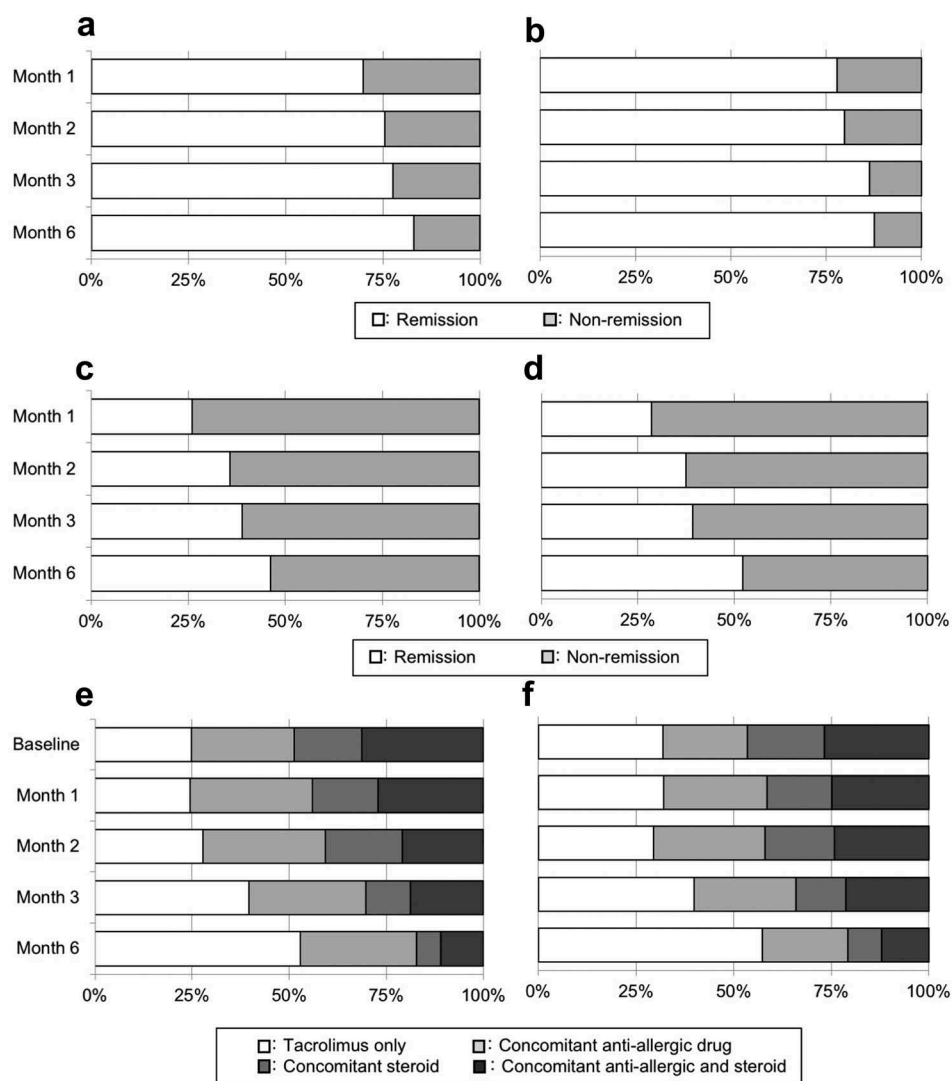


Figure 4. Clinical remission rate of papillae-limbus-corneal (PLC) grading score (definition of remission is ≤ 5 points) in with-AD patients (a) and without-AD patients (b) at each observational point. Symptom resolution rate (definition of remission is zero points) in with-AD patients (c) and without-AD patients (d) at each observational point. Concomitant medication on topical tacrolimus therapy in with-AD patients (e) and without-AD patients (f) at each observational point.

Table 3. Generalized estimating equation least squares means analyses for differences in chronic allergic conjunctival disease remission rates.

Papillae-limbal-conjunctival score ≤ 5			Papillary subscore ≤ 4			Limbal subscore = 0			Corneal subscore ≤ 1			Symptom score = 0		
	Odds ratio	P	Odds ratio	P		Odds ratio	P		Odds ratio	P		Odds ratio	P	
Concomitant atopic dermatitis (AD)														
Without-AD	Reference		Reference			Reference			Reference			Reference		
With-AD	0.92 (0.51–1.65)	0.7790	0.89 (0.46–1.72)	0.7240		0.51 (0.24–1.12)	0.0952		1.08 (0.58–2.01)	0.8112		1.43 (0.88–2.35)	0.1525	
Sex														
Male	Reference		Reference			Reference			Reference			Reference		
Female	1.19 (0.88–1.61)	0.2609	0.99 (0.72–1.36)	0.9382		1.14 (0.82–1.59)	0.4380		0.93 (0.71–1.22)	0.6086		0.99 (0.79–1.23)	0.8985	
Age group														
< 10 years	Reference		Reference			Reference			Reference			Reference		
10–19 years	1.42 (1.06–1.91)	0.0177	1.45 (1.08–1.95)	0.0140		1.09 (0.78–1.51)	0.6195		0.92 (0.71–1.20)	0.5571		0.92 (0.74–1.15)	0.4756	
20–29 years	1.40 (0.92–2.13)	0.1178	1.39 (0.93–2.07)	0.1075		0.66 (0.40–1.08)	0.0999		0.69 (0.48–0.99)	0.0440		1.20 (0.88–1.64)	0.2519	
30–39 years	1.09 (0.66–1.82)	0.7326	1.40 (0.83–2.35)	0.2057		1.07 (0.63–1.82)	0.8037		0.70 (0.45–1.09)	0.1108		1.91 (1.31–2.81)	0.0009	
≥ 40 years	1.62 (0.91–2.87)	0.0991	1.07 (0.59–1.95)	0.8128		1.81 (1.10–2.97)	0.0194		0.58 (0.36–0.94)	0.0273		1.42 (0.94–2.14)	0.0979	
Study visit														
Baseline	Reference		Reference			Reference			Reference			Reference		
Month 1	6.55 (5.69–7.53)	< 0.0001	4.41 (3.90–5.00)	< 0.0001		3.86 (3.38–4.40)	< 0.0001		0.89 (0.76–1.06)	0.1958		16.54 (11.71–23.37)	< 0.0001	
Month 2	9.07 (7.68–10.71)	< 0.0001	6.76 (5.76–7.94)	< 0.0001		5.16 (4.37–6.09)	< 0.0001		0.72 (0.60–0.87)	0.0007		26.60 (18.70–37.84)	< 0.0001	
Month 3	12.65 (10.15–15.77)	< 0.0001	9.44 (7.68–11.59)	< 0.0001		6.65 (5.43–8.14)	< 0.0001		0.67 (0.55–0.83)	0.0003		29.13 (20.27–41.85)	< 0.0001	
Month 6	17.96 (13.36–24.16)	< 0.0001	12.19 (9.24–16.10)	< 0.0001		10.19 (7.54–13.77)	< 0.0001		0.51 (0.40–0.66)	< 0.0001		45.49 (31.07–66.60)	< 0.0001	
Concomitant anti-allergic agent use														
No topical use	Reference		Reference			Reference			Reference			Reference		
Topical use	1.18 (0.91–1.52)	0.2024	0.95 (0.73–1.24)	0.6989		0.95 (0.72–1.25)	0.7095		0.93 (0.74–1.17)	0.5406		1.05 (0.86–1.27)	0.6358	
No systemic use	Reference		Reference			Reference			Reference			Reference		
Systemic use	0.87 (0.62–1.21)	0.4028	0.84 (0.62–1.16)	0.2903		0.65 (0.43–0.99)	0.0428		1.07 (0.80–1.43)	0.6559		0.94 (0.74–1.19)	0.5981	
Concomitant steroid use														
No topical use	Reference		Reference			Reference			Reference			Reference		
Topical use	1.82 (1.42–2.34)	< 0.0001	1.56 (1.21–2.03)	0.0008		1.12 (0.86–1.46)	0.4178		0.81 (0.64–1.02)	0.0687		1.39 (1.16–1.67)	0.0004	
No systemic use	Reference		Reference			Reference			Reference			Reference		
Systemic use	1.61 (0.98–2.64)	0.0575	1.34 (0.80–2.27)	0.2690		0.88 (0.41–1.87)	0.7366		1.28 (0.73–2.26)	0.3943		0.72 (0.46–1.13)	0.1535	

Table 4. Incidence of adverse drug reactions for 6 months.

Adverse drug reaction	Number of events (%)						Overall (n = 1821)	With-AD (n = 802)	Without-AD (n = 1016)	P (With-AD vs without AD)
	< 30 days		30 — < 90 days		≥ 90 days					
	With-AD	Without-AD	With-AD	Without-AD	With-AD	Without-AD				
Transient burning sensation in eye	21	51	2	—	—	—	74 (4.1)	23 (2.9)	51 (5.0)	0.0229
Eye irritation	20	28	2	2	—	—	52 (2.9)	22 (2.7)	30 (3.0)	0.8875
Conjunctival hyperemia	3	6	—	2	—	2	13 (0.7)	3 (0.4)	10 (1.0)	0.1640
Eye pain	4	5	1	—	1	—	11 (0.6)	6 (0.7)	5 (0.5)	0.5509
Hordeolum	2	2	1	—	2	2	9 (0.5)	5 (0.6)	4 (0.4)	0.5192
Lacrimation	3	4	—	—	—	—	7 (0.4)	3 (0.4)	4 (0.4)	> 0.9999
Foreign body sensation in eye	2	3	1	—	—	—	6 (0.3)	3 (0.4)	3 (0.3)	> 0.9999
Eye pruritus	1	3	1	—	1	—	6 (0.3)	3 (0.4)	3 (0.3)	> 0.9999
Eye discharge	1	1	—	—	2	1	5 (0.3)	3 (0.4)	2 (0.2)	0.6599
Punctate keratitis	1	1	2	—	—	1	5 (0.3)	3 (0.4)	2 (0.2)	0.6599
Chalazion	1	2	—	1	—	1	5 (0.3)	1 (0.1)	4 (0.4)	0.3915
Intraocular pressure elevation	—	1	2	1	—	1	5 (0.3)	2 (0.2)	3 (0.3)	> 0.9999
Photophobia	2	1	—	—	1	—	4 (0.2)	3 (0.4)	1 (0.1)	—
Blepharitis	1	1	1	—	—	1	4 (0.2)	2 (0.2)	2 (0.2)	—
Chemosis	1	2	—	—	—	1	4 (0.2)	1 (0.1)	3 (0.3)	—
Corneal erosion	1	—	—	3	—	—	4 (0.2)	1 (0.1)	3 (0.3)	—
Corneal ulcer	2	1	—	—	1	—	4 (0.2)	3 (0.4)	1 (0.1)	—
Bacterial keratitis	1	—	—	1	1	—	3 (0.2)	2 (0.2)	1 (0.1)	—
Lid herpes	—	1	—	—	2	—	3 (0.2)	2 (0.2)	1 (0.1)	—
Visual loss	2	—	—	1	—	—	3 (0.2)	2 (0.2)	1 (0.1)	—
Herpetic keratitis	1	—	—	—	—	1	2 (0.1)	1 (0.1)	1 (0.1)	—
Other events (1 each in 32 cases)	6	11	3	3	5	4	1 (0.1)	1 (0.1)	1 (0.1)	—
Total number of patients	56 (73.7)	90 (82.6)	12	10	8	9	185 (10.2)	76 (9.5)	109 (10.7)	0.3913

P values calculated using Fisher's exact tests. *P* values were not calculated when there were fewer than 5 cases. No adverse drug reactions were observed in 3 patients in whom we were unable to determine whether or not atopic dermatitis (AD) was present.

Predictors of topical tacrolimus treatment outcomes

Factors influencing remission rates during topical tacrolimus treatment are summarized in Table 3 for chronic ACD patients with and without AD. As indicated by each group's odds ratio, the presence of concomitant AD did not significantly affect the remission rate, determined using the overall PLC grading score ($P = 0.7790$). The odds ratio for being in remission progressively increased over the 6-month study treatment and observation period. Concomitant use of anti-allergic agents was not associated with the PLC grading (topical use: $P = 0.2024$, systemic use: $P = 0.4028$) or subjective symptom (topical use: $P = 0.6358$, systemic use: $P = 0.5981$) score. However, the use of topical steroids significantly increased the likelihood for remission (odds ratio = 1.82, $P < 0.0001$), with an association with the papillary sign subscore (odds ratio = 1.56, $P = 0.0008$).

Data are not shown, but as a result of the GEE analysis with parameter estimates for the response model, the with- or without-AD as variables indicated no interaction with the factors shown in Table 3 ($P > 0.05$, with sex, age group, study visit, and concomitant use of an anti-allergic agent and steroid).

Tacrolimus therapy safety

Adverse reactions occurred in 185 (10.2%) of 1821 patients included in the analyses (Table 4). The most common adverse reaction was a transient burning sensation upon drop instillation (74 patients [4.1%]). The incidence of adverse reactions was not significantly different between patients with (9.5%) and without (10.7%) AD ($P = 0.3913$), with the exception of the transient burning sensation upon installation (with AD: 2.9%, without AD: 5.0%; $P = 0.0229$). One hundred and forty-six out of 185 cases (78.9%) developed the adverse event within 30 days after instillation initiation of the tacrolimus

ophthalmic suspension, and the frequency of the adverse event decreased after this 30-day period. Intraocular pressure increases were observed in 5 cases as side effect, 3 cases of these had been concomitant use of topical steroid (Table 4).

Discussion

In the current study, the efficacy, safety, and influence of AD on topical tacrolimus therapy for chronic ACD was specifically investigated by comparing the clinical signs and symptoms of ACD in patients with and without AD. The GEE analyses showed that the presence of complicated AD only minimally affected the chronic ACD remission rate after 6 months of topical tacrolimus therapy. Additionally, longer term use of tacrolimus led to higher remission rates, and the concomitant use of topical steroids improved clinical chronic ACD signs, including papillary signs with a statistically significant, but low odds ratio.

Established grading scales¹⁰ for papillae formation, limbal lesions, and corneal epithelial signs were used to objectively determine the PLC grading score and clinical subscores. Conjunctival proliferative changes, including giant papillae and limbal gelatinous hyperplasia, are associated with chronic ACD severity.¹⁹ Because the PLC grading score assesses conjunctival proliferative changes and related signs, it may be considered suitable for evaluating the therapeutic effects of drug therapies in patients with chronic ACD. Objective findings in eyes with chronic ACD, including VKC and AKC, form a disease activity index (includes evaluations of giant papillae, limbal gelatinous hyperplasia, limbal Trantas' dot spots, and corneal shield ulcers) that can be used to determine disease remission, as indicated by flattening of giant papillae and loss of limbal findings.^{16,19–21} In the current study, a patient was considered to be in remission when the total PLC grading score was ≤ 5 . Papillary, limbal, and corneal

signs were considered to be resolved when subscores were ≤ 4 , 0, and ≤ 1 , respectively. Based on the PLC grading score, the overall remission rate of chronic ACD after 6 months of topical tacrolimus therapy was more than 85%. The remission rate obtained in this study indicates that topical tacrolimus treatment for chronic ACD patients who are untreated or have had a poor response to existing treatment is a clinically useful therapeutic approach.

Our GEE analyses performed on data collected after 6 months of topical tacrolimus therapy revealed that the presence of AD did not influence therapy efficacy. A decrease in PLC grading score and clinical subscores indicated that continued tacrolimus treatment improved objective measures of disease severity and maintained disease remission. The with-AD group developed more severe clinical findings (e.g., shield ulcers) than the without-AD group. Shield ulcers have a healing time of approximately one-to-three months, which may explain why patients with severe ACD had a delayed reduction in the corneal epithelial sign subscore and an increase in disease remission. Together, these results indicate that topical tacrolimus may be acceptable as a first-line chronic ACD treatment for 6 months, regardless of disease severity or individual allergic ACD background. Furthermore, the PLC grading score progressively decreased and the remission rate and odds ratio of attending a clinic visit progressively increased over the study period. Therefore, these results indicate that mild chronic ACD generally goes into clinical remission within 6 months of beginning tacrolimus therapy, and that longer use of tacrolimus led to higher efficacy. This finding is important to consider when planning tacrolimus treatment courses in chronic ACD patients. The current study showed that the concomitant use of topical steroids with tacrolimus significantly improved chronic ACD remission rates in patients with and without AD. However, topical steroids should be used with caution because they are associated with significant adverse reactions, including steroid-induced glaucoma, cataract, and infectious keratitis.^{2,9,21} Therefore, topical tacrolimus therapy may be a better treatment choice for ACD patients, reserving steroid/tacrolimus combination therapy for cases that are severe (high papillary sign subscore).

Chronic ACD signs and symptoms are likely induced by allergic inflammation in the conjunctiva and the accompanying keratopathy. Prior studies have shown that chronic ACD signs and symptoms generally improve within 1 month of beginning topical tacrolimus therapy.^{8,17} In agreement, we observed a marked improvement in both clinical findings scores and subjective symptom scores after 1 month of treatment in chronic ACD patients with and without AD. Tacrolimus likely improves chronic ACD signs and symptoms via allergic inflammation inhibition, as indicated by several animal studies. One study in a mouse model of experimental allergic conjunctivitis showed that tacrolimus inhibits allergic inflammation in the conjunctiva via inhibition of eosinophil and CD4-positive T cell infiltration.²² This mouse study also showed that steroid and tacrolimus eye drops have similar effects on ACD signs.²² Tacrolimus also decreased conjunctival inflammation by inhibiting T cell interleukin-4 production in an ovalbumin (OVA) sensitized rat model of immune-mediated blepharoconjunctivitis.²³

Furthermore, tacrolimus improved OVA-sensitized allergic conjunctivitis in guinea pigs, a steroid-resistant species, by inhibiting the late phase of immediate-type and delayed-type conjunctival hypersensitivity.²⁴ A continuous administration of the tacrolimus ophthalmic suspension in chronic ACD patients may be necessary to maintain conjunctival remission. In the current study, a 6-month treatment course with tacrolimus eye drops resulted in a chronic ACD remission rate of 85.2%. However, approximately 10%–15% of patients did not respond to topical tacrolimus treatment. These patients often had conjunctival proliferative changes, including giant papillae, so novel therapies are needed to treat these patients.

This study, conducted on post-marketing survey data, had several limitations. First, patients registered in this study were able to receive any concomitant treatments along with topical tacrolimus therapy. However, it is likely that confounding effects of concomitant therapies were minimal because all included patients were either untreated or responded poorly to non-tacrolimus therapies. Second, though this study objectively and subjectively evaluated tacrolimus efficacy, it did not examine tacrolimus allergic or immunological effects. Future research should investigate how topical tacrolimus therapy affects ocular surface immunology in the clinical setting and identify patient characteristics associated with poor responses to the drug. Third, the visual prognosis was not evaluated in this study. Because severe visual impairment occurs in ACD patients with severe corneal epitheliopathy including shield ulcer, atopic cataract, and retinal detachment, the visual prognosis and therapeutic effect of tacrolimus ophthalmic suspension for visual and refractive outcomes of the patients with chronic ACD are crucial research themes for future studies. Fourth, only complication of atopic dermatitis was considered as a background factor of the chronic ACD patients in this study. However, the cluster analysis based on more background factors, including the disease severity of AD, the use of topical and systemic treatments for AD, and complications of other allergic diseases may help clarify the therapeutic effect of tacrolimus ophthalmic suspensions.

In conclusion, tacrolimus ophthalmic suspensions are useful for treating chronic ACD with and without AD. The proper selection of concomitant medications, including topical steroids, is crucial to therapy success. Additionally, more severe cases of ACD may require a longer tacrolimus treatment course. Furthermore, the PLC grading score can be used in the clinical setting to assess tacrolimus efficacy.

Acknowledgments

Contribution: JS: design, analysis of data, and drafting of the manuscript.

YO, AF, ET, HF, DM, NE, EU, KN, NK, SO: design, acquisition and interpretation of data, and revising the manuscript.

All of the authors approved the manuscript to be published, and agree to be accountable for all aspects of the study.

We express our deepest condolences regarding the passing of Dr. Yayoi Nakagawa. Dr. Nakagawa worked closely with us and we are extremely grateful for her contributions.

Funding

This work was supported by Senju Pharmaceutical Co., Ltd. (Osaka, Japan). The funding organization participated in data collection, data management, and manuscript review.

Declarations of interest

JS has received personal fees from Santen, and Senju and Alcon Japan; YO has received personal fees from Santen, Senju, and HOYA; AF has received personal fees from Santen, Kowa, Alcon, Senju, Kyowa-Kirin, Tanabe-Mitsubishi, Kissei, Otsuka, Abbie, Eisai, and non-financial support from Santen, Kowa, Alcon, Senju, Kyowa-Kirin, Tanabe-Mitsubishi, Kissei, Otsuka, Abbie, Eisai; ET has received personal fees from Santen, Otsuka, and Senju; HF has received research funds from Santen, Senju, and Kobayashi, Alcon Laboratories, White Medical, and Allergan and personal fees from Otsuka; DM, NE, EU, KN, NK, and SO have no conflicts of interest.

Funding

This work was supported by Senju Pharmaceutical Co., Ltd. (Osaka, Japan). The funding organization participated in data collection, data management, and manuscript review.

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