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Steroid-Sparing Effect of 0.1% Tacrolimus Eye Drop for Treatment of Shield Ulcer and Corneal Epitheliopathy in Refractory Allergic Ocular Diseases

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Purpose: To evaluate the effects of 0.1% topical tacrolimus alone or in combination with steroids for the treatment of shield ulcers and corneal epitheliopathy in patients with refractory allergic ocular diseases.

Design: Open cohort study.

Participants: Patients with refractory allergic conjunctivitis epitheliopathy, shield ulcers, or corneal plaques (N = 791).

Methods: The 791 patients were treated with topical tacrolimus alone or in combination with topical or oral steroids. The effectiveness of the treatments was determined by a corneal epitheliopathy score during the 3-month follow-up period. The clinical signs were rated on a 4-grade scale. Corneal epitheliopathy with no corneal staining was graded as 0, and shield ulcers or plaques were graded as 3, the highest grade. The effects of tacrolimus with and without topical steroids on the epitheliopathy scores were assessed after adjustments for the severity of the clinical signs and characteristics.

Main Outcome Measures: Changes in the corneal epitheliopathy score.

Results: Adjusted mean epitheliopathy score at the baseline was 1.73 (95% confidence interval [CI], 1.65−1.81) for patients treated with tacrolimus alone, and this was significantly reduced by −0.93 at 1 month. The reduction of the score by topical and oral steroids was −0.02 for fluorometholone, 0.02 for betamethasone, and −0.02 for oral steroids, and these reductions were not significant compared with the reduction effect of topical tacrolimus alone at −0.93. The 238 patients with shield ulcer (score 3) were analyzed with adjustments, and the mean epitheliopathy score at 1 month was reduced to 1.38 with tacrolimus alone (95% CI, 1.24−1.51), 1.41 (95% CI, 1.26−1.56) with adjuvant fluorometholone, and 1.46 (95% CI, 1.32−1.61) with adjuvant betamethasone. No significant difference was observed in the adjunctive topical steroids. The presence of severe palpebral conjunctival symptoms, including giant papillae, was a significant resisting factor for topical tacrolimus.

Conclusions: The significant effects of topical tacrolimus alone on shield ulcers and corneal epitheliopathy suggest that it may be used without the need for steroids. *Ophthalmology 2017;124:287-294 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Severe allergic conjunctival diseases, for example, atopic keratoconjunctivitis and vernal keratoconjunctivitis, are relatively rare; however, they are important diseases because they can cause severe corneal and conjunctival alterations leading to visual morbidity. Topical steroids are standard treatments for severe ocular allergies, but they generally do not lead to a complete remission for the severest form of ocular allergy with corneal involvement. In addition, topical steroids usually require months or years in treatment, and infectious episodes and elevations of intraocular pressure (IOP) can occur during the lengthy treatment period before the corneal epitheliopathy is resolved. If corneal epitheliopathy or shield ulcers can be cured without steroids, such complications could be avoided.

Topical calcineurin inhibitors were recently introduced to treat severe allergic conjunctival diseases, and they have had remarkable success.[1−5] Topical calcineurin inhibitors also can resolve the symptoms and signs of autoimmune keratitis and the ocular complications of graft-versus-host disease (GVHD).[1,6,7] We have reported that topical tacrolimus is effective in treating severe allergic conjunctival diseases.[3] However, how tacrolimus could be used in combination with conventional steroidal treatment has not been determined, and population-based data have not been published on whether topical tacrolimus can reduce the use of steroids or allow nonsteroidal therapy.

Thus, the purpose of this study was to determine whether topical tacrolimus alone or with adjuvant steroids can cure corneal epitheliopathy and shield ulcers. We also evaluated the clinical characteristics of patients who resisted the topical tacrolimus with or without steroids. To accomplish

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this, we retrospectively analyzed the therapeutic effects of topical tacrolimus with or without steroids in 791 eyes with corneal epitheliopathy or shield ulcers.

Methods

Patient Eligibility Criteria

The medical records of 791 refractory allergic conjunctivitis cases with epitheliopathy or shield ulcers were retrospectively analyzed. All of the cases were followed at 330 ophthalmological institutions in Japan between 2008 and 2016. All of the patients responded poorly to conventional anti-allergy medications and were diagnosed with refractory allergic conjunctivitis. The inclusion criteria were presence of corneal epitheliopathy or shield ulcers, persistent or relapsing allergic conjunctivitis, and age <40 years.

This study was designed to assess the efficacy of topical tacrolimus among an open cohort, and all of the patients were treated with 0.1% tacrolimus (Senju Pharmaceutical, Osaka, Japan) alone or in combination with topical or oral steroids. The diagnosis of allergic conjunctivitis was based on published guidelines.[8–10] The study protocol was approved by the ethics committee of the Pharmaceuticals and Medical Devices Agency in Japan.

The corneal epitheliopathy score and giant papilla score were graded from 0 to 3, with 3 being the most severe. For the epitheliopathy score, the presence of a shield ulcer was coded as 3, exfoliation superficial punctate keratitis was coded as 2, superficial keratitis was coded as 1, and none was coded as 0. For giant papillae (size ≥1 mm), elevated papillae in one half or more of the upper palpebral conjunctiva were graded as 3, elevated papillae in one half of the upper palpebral conjunctiva were graded as 2, flat papillae were graded as 1, and no papillae were graded as 0.

Seven clinical signs also were evaluated: hyperemia, edema, and follicles of the palpebral conjunctiva, hyperemia and edema of the bulbar conjunctiva, and Trantas' dot and swelling of the limbus. Each sign was graded from 0 to 3, with 3 the most severe.[3]

Ophthalmologists in charge of respective participating hospitals scored each parameter using the scoring chart of representative photographs provided by our study group (not shown). The signs were scored at baseline just before beginning tacrolimus and at 1, 2, and 3 months after beginning tacrolimus. The use of topical and oral steroids also was monitored at 1, 2, and 3 months for strength, dose, and duration. Ocular infection episodes and IOP at the follow-up visits were recorded.

Statistical Analyses

Data are presented as means ± standard deviations. For each patient, the eye with the higher total clinical score was used for the statistical analyses. Unpaired t tests and Mann–Whitney U tests were used to determine the significance of the differences between groups. The effects of steroids on the corneal epitheliopathy score were the primary end point, and the data were analyzed by a generalized mixed linear regression model. Steroid potency was coded as 1 for fluorometholone or an equivalent and 2 for betamethasone or an equivalent.

The topical or oral steroids and clinical characteristics were included as fixed effects and analyzed as the subject-specific means. The participants, random intercepts, responsiveness to the treatment, and score reduction slope as a random slope were included as random effects to adjust for individual variations.

A mixed ordered logistic analysis was used with the random intercept and slope to calculate the subject-specific odds ratio (OR) for the effects of steroids or clinical signs on changes in the epitheliopathy score. The number of months after the treatment was included after a square-root transformation. Statistical analyses were performed with the Stata 14 software (StataCorp LP, College Station, TX). A P value <0.05 was considered statistically significant.

Results

Baseline Characteristics of Eyes with Refractory Allergic Conjunctivitis

A total of 791 eyes of 791 patients with corneal epitheliopathy or shield ulcers were studied. The percentage of male patients was 82.8%, and the mean age of the patients was 15.9±9.0 years (Table 1). Eczema was present in 54.5%, asthma was present in 22.6%, and allergic rhinitis was present in 25.5% of these patients. Of the 431 patients with eczema, 112 (26.0%) also had allergic rhinitis and 127 (29.5%) also had asthma.

Among the 791 eyes, 454 (57.4%) were being treated with topical steroids before the beginning of the tacrolimus eye drop treatment. During the follow-up visits, the percentage of eyes with adjunctive topical steroids decreased to 54.8% at 1 month, 47.7% at 2 months, and 43.9% at 3 months. The percentage of eyes with adjunctive betamethasone eye drops was 28.9%, 25.1%, and 21.1% at 1, 2, and 3 months, respectively, and the percentage of eyes with adjunctive fluorometholone eye drops was 23.5%, 21.3%, and 20.7% at 1, 2, and 3 months, respectively. The percentage of patients using adjunctive oral steroids was 3.4%, 4.2%, and 2.4% at 1, 2, and 3 months, respectively.

The overall severity of disease was assessed by the sum of the 9 clinical scores. At baseline, the mean summed score was 14.5±4.8 for the patients who were to be treated with tacrolimus eye drops alone. The summed score at baseline of the patients who were later treated with adjuvant topical fluorometholone

Table 1. Characteristics of Patients at Baseline

	Total	Patients without Topical Steroids at Baseline (n = 337)	Patients with Topical Steroids at Baseline (n = 454)
Age (yrs), mean ± SD	15.9±9	17.2±9.6	15.0±8.4
Male sex	655 (82.8)	269 (34.0)	386 (48.8)
Eczema	431 (54.5)	177 (22.4)	254 (32.1)
Asthma	179 (22.6)	76 (9.6)	103 (13.0)
Allergic rhinitis	202 (25.5)	78 (9.9)	124 (15.7)
Oral steroid use	18 (2.3)	6 (0.8)	12 (1.5)

SD = standard deviation.
Data are no. (%) unless otherwise indicated.