The treatment of refractory anterior segment inflammatory diseases is still a dilemma. Most cases require steroids to be used over a long time, but such treatment should be used with caution due to the risk of steroid induced cataract, glaucoma [1], and superinfections [2].

Tacrolimus, referred to as FK506, is a potent immunosuppressive macrolide agent, which is isolated from Streptomyces tsukubaensis [3]. Tacrolimus inhibits T-cell activity by decreasing the transcription of interleukin-2 and lymphokines [4]. These inflammatory cytokines have been blamed in the pathogenesis of many ocular surface disorders. Systemic tacrolimus has been used to prevent allograft rejection in liver, kidney, and heart transplantation patients [5-7]. Topical tacrolimus (Protopic ointment 0.03%; Astellas Pharma, Tokyo, Japan) has been proven effective in the treatment of atopic dermatitis [8]. However, there are only a few reports regarding its use for the treatment of anterior segment inflammatory disorders [9-11]. Recently, several studies have been conducted on topical tacrolimus,

**Therapeutic Effect of 0.03% Tacrolimus Ointment for Ocular Graft versus Host Disease and Vernal Keratoconjunctivitis**

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**Purpose:** To determine whether topical tacrolimus might prove effective in the treatment of refractory anterior segment inflammatory diseases, and to evaluate its efficacy in eyes with ocular graft versus host disease (GVHD), and vernal keratoconjunctivitis (VKC).

**Methods:** Twenty-eight eyes of 14 patients with anterior segment inflammation refractory to steroid treatment were treated with 0.03% tacrolimus ointment at the Samsung Medical Center, Seoul, Korea from March 2008 through August 2009. Seven patients had ocular GVHD and seven had VKC. We evaluated the conjunctival and corneal inflammatory change at one, two, four, and eight weeks after treatment with a scoring system. Time to initial response of treatment and therapeutic effect between GVHD and VKC was also analyzed. After the eight-week treatment period, patients were divided into two groups (maintenance group and discontinuance group). Eight patients maintained the treatment for an additional four months, and six patients discontinued the treatments. Therapeutic effect was also compared between the groups at eight weeks and six months after treatment.

**Results:** The mean conjunctival and corneal inflammation score was reduced significantly at eight weeks after treatment ($p < 0.0001$). The therapeutic effect in conjunctival inflammation was first noted at week two after the initial treatment ($p = 0.002$); reduction in corneal inflammation was first noted at one week ($p = 0.0009$). When compared according to diagnosis, no therapeutic difference was detected between the groups ($p > 0.05$). Six months after treatment, we noted no therapeutic differences between the maintenance group and discontinuance group ($p > 0.05$).

**Conclusions:** 0.03% tacrolimus ointment was safe and effective for use in anterior segment inflammatory disease refractory to steroid.

**Key Words:** Allergic conjunctivitis, Graft vs host disease, Tacrolimus
but the majority of these have been case reports. However, no studies have yet been reported to determine the time required for the medication to show an effect or to determine the proper time to discontinue that treatment.

The principal objective of this study was to determine whether topical tacrolimus treatment is effective in anterior segment inflammatory disorders such as chronic ocular graft versus host disease (GVHD) and vernal keratoconjunctivitis (VKC), which have dependency to steroid or are refractory to said therapy. Also, we aimed to evaluate the time period required to achieve a significant effect after tacrolimus therapy and the proper duration of treatment. Thus, this is the first study to analyze the timeframe of the use of this medication, and our results should also prove useful in guiding the use of tacrolimus in ophthalmology.

Materials and Methods

This prospective study was conducted at Samsung Medical Center, Seoul, from March 2008 to August 2009. Thirty-two eyes of 16 patients who provided informed consent were enrolled after approval from the institutional review board. The study was carried out within the tenets of the Declaration of Helsinki. The inclusion criteria were: patients with ocular GVHD and VKC refractory to standard steroid therapy, worsening of symptoms during steroid tapering or having steroid induced complications, and no posterior segment inflammation. We focused on these two disorders for our study as they are relatively common, always require steroid therapy, and have mostly unsatisfactory outcomes. Exclusion criteria were patients with a history of herpes and patients already on cyclosporine.

Before commencing the treatment all patients underwent a detailed slit lamp examination and an anterior segment photograph was taken for follow-up analysis. The patients were asked to apply 0.03% tacrolimus ointment in the lower conjunctival sac twice a day after using a drop of 1% prednisolone eye drop. Prior to tacrolimus treatment, the mean frequency of prednisolone acetate 1% was 4.3 ± 3.1 per day and the mean duration was 5.6 ± 4.7 months.

Patients were made aware that the ointment is used for skin conditions and this study is an off label use. They were informed that the ointment may cause burning, stinging sensation, and blurred vision due to its oil based formulation. Two patients refused to use the ointment due to a burning sensation during the first week of treatment and so we were left with 14 patients. Seven patients of those remaining had ocular GVHD and seven persons had VKC.

All patients received tacrolimus treatment for eight weeks, and we evaluated them at weeks one, two, four, and eight. At every follow-up, we looked for inflammatory changes and also noted complaints such as a burning or foreign body sensation.

At every follow-up, patients were asked to gradually reduce the steroid eye drop usage. Also, we prescribed artificial tear drops to all patients. For the GVHD patients, there were no changes of systemic immunosuppressive treatment during this study period.

After an initial period of eight weeks of treatment, we gave all patients the option to maintain or to discontinue the treatment, eight patients who wished to continue treatment maintained the therapy (maintenance group) for an additional four months, and treatment was discontinued for another six patients (discontinuance group).

To assess the changes in inflammatory status, we used an inflammatory score given by Tanaka et al. [12]. The inflammation of conjunctiva was scored by four levels and inflammation of the cornea was scored by five levels. The conjunctival inflammation was scored with the following four levels: 0, none; 1, mild (mild hyperemia and flat papillary hypertrophy); 2, moderate (moderate hyperemia and papillary hypertrophy); 3, severe (severe hyperemia and high papillary hypertrophy). Corneal inflammation was scored with inflammation scores of (five levels): 0, none; 1, mild (superficial punctuate keratitis [SPK] less than half of cornea); 2, moderate (SPK more than half of cornea); 3, severe (corneal epithelial defect); 4, very severe (corneal ulcer or plaque) [12]. At all follow-up times, anterior segment photography was performed, and two examiners assessed the resulting image and gave marks blindly. At the final six-month follow-up, we compared surface inflammation between the maintenance group and the discontinuance group.

For statistical analysis, PASW ver. 17.0 (SPSS Inc., Chicago, IL, USA) was used. We utilized the Wilcoxon signed rank test with Bonferroni’s correction to determine the time point at which the reduction of inflammation first appeared after beginning treatment. The Wilcoxon signed rank test was utilized to analyze the reduction of the instillation frequencies of topical steroids after treatment. To assess differences arising in diagnoses and maintenance, we utilized a Mann-Whitney test with Bonferroni’s correction. A p-value of less than 0.05 was considered significant.

Results

The mean age of the patients was 26.9 ± 19.04 years (range, 9 to 62 years), and the ratio of males to females was 7 : 7. Among these patients, 14 eyes from seven patients had ocular GVHD and 14 eyes of seven patients had VKC (Table 1).

The mean conjunctival inflammation and corneal inflammation scores prior to treatment were 2.46 ± 0.79 and 2.75 ± 1.00, respectively. After treatment with tacrolimus ointment, the scores were 2.21 ± 0.63 and 2.25 ± 1.04 at a week one, 1.79 ± 0.73 and 1.71 ± 0.84 at week two, 1.29 ± 0.50 and 1.23 ± 0.71 at week four, and 0.75 ± 0.40 and 0.80 ± 0.61 at week eight, respectively. The mean conjunctival