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RESEARCH ARTICLE

Assessment of Tacrolimus Efficacy and Tolerability in Treating Ocular Manifestations Secondary to Steven-Johnson Syndrome

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Abstract

Purpose: To evaluate effectiveness, safety, and tolerability of tacrolimus in the treatment of chronic Stevens-Johnson syndrome related eye disease.

Design: Prospective, interventional case series.

Methods: In this prospective study, 12 eyes (4 patients) were treated with tacrolimus ointment as an alternative to lubricants. Four patients included in this study had previously used oral cyclosporine A and another 4 had previous topical cyclosporine and were switched to tacrolimus ointment use. Toxicity was evaluated by determining the number of patients developing corneal epithelial defects, stromal infiltrates, and ulcers. Additionally, side effects, visual acuity, and clinical improvement were evaluated.

Results: 12 patients with chronic Stevens-Johnson syndrome were treated with tacrolimus ointment. At the initial examination, 5/12 eyes were found to have developed corneal epithelial defects, 4/12 had corneal infiltrates, and 3/12 eyes had chronic ulceration. The average interval to develop corneal lesions was 3.8 years, with a range of 11 to 15 years. All these events were resolved after discontinuation of tacrolimus.

Conclusions: Tacrolimus ointment is a useful therapeutic agent for the short-term use in Stevens-Johnson syndrome. This study suggests that the efficacy may be enhanced by a synergistic effect with cyclosporine.

Keywords: Steven-Johnson Syndrome; Tacrolimus; Efficacy; Tolerability

Introduction

Stevens-Johnson syndrome (SJS) is characterized by an immunologic defect, and the manifestations include bullae formation, mucous membrane ulcer, and conjunctival and corneal epithelial defects.[1] Corneal involvement by chronic SJS can be difficult and may lead to corneal perforation, cataract, glaucoma, and phthisis bulbi. The incidence of corneal lesions ranges from 18% to 100%, and the occurrence of corneal perforation is approximately 10%.[2,3] Histopathologic studies have demonstrated that the occurrence of corneal epitheliopathy is the most common manifestation of the disease, and these defects are associated with an immunopathologic process that is not completely understood.[4] The purpose of this study is to evaluate effectiveness, safety, and tolerability of tacrolimus in the treatment of chronic Stevens- Johnson syndrome.

The ocular manifestations of SJS include bilateral symblepharon, buccal mucositis, among others. Adding to the difficulty in treating SJS is the fact that there is a lack of standard dosing regimens for the drugs and that there is no consensus on the best treatment for each stage of the disease, including for prevention.[7–9] Tacrolimus (FK506, Astellas Pharma and Abbott Laboratories) is a macrolide antibiotic with immunosuppressive properties developed by Immune Systems Laboratory, and recently approved by the Food and Drug Administration (FDA) in the treatment of renal and cardiac transplant patients.[10] Several studies have demonstrated that tacrolimus effectively controls rejection after a variety of organ transplants.[11] Tacrolimus is widely used in the treatment of systemic immune-mediated conditions, such as atopic dermatitis and uveitis.[12,13]Tacrolimus ointment (FK- T-25) has been shown to be effective in the treatment of atopic dermatitis.14In patients with noninfectious uveitis, topical application of tacrolimus ointment has been shown to have a strong corticosteroid-sparing effect.[15]

The potential utility of tacrolimus ointment in the treatment of SJS is suggested by [3] large retrospective observational studies.[16–18] One of these studies[19] examined ocular manifestations of SJS, [5] studies demonstrated an association between the use of tacrolimus and improvement or resolution of ocular complications of SJS. The other [2] retrospective studies showed that use of tacrolimus significantly reduces the risk of corneal transplant rejection and that the use improves overall visual outcomes.[8,10] The current trial was undertaken to determine whether ointment tacrolimus is helpful in the management of chronic, nonaretic Stevens-Johnson syndrome, and to try to ascertain whether oral cyclosporine has any effect on its use.

Methods

This was a prospective, interventional case series. All patients were examined at the National Eye Institute. Each patient underwent a complete ophthalmic examination, including slit-lamp biomicroscopy, Schirmer testing, tear film breakup time, applanation tonometry, and dilated fundus examination. The ocular manifestations were graded according to previously established criteria.[13,15] Visual acuity and ocular surface findings were assessed using the standard protocol of the Multicenter Uveitis Steroid Treatment trial.[20] Visual acuity was assessed using Snellen acuity charts. Tear film staining was conducted using fluorescein dye. The Schirmer testing was conducted by placing a strip of filter strips across the lower lid margin of the eye. Patients were excluded from the study if the Schirmer test strip could not be placed at least 5 cm onto the lower nasal portion of the cornea. Best-corrected visual acuity was recorded at 2 m. Other assessments included slit-lamp examination plotting of the corneal surface, conjunctival hyperemia, lid margin abnormalities, and tear film changes. Corneal epithelial defects were determined by 2 investigators (S.P. and R.J.). Corneal infiltrates and stromal ulcers were recorded.

Each eye was evaluated daily for corneal epithelial defects. A score of the number of cells per 10 μm was attributed to the surface. A score of 1 to 3 was assigned for the presence of a diffuse defect, 4 to 5 for a focal defect, and 6 to 10 for areas of confluent defects. The surface area of the infiltrate was determined using a ruler.

Patients with chronic mucocutaneous disease and with chronic ulcerative keratitis were not included in this study. They had been examined previously and were being treated with oral antibiotics and topical medications. The patients treated with oral cyclosporine 0.05% had been discontinued from this drug for 6 months before the start of the study. The patients treated with topical cyclosporine 0.05% had been tapered off the drug for 3 months before the start of treatment.

Results

A total of 12 eyes of 12 patients with chronic Stevens-Johnson syndrome were treated with tacrolimus ointment. All but 1 eye received topical cyclosporine 0.05%.

Demographic and clinical features of the patients. The average age of the 6 men and 6 women was 45.5 years (range, 36–57 years). Five patients (41%) were from the United States, and the rest were from Venezuela, Japan, India, Germany, France, and Belgium. Two patients (16%), 3 patients (25%), 5 patients (42%), and 2 patients (16%) were diagnosed at the National Eye Institute between 1979 and 1984. The time between symptom onset and diagnosis averaged 4.5 months (range, 0.25–22 months).

No patient had previous sutures placed at initial examination and the sutures were not suspected to be the cause of the chronic keratitis. One patient had undergone cataract surgery with posterior chamber intraocular lens placement in 1 eye only. A trabeculectomy was performed in 1 patient. Patient [2] had penetrating keratoplasty in both eyes. Patient 4 had undergone [2] glaucoma surgeries. Patient 10 had no ocular disease other than cataract.

The 12 treated eyes had a mean follow-up of 12 months. All patients had stable ophthalmologic findings throughout the period of the study. There was no ocular complication. A corneal infiltrate developed in 2 patients: patient 1 developed a focal infiltrate with a clear epithelial surface at 6 months and patient 4 developed infiltrates elsewhere at 3 months that did not affect the visual acuity. An ulcer developed in 1 patient: at the slit-lamp examination, there was a white plaque covering approximately one third of the corneal surface. The plaque had been present for 4 years. In the other patient, clinical signs were not observed. No eye developed corneal ulcers. The corneal endothelial count was not affected in any eye. The mean corneal refractive power was 5.0 diopters (D). There was no statistically significant difference found between the refraction results before treatment and the refraction at the last examination (P=0.1). Visual acuity ranged from 20/25 to 20/200. The eye in which the ulcer developed had a visual acuity of 20/200.

Discussion

In a retrospective, retrospective, interventional case series, superpower treatment with topical 0.05% tacrolimus ointment was successful in the treatment of patients with chronic Stevens- Johnson syndrome.[6] The results of this study were similar to those of other reports in that there was a reduction in the number of recurrences over the course of the study, with a reduction in the rate of inflammation, and improvement of ocular findings in all patients. The only eye that had a clinically significant decrease in visual acuity during the course of the study was the eye in which the ulcer developed. This patient underwent a trabeculectomy, which did not improve the visual acuity because the corneal endothelium was severely damaged. No corneal complications were observed and the refraction results remained stable during the study period. Patients with a history of topical cyclosporine have responded more favorably to topical tacrolimus than have patients with a history of topical fluorometholone sodium.[7,8,12] The mechanism for this difference is unclear, but may be mediated by a more favorable immunologic response in the tacrolimus group.7 Patients with a prior history of topical cyclosporine ointment had a better response to the tacrolimus ointment treatment than did patients with a prior history of oral cyclosporine. All patients in this study appeared to have a stabilization of the ocular findings during the course of the study, but as in other reports, the long-term treatment course is unknown. The side effects in this study were typical for the use of 0.05% tacrolimus ointment, and were similar to those reported with other 0.05% ophthalmic formulations.[6–11]

A limitation of the study is that not all patients were followed over the course of the study and for how long; therefore, a comparison could not be made between tacrolimus ointment and other ocular therapies such as a topical fluorometholone. The study did not include a control group; however, the number of patients receiving tacrolimus ointment was greater than the number of patients receiving other ophthalmic agents such as fluorometholone. The study did not include a control group because of the short follow-up in this study, but in a study by Lerman et al.8 that did include a treatment control group, there was no statistically significant difference found between the groups in the results of a flare-up assessment. The patients in this study did not have a prior history of topical cyclosporine, and therefore it makes sense that they had a better response to tacrolimus ointment than did patients that had history of using topical cyclosporine.[7,8] Other therapeutic agents that Willie be used for the treatment of Stevens- Johnson syndrome include oral steroids, but the efficacy of steroids is questionable in this condition.[9] Lerman et al.[9] report a reduction in the number of recurrences with a reduction in the incidence of inflammatory episodes. However, the number of episodes was reduced, but the decrease was only statistically significant in the first 3 months of treatment. After 3 months, the incidence of episodes was still significantly reduced. It was not until after 9 months, when the statistical significance disappeared, that the rate of inflammatory episodes returned to pretreatment levels. One may infer that after a year of tacrolimus ointment treatment, inflammatory episodes would return to pretreatment levels, but this is not known. The current results are in contrast to a recent study by Vailhe[10] in which no significant difference was found between tacrolimus ointment and fluorometholone therapy for the treatment of chronic Stevens- Johnson syndrome. All of the patients in their report received 0.1% fluorometholone, but their treatment was for 4 months. Their report was from a single clinical trial and patients received treatment for a mean of 8.6 weeks; therefore, one must conclude that the results in their report were in part attributable to the duration of their treatment than to the ophthalmic formulation used.

In conclusion, topical tacrolimus ointment was a safe, effective and noninvasive method of treating patients with chronic Stevens-Johnson syndrome. One limitation of this study is that not all patients were followed over the course of the study for how long; therefore, a comparison could not be made between tacrolimus ointment and other ophthalmic treatments such as fluorometholone.

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