Clinical Treatment of Dry Eye Using 0.03% Tacrolimus Eye Drops

ARTICLE in CORNEA · APRIL 2012
Impact Factor: 2.04 · DOI: 10.1097/ICO.0b013e31823f8c9b · Source: PubMed

CITATIONS
21

READS
645

6 AUTHORS, INCLUDING:

Bernardo Kaplan Moscovici
Universidade Federal de São Paulo
9 PUBLICATIONS  31 CITATIONS

SEE PROFILE

Ricardo Holzchuh
Santa Casa Medicine School, São Paulo
16 PUBLICATIONS  55 CITATIONS

SEE PROFILE

Richard Yudi Hida
Santa Casa de São Paulo
33 PUBLICATIONS  151 CITATIONS

SEE PROFILE

Available from: Bernardo Kaplan Moscovici
Retrieved on: 10 November 2015
Clinical Treatment of Dry Eye Using 0.03% Tacrolimus Eye Drops

Bernardo K. Moscovici, MD,*† Ricardo Holzchuh, MD,*† Brenda B. Chiacchio, MD,* Ruth M. Santo, MD,* Jun Shimazaki, MD, PhD,‡ and Richard Y. Hida, MD*†‡

**CASE REPORT**

**Purpose:** To report the clinical outcome of the treatment of dry eyes using 0.03% tacrolimus eye drops (olive oil + tacrolimus 0.03%) (Ophthalmos, Sao Paulo, Brazil).

**Methods:** Sixteen eyes of 8 patients with Sjögren syndrome dry eyes (age, 51.13 ± 9.45 years) were enrolled in this study (prospective noncontrolled interventional case series). Patients were instructed to use topical 0.03% tacrolimus eye drops twice a day (every 12 hours) in the lower conjunctival sac. Schirmer I test, instilled sicca, cornea, tacrolimus, FK506

**Key Words:** dry eye syndrome, Sjögren syndrome, keratoconjunctivitis sicca, cornea, tacrolimus, FK506

**Conclusions:** Topical 0.03% tacrolimus eye drops successfully improved tear stability and ocular surface status in patients with dry eyes.

**Sjögren syndrome (SS) is a chronic inflammatory systemic disease of autoimmune etiology.** The lacrimal and salivary glands are the main organs affected by lymphoplasmaocytic infiltration, resulting in dysfunction that causes, among several changes, dry eyes. SS primarily affects middle-aged women. It results from the hyperreactivity of B lymphocytes, which then differentiate into plasmacyes and produce antibodies against antigens of the acinar epithelium and exocrine ducts.1–3 Dry eye is treated with ocular lubrication, lacrimal punctum occlusion, use of autologous serum, topical immunosuppressive agents, and topical corticotherapy.1–3 As long-term topical corticotherapy leads to ocular complications, use of topical immunosuppressants has increased in recent years; they decrease the inflammatory process and even increase tear production in some cases.1–3

Tacrolimus, also known as FK506, is a macrolide with immunomodulatory action that was isolated from Streptomyces tsukubaensis fermentation. Its mechanism of action is similar to cyclosporine A (CsA); however, it is described to be 10 to 100 times more potent, despite differing chemical structures. Tacrolimus becomes biologically active only when it binds to immunophilin and, when active, it acts by inhibiting calcineurin, limiting transduction of the signal that carries information from the cell membrane to the nucleus, with the aim of stimulating interleukin (IL)-2 synthesis, and inhibiting T and B lymphocyte activation.6–12 Generally, tacrolimus suppresses the immune response by inhibiting the release of other inflammatory cytokines (eg, IL-3, IL-4, IL-5, IL-8, interferon-γ, and tumor necrosis factor-α).13–16

In ophthalmology, systemic use of tacrolimus is already well established in the treatment of immune-mediated diseases, uveitis,17,18 dry eyes related to graft-versus-host disease, corneal transplants, and ocular pemphigoid.4–10 It is also used topically, as an ointment, to treat ocular allergies, especially atopic blepharokeratoconjunctivitis. Recently, 0.1% tacrolimus eye drops (olive oil + tacrolimus 0.03%) (Ophthalmos, Sao Paulo, Brazil), were reported to be effective in treating severe allergic conjunctivitis.19 Its use in humans for treating keratoconjunctivitis sicca (KCS) has not been described, although its use has already been described in animals with KCS.2–19 This study describes the clinical outcome of SS dry eyes treated with 0.03% tacrolimus eye drops.

**MATERIALS AND METHODS**

This prospective noncontrolled interventional case series study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board/Ethics Committee of the “Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (USP)” (Comissão de Ética para Análise de Projetos de Pesquisa- CAPPesq) under protocol number 1307/09 (January 1,
2010). Informed consent was obtained from all study participants after the nature and possible consequences of the study had been explained to them in detail.

Sixteen eyes of 8 patients with SS dry eyes (age, 51.13 ± 9.45 years) diagnosed by a qualified rheumatologist and an ophthalmologist (following the European criteria) were enrolled in this study. This noncomparative interventional case series was performed at the outpatient clinic of the Department of Ophthalmology, School of Medicine, University of São Paulo (Hospital das Clínicas of Faculdade de Medicina da Universidade de São Paulo).

All patients enrolled in our study met the following criteria: (1) SS was diagnosed according to the SS European Criteria, (2) chronic symptoms of burning, foreign body sensation, or itching in both eyes; (3) daily need for artificial tears; (3) abnormal Schirmer I test (sensation, or itching in both eyes; (3) daily need for artificial tears; (3) abnormal Schirmer I test (<5 mm) or break-up time (BUT) (<5 seconds).

Patients with (1) any structural abnormalities (lid scarring, entropion, trichiasis, etc.); (2) any inflammation or active structural change in the iris or anterior chamber; (3) glaucoma; (4) previous eye surgery or punctal occlusion; (5) use of any other topical medication other than artificial tears; (6) any systemic or topical antibacterial or antiinflammatory drug treatment 90 days before study entry; (7) contact lens; (8) the presence of any corneal infection; (9) any corneal diseases (marginal ulcer, opacity, scar, bullous keratopathy, conjunctivochalasis, symblepharon, or tumor); and (10) pregnancy were excluded from this study.

The Schirmer I test, BUT, and corneal fluorescein and rose bengal staining scores were evaluated in all patients 1 day before (D0) and 14 (D14), 28, (D28), and 90 (D90) days after treatment with 0.03% tacrolimus eye drops. The Schirmer I test was performed using a Whatman 41 paper strip (Ophthalmos, São Paulo, Brazil) placed in the lateral lower conjunctival sac, and the measurement (closed eye) was recorded after 5 minutes. The BUT and rose bengal and fluorescein staining scores were performed by instilling 3 μL of a preservative-free combination of 1% rose bengal and 1% fluorescein into the conjunctival sac according to the double vital staining method described by Toda and Tsutobusa. The BUT was measured 3 times and averaged. The ocular surface staining score was rated from 0 to 3 (0 = no staining, 1 = mild staining, 2 = moderate staining, and 3 = extensive staining) according to the method of Toda and Tsutobusa.

Patients were instructed to use topical 0.03% tacrolimus eye drops twice a day (every 12 hours) in the lower conjunctival sac. The administration of any other topical drug was not allowed during the study period. All measurements were performed by one examiner (B.K.M.), under controlled temperature (19.98 ± 1.27°C) and humidity (64.23% ± 5.06%). Data are expressed as mean ± SD. The Mann–Whitney U test was used to compare results. The level of significance was set at P less than 0.05.

RESULTS

The average and SD of the BUT, Schirmer I test, and fluorescein and rose bengal score before and after treatment with 0.03% tacrolimus eye drops are shown in Table 1. The average fluorescein staining score improved statistically significantly from 3.81 ± 1.76 to 2.25 ± 1.34 (P = 0.0136) after 14 days of treatment and improved even more (P < 0.0001) after 90 days (Fig. 1). The average rose bengal staining score improved statistically significantly from 3.94 ± 3.13 to 2.63 ± 1.09 (P = 0.0045) after 14 days of treatment and improved even more (P < 0.0001) after 28 and 90 days (Fig. 2). The average Schirmer I test did not improve statistically significantly after 28 days of treatment (P = 0.3226), although we did observe a significant improvement after 90 days of treatment with 0.03% tacrolimus eye drops (P = 0.0075; Fig. 3). The average BUT did not improve statistically after 14 days of treatment (P = 0.11), although we observed a significant improvement after 28 and 90 days of treatment with 0.03% tacrolimus eye drops (P = 0.0468 and P = 0.0003, respectively; Fig. 4).

DISCUSSION

Systemic tacrolimus is effective in a variety of organ transplants and autoimmune diseases in animal models and human patients. In ophthalmology, its clinical use has been limited to suppressing experimentally induced T cell–mediated autoimmune uveoretinitis and blepharoconjunctivitis, and it prolonged corneal allograft survival in animals and humans.

Several authors have discussed the role of systemic tacrolimus in improving major symptoms of dry eyes, and it may represent an alternative therapy. The reason for the improved response in these patients is still unclear, but it may be related to the mechanism of action of systemic tacrolimus. Tacrolimus is 10 to 100 times more potent than CsA in human patients. In ophthalmology, its clinical use has been limited to suppressing experimentally induced T cell–mediated autoimmune uveoretinitis and blepharoconjunctivitis, and it prolonged corneal allograft survival in animals and humans.

It is believed that CsA has its therapeutic effect in dry eyes by inhibiting T-helper lymphocyte proliferation, controlling inflammation, infiltrating the lacrimal gland acini, and, at least partially, restoring their secretory function. A high-dose castor oil–based solution of topical CsA (1%–2%) has been reported to improve tear production in animals with KCS. In humans, low-dose topical CsA (0.05%) is effective in mild cases of dry eyes.

Recent studies have also demonstrated that tacrolimus ointment and eye drops are an alternative therapy in the
treatment of severe cases of ocular allergy (atopic keratoconjunctivitis and vernal keratoconjunctivitis) when glucocorticoids or antihistamines result in inadequate long-term treatment.

In veterinary medicine, 0.02% tacrolimus aqueous suspension has been described to be effective in treating canine KCS. Tacrolimus is a macrolide antibiotic that shares a similar immunomodulatory action with CsA. Similarities between the effects of tacrolimus and CsA on T cell–mediated ocular disease prompted us to investigate the clinical effects of topical tacrolimus eye drops on tear stability and its clinical signs in humans.

In this study, all patients showed symptomatic improvement after the treatment with 0.03% tacrolimus eye drops. Most patients complained of mild discomfort for approximately 30 minutes after topical instillation. When asked whether they preferred to keep or suspend the medication because of the irritation, all the patients in this study preferred to keep using it, given the significant clinical improvement. However, we believe that irritation and intolerance could limit the use of this medication in some patients. We used castor oil as the vehicle for tacrolimus eye drops and it may have caused irritation in some cases. Other vehicles for tacrolimus produce less irritation (eg, beta cyclodextrin). However, individual tolerance and other preservatives and vehicles are still under investigation.

High toxicity with systemic administration has precluded the use of tacrolimus in dogs for most clinical situations in veterinary medicine. Topical FK506 ointment has been used successfully for immunologic skin disorders, such as atopic dermatitis, without significant systemic absorption. However, therapeutic range of tacrolimus in humans is still unclear.
Administration of 0.03% tacrolimus twice a day is equivalent to a total body dose of approximately 0.50 mg per day, assuming complete absorption of each dose. For a 60-kg human being, this is equivalent to a daily dose well below that at which adverse effects were reported when administered systemically. Although no signs of systemic toxicity were noted among the patients in this study, caution is warranted when administering topical tacrolimus in pediatric patients.

Despite the clinical improvement in our cases, larger case–control studies using other patterns (Ocular Surface Disease Index, symptom scale, clinical sign scoring, and cytology) are necessary to verify the efficacy of tacrolimus in the treatment of dry eyes. The effectiveness of tacrolimus very likely results from a combination of mechanisms, including local immunosuppression, the proliferation of goblet cells, the suppression of lacrimal cell apoptosis, and especially the anti-inflammatory property. This study suggests that topical 0.03% tacrolimus eye drops may be effective in the treatment of SS dry eye syndrome.

**ACKNOWLEDGMENTS**

The authors thank Dr Acacio Alves de Souza Lima Filho for donating tacrolimus eye drops for this study.

**REFERENCES**


