ORIGINAL ARTICLE

Arquivos Brasileiros de Oftalmologia

Topical cyclosporine A 0.05% before and after surgery to prevent pterygium recurrence

Ciclosporina A 0,05% antes e após a cirurgia do pterígio para a prevenção da recorrência

Roberta Lilian Fernandes de Sousa Meneghim[1], Larissa Horikawa Satto[1], Kryscia Leiko Natsuaki[1], Alessandro Carvalho de Oliveira[1], Carlos Roberto Padovani[2], Magda Massae Hata Viveiros[1], Silvana Artioli Schellini[1]

1. Department of Ophthalmology, Botucatu Medical School, Universidade Estadual Paulista "Julio de Mesquita Filho", Botucatu, SP, Brazil.

2. Department of Biostatistic, Biosciences Institute, Universidade Estadual Paulista "Julio de Mesquita Filho", Botucatu, SP, Brazil.

ABSTRACT | Purpose: We evaluated the role of the conjunctival flap rotation technique using 5-fluorouracil and adjuvant therapy with topical cyclosporine A at 0.05% during short pre- and postoperative periods for the prevention of primary pterygium recurrence. **Methods:** In this prospective study, 76 patients with primary pterygium (76 eyes) were categorized into two groups: the control group with 31 patients who did not receive cyclosporine treatment, and the cyclosporine group with 45 patients who received topical cyclosporine A (0.05%) twice a day, for 10 days before and 10 days after the pterygium excision operations. Patients were examined for disease recurrence, side effects, and complications at 10 and 21 days, and at 2 and 6 months after the operation. Data on demography, systemic diseases, and ophthalmologic histories were obtained from all patients, and these data were analyzed using descriptive statistics involving the absolute and relative percentages of frequency distribution. Goodman test was used for contrasts among multinomial populations to study the association between cyclosporine A and recurrence. **Results:** Most patients were between 30 and 60 years of age, and 67.1% were women. We confirmed a higher recurrence in patients with occupational sunlight exposure. The cyclosporine A used topically 10 days before and 10 days after the pterygium removal did not significantly reduce the recurrence of the pterygium. **Conclusion:** Topical 0.05% cyclosporine A when used for 10 days before and 10 days after the pterygium removal does not prevent or reduce the recurrence of primary pterygium.

Keywords: Cyclosporine/administration and dosage; Pterygium/prevention and control; Recurrence

RESUMO | Objetivo: Avaliamos os resultados da técnica de rotação de retalho conjuntival com uso de 5-fluorouracil e terapia adjuvante com ciclosporina A tópica a 0,05%, usada no pré e pós-operatório por curto período, quanto à prevenção da recidiva do pterígio primário. **Métodos:** Estudo prospectivo, com 76 pacientes portadores de pterígio primário (76 olhos), divididos em dois grupos: controle com 31 pacientes que não receberam tratamento com ciclosporina e grupo ciclosporina com 45 pacientes que receberam ciclosporina tópica A (0,05%) duas vezes ao dia, por 10 dias antes e 10 dias após a cirurgia de excisão do pterígio. Os pacientes foram avaliados quanto à recorrência, efeitos colaterais e complicações com 10, 21 dias, 2 e 6 meses de pós-operatório. Dados demográficos, doenças sistêmicas e histórico oftalmológico foram coletados de todos os pacientes e esses dados foram analisados por meio de estatística descritiva envolvendo o percentual absoluto e relativo de distribuição de frequência. O teste de Goodman para contrastes entre populações multinomiais foi utilizado para o estudo da associação entre a ciclosporina A e a recorrência. **Resultados:** A maioria dos pacientes tinha entre 30 e 60 anos e 67,1% eram mulheres. Confirmamos uma maior recorrência em pacientes com exposição ocupacional ao sol. A ciclosporina A tópica utilizada 10 dias antes e 10 dias após a remoção do pterígio não reduziu significativamente a sua recorrência. **Conclusão:** A ciclosporina A tópica a 0,05% quando utilizada por 10 dias no pré e 10 dias no pós-operatório, não previne ou reduz a recidiva do pterígio primário significativamente.

Descritores: Ciclosporina/administração & dosagem; Pterígio/prevenção & controle; Recidiva

INTRODUCTION

Pterygium is a subepithelial fibrovascular hyperplasia of the conjunctival tissue that overgrows on the cornea, causing decreased visual acuity. Although there are

Submitted for publication: May 18, 2018
Accepted for publication: December 29, 2018

Funding: No specific financial support was available for this study.

Disclosure of potential conflicts of interest: The authors have no competing interests to disclose.

Corresponding author: Silvana Artioli Schellini.

Departamento de Oftalmologia, Faculdade de Medicina de Botucatu. Universidade Estadual Paulista – UNESP - Av. Prof. Montenegro s/n, Distrito de Rubião Júnior Botucatu - SP - 18610-000 - Brazil - E-mail: sartioli@fmb.unesp.br

Approved by the following research ethics committee: Faculdade de Medicina de Botucatu – Universidade Estadual Paulista "Júlio de Mesquita Filho" (Protocolo CEP 3319- 2009).

 http://dx.doi.org/10.5935/0004-2749.20190075

several hypotheses on the pathogenesis of pterygium, the epidemiology of the disease remains uncertain[1]. Exposure to ultraviolet radiation of sunlight and chronic conjunctival inflammation because of dust, wind, air pollution, and other environmental agents are associated with pterygium development and recurrence after excision[2,3]. Although surgical excision is the first-line treatment for pterygium, recurrence is a frequent complication. Use of different surgical techniques and adjuvant therapies such as mitomycin C[4], 5-fluorouracil[5,6], (5-FU), and Avastin[7] has not been completely successful in preventing the high recurrence rate[8], justifying the search for an ideal adjuvant therapy.

Cyclosporine A (CsA), isolated from the fungus *Tolypocladium inflatum*, is the first immunosuppressive drug that selectively allows immunomodulation of T cells without causing excessive toxicity[9]. CsA is widely used for the treatment of aplastic anemia and prophylactic treatment of graft-versus-host disease after kidney, lung, heart, liver, or hematopoietic stem cell tranplantation[10]. In ophthalmology, CsA has proven safety and efficacy in the treatment of dry eyes[11] and vernal keratoconjunctivitis[12]. In addition, CsA is used for the treatment of chronic ocular surface inflammatory diseases, such as blepharitis[13], punctate keratitis[14], chronic follicular conjunctivitis[15], and Behçet disease[16], as well as in pterygium, with promising outcomes[17-19], reducing the recurrence rate from 45.2% to 12.9% when applied for 6 months after the surgery[20]. A recent meta-analysis revealed that conjunctival autograft and adjuvant therapy with cyclosporine eye drops[21] may be the best treatment for preventing pterygium recurrence.

Few in vitro studies have demonstrated that CsA (0.05%) significantly reduces the proliferation of Tenon's capsule fibroblasts from primary and recurrent pterygiums, as well as the proliferation of fibroblasts from the normal conjunctiva[22,23]. Based on those results, we performed this study to evaluate the role of a conjunctival flap rotation technique using 5-FU and adjuvant therapy with topical CsA at 0.05% during short pre- and postoperative periods to prevent primary pterygium recurrence.

METHODS

Study groups

This prospective controlled study was conducted in accordance with the Helsinki Declaration and was approved by the Institutional Review Board and Research Ethics Committee of the Botucatu Medical School. Informed consent was obtained from all study participants.

A total of 76 patients with primary pterygium (76 eyes) were randomly divided into either the control group (n=31) which received an antibiotic and steroid eye drops, four times a day for 21 postoperative days, or the CsA group (n=45) that received topical 0.05% CsA (Restasis, Allergan Pharmaceutical, Brazil), twice a day for 10 preoperative and 10 postoperative days, in addition to the same combination of an antibiotic and steroid eye drops that was used for the control group patients. At the end of the procedure, both groups received a 0.2-mL subconjunctival injection of 5-FU at 25 mg/mL, in the remaining pterygium body.

The exclusion criteria were recurrent pterygium, previous ocular surgeries (e.g., glaucoma filtering surgery), or concomitant ocular diseases (e.g., keratoconjunctivitis sicca, pemphigoid, or idiopathic stem cell deficiency).

Data on demography (age, sex, and occupation), ophthalmic history (symptoms, estimated time with the pterygium, previous and current use of eye drops, and previous ocular surgery), and the presence of systemic diseases were obtained for all patients.

The ophthalmic evaluations included visual acuity with and without optical correction and slit-lamp examination. Pterygium was classified according to Cornand[24], as follows: grade I, pterygium head overgrowth on the cornea less than 2 mm; grade II, pterygium head overgrowing on the cornea from 2 to 4 mm; and grade III, pterygium head overgrowing on the cornea more than 4 mm. In addition, pterygium types were categorized as atrophic or fleshy according to the lesion thickness. Pterygium recurrence was defined as regrowth of fibrovascular tissue onto the clear cornea, in the region of previous pterygium removal.

Surgical procedure

Six surgeons performed all the operations at approximate equal numbers and using the same surgical technique. After topical application of 0.5% proxymetacaine hydrochloride (Alcon, Sao Paulo, SP, Brazil) and administration of subconjunctival anesthetic (lidocaine 2% with epinephrine; AstraZeneca, Cotia, SP, Brazil) under the pterygium body, the pterygium head was dissected from the cornea by using a number-15 blade and part of the pterygium body and Tenon capsule were removed using Westcott scissors. Subsequently, a superior and inferior conjunctival flap was slipped and the conjunctiva was closed at the limbal area using 10-0 nylon suture (Ethilon®; Ethicon, Sao Jose dos Campos, SP, Brazil), overlying the denuded sclera. All patients received a 0.2-mL subconjunctival injection of 5-FU at

25 mg/mL (Roche, Sao Paulo, Brazil) in the remaining pterygium body at the end of the procedure. A combination of an antibiotic and steroid eye drops was instilled into the eye and an ointment containing retinoic acid, chloramphenicol, and vitamin A was applied to the eye, which was then covered with a double patch for 24 h.

Outcome measures

Patients were evaluated postoperatively after 10 (for removal of the sutures) and 21 days, and after 2 and 6 months. The main outcome measures included presence of pterygium recurrence, patient complaints, and other postoperative complications.

Statistical analysis

The collected data were analyzed using descriptive statistics in terms of absolute and relative percentages of frequency distribution. Goodman test was used for contrasts among multinomial populations to evaluate the association between CsA and disease recurrence[25,26]. The significance level was set at <0.5%.

RESULTS

Most patients were between 30 and 60 years of age, and 67.1% (n=51) were women (Table 1). There was no statistical association between age and pterygium recurrence (Table 2).

Regarding exposure to UV radiation, 59 (77.63%) patients had high exposure to sunlight, whereas only 16 (21%) patients had occupations with low sunlight exposure (Table 1).

Regarding pterygium onset, 16 (21%) patients had been experiencing pterygium from 1 to 3 years, 24 (31.58%) patients from 3 to 5 years, and 36 (47.37%) patients for more than 5 years.

Regarding the eye drops that were previously used, 31 (40.79%) patients reported using no eye drops, whereas 41 (53.95%) were using eye drops without symptom improvement.

The main ocular complaints reported by patients before the surgery were hyperemia, burning, and/or foreign body sensation. Other complaints included tearing, itchiness, visual haze, pain, and swelling.

Regarding pterygium grades, 38 (50%) patients were classified as having grade I disease, 30 (39.5%) as having grade II disease, and 6 (7.89%) as having grade III disease. The lesions were evenly distributed between both groups, and we found no statistical difference on the distribution of patients between groups according to the pterygium classification. We found 53 (69.73%) atrophic and 23 (30.26%) fleshy pterygiums.

The recurrence was higher in patients with professional occupations that required increased exposure to sunlight (Table 1).

We found that the pterygium grade or surgeon's experience was not associated with the recurrence rate (Tables 3 and 4).

Control group patients had more recurrences than CsA group patients, but the difference was not statistically significant (p>0.05). Thus, our results showed that CsA used for 10 preoperative and 10 postoperative days did not prevent or reduce the recurrence of the primary pterygiums (Table 1, Figure 1).

Table 1. Demographics and ophthalmic manifestations in patients who did not receive topical cyclosporine A at 0.05% (Control group) and in those who received the medication (CsA group)

	Control group	CsA group	
	n (%)	n (%)	p value
Age in years			
20-30	2 (6.5)	5 (11.1)	>0.05
31-40	12 (38.7)	6 (13.3)	>0.05
41-50	8 (25.8)	12 (26.7)	>0.05
51-60	5 (16.1)	15 (33.3)	>0.05
>60	4 (12.9)	7 (15.6)	>0.05
Gender			
Male	10 (32.3)	16 (35.6)	>0.05
Female	21 (67.7)	30 (64.4)	>0.05
Occupation			
UV exposure	22 (71.0)	38 (84.5)	>0.05
No UV exposure	9 (29)	7 (15.5)	>0.05
Pterygium grade			
Grade I	16 (55.2)	22 (50.0)	>0.05
Grade II	11 (37.9)	18 (40.9)	>0.05
Grade III	2 (6.9)	4 (9.1)	>0.05
Recurrence			
Yes	19 (29,0)	18 (40.0)	>0.05
No	12 (38.7)	27 (60.0)	>0.05

p values represent 5% level of significance.

Table 2. Age group distribution in patients with recurrence according to their use of cyclosporine A

	Age group					
Cyclosporine	G2	G3	G4	G5	G6	p value
Without CsA	2 (6.5)	12 (38.7)	8 (25.8)	5 (16.1)	4 (12.9)	>0.05
With CsA	5 (11.1)	6 (13.3)	12 (26.7)	15 (33.3)	7 (15.6)	>0.05
p value	>0.05	>0.05	>0.05	>0.05	>0.05	

Table 3. Surgeon distribution according to cyclosporine A use and pterygium recurrence

CsA use	Recurrence grade	Surgeon 1	2	3	4	5	6	Total
With	I	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	3 (30.0)	3 (30.0)	10
	II	0 (0.0)	2 (33.3)	0 (0.0)	1 (16.7)	1 (16.7)	2 (33.3)	6
	III	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2
	IV	1 (6.3)	2 (12.5)	3 (18.8)	3 (18.8)	2 (12.5)	5 (31.2)	16
Without	I	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	3
	II	2 (25.0)	0 (0.0)	0 (0.0)	2 (25.0)	3 (37.5)	1 (12.5)	8
	III	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
	IV	4 (22.2)	4 (22.2)	4 (22.2)	2 (11.1)	1 (5.6)	3 (16.7)	18

Surgeons 1 and 3: second year residents.
Surgeons 2 and 4: third year residents.
Surgeons 5 and 6: hired doctors.

Table 4. Surgeon distribution according to the grade of pterygium recurrence with and without the use of cyclosporine A

Use of CsA	Surgeon	I	II	III	IV
With	**R2**	0.333	0.000	0.000	0.667
	R3	0.182	0.273	0.091	0.455
	HD	0.353	0.176	0.059	0.412
Without	**R2**	0.000	0.182	0.091	0.727
	R3	0.111	0.222	0.000	0.667
	HD	0.200	0.400	0.047	0.400
		P>0.05	P>0.05	P>0.05	P>0.05

R2= second year residents; R3= third year residents; HD= hired doctors.

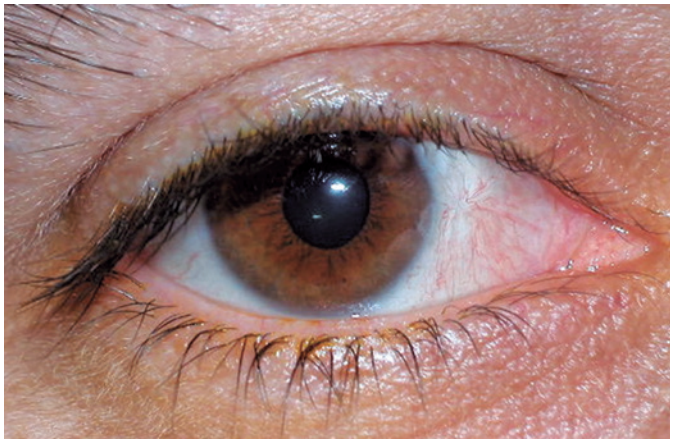

Figure 1. Patient in the cyclosporine A group with pterygium recurrence, after 2 months of follow-up.

DISCUSSION

We evaluated the efficacy of topical CsA at 0.05% in the pre- and postoperative periods of primary pterygium excision using the conjunctival flap rotation technique and 5-FU injection for the prevention of pterygium recurrence. The high rates of recurrence justify the use of adjuvant therapies such as antimetabolite drugs (mitomycin C or 5-FU), antiangiogenic agents (bevacizumab), or immunomodulatory agents (CsA) to reduce fibroblast proliferation[21,27].

The majority of our patients were between 30 and 60 years of age, and most of them had high sunlight exposure while working in exterior locations and they returned to those activities after the operation, which may justify the high recurrence rate.

CsA acts by binding to T lymphocytes, preventing the transcription of interleukin-2, cytokines, and associated lymphokines, causing decrease in the function of effector T cells without cytotoxic activity[28]. Although T lymphocytes are rarely identified in the conjunctiva, they are found in high levels in pterygium tissues[29], which supports the potential effects of CsA on the reduction of pterygium recurrence (as there is a strong correlation between cellular immunity and cytokine expression in the pathogenesis of pterygium[30]).

Although the use of CsA in previous studies has shown promising results in preventing pterygium recurrence[19,21], we found that the use of CsA did not prevent or reduce the recurrence of the pterygium. This finding may be attributed to the short period of CsA use, which was applied only for 10 preoperative and 10 postoperative days.

Some studies have revealed that a 3-month CsA application after the limbal conjunctival autograft technique can achieve a recurrence rate of 3.4%[17], and similar studies have associated the use of topical CsA for 6 postoperative months with low recurrence rates after procedures using the conjunctival flap rotation technique[18-20].

Our hypothesis at the beginning of the study was that starting CsA preoperatively would allow the beginning of action for a short-term use in the postoperatively. However, CsA has been shown to inhibit the inflammatory processes only when used for longer periods[17-20,31].

The disadvantage of CsA use is the extended period necessary to achieve satisfactory results (3-6 months), which can lead to decreased compliance and increased treatment cost for the patient. However, our results showed that treatment with CsA for a short period is not effective.

Overall, further studies are necessary to evaluate the efficacy of CsA to prevent pterygium recurrence when used for different time periods and to assess how many days of preoperative use of CsA provides any benefit.

REFERENCES

1. Todani A, Melki SA. Pterygium: current concepts in pathogenesis and treatment. Int Ophthalmol Clin. 2009;49(1):21-30.
2. Hill JC, Maske R. Pathogenesis of pterygium. Eye (Lond). 1989;3(2): 218-26.
3. Di Girolamo N, Chui J, Coroneo MT, Wakefield D. Pathogenesis of pterygia: role of cytokines, growth factors, and matrix metalloproteinases. Prog Retin Eye Res. 2004;23(2):195-228.
4. Kheirkhah A, Hashemi H, Adelpour M, Nikdel M, Rajabi MB, Behrouz MJ. Randomized trial of pterygium surgery with mitomycin C application using conjunctival autograft versus conjunctival-limbal autograft. Ophthalmology. 2012;119(2):227-32.
5. Shiratori CA, Hoyama E, Schellini SA, Padovani CR. Infiltração de 5-fluorouracil no pré-operatório do pterígio. Arq Bras Oftalmol. 2003;66(4):499-503.
6. Valezi VG, Schellini SA, Viveiros MM, Padovani CR. Segurança e efetividade no tratamento do pterígio usando infiltração de 5-fluoruracila no intraoperatório. Arq Bras Oftalmol. 2009;72(2):169-73.
7. Hu Q, Qiao Y, Nie X, Cheng X, Ma Y. Bevacizumab in the treatment of pterygium: a meta-analysis. Cornea. 2014;33(2):154-60.
8. Fernandes M, Sangwan VS, Bansal AK, Gangopadhyay N, Sridhar MS, Garg P, et al. Outcome of pterygium surgery: analysis over 14 years. Eye (Lond). 2005;19(11):1182-90.
9. Tedesco D, Haragsim L. Cyclosporine: a review. J Transplant. 2012; 2012:230386.
10. Willis L, Rexwinkle A, Bryan J, Kadia TM. Recent developments in drug therapy for aplastic anemia. Ann Pharmacother. 2014; 48(11):1469-78.
11. Perry HD, Donnenfeld ED. Topical 0.05% cyclosporin in the treatment of dry eye. Expert Opin Pharmacother. 2004;5(10):2099-107.
12. Pucci N, Novembre E, Cianferoni A, Lombardi E, Bernardini R, Caputo R, et al. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. Ann Allergy Asthma Immunol. 2002; 89(3):298-303.
13. Pflugfelder SC, Karpecki PM, Perez VL. Treatment of blepharitis: recent clinical trials. Ocul Surf. 2014;12(4):273-84.
14. Hasanreisoglu M, Avisar R. Long-term topical cyclosporin A therapy in Thygeson's superficial punctate keratitis: a case report. Cases J. 2008;1(1):415.
15. Ragam A, Kolomeyer AM, Kim JS, Nayak NV, Fang C, Kim E, et al. Topical cyclosporine a 1% for the treatment of chronic ocular surface inflammation. Eye Contact Lens. 2014;40(5):283-8.
16. Arevalo JF, Lasave AF, Al Jindan MY, Al Sabaani NA, Al-Mahmood AM, Al-Zahrani YA, et al.; KKESH Uveitis Survey Study Group; KKESH Uveitis Survey Study Group. Uveitis in Behçet disease in a tertiary center over 25 years: the KKESH Uveitis Survey Study Group. Am J Ophthalmol. 2015;159(1):177-84.e1.
17. Aydin A, Karadayi K, Aykan U, Can G, Colakoglu K, Bilge AH. Effectiveness of topical ciclosporin A treatment after excision of primary pterygium and limbal conjunctival autograft. J Fr Ophtalmol. 2008;31(7):699-704.
18. Turan-Vural E, Torun-Acar B, Kivanc SA, Acar S. The effect of topical 0.05% cyclosporine on recurrence following pterygium surgery. Clin Ophthalmol. 2011;5:881-5.
19. Özülken K, Koç M, Ayar O, Hasiripi H. Topical cyclosporine A administration after pterygium surgery. Eur J Ophthalmol. 2012;22 Suppl 7:S5-10.
20. Yalcin Tok O, Burcu Nurozler A, Ergun G, Akbas Kocaoglu F, Duman S. Topical cyclosporine A in the prevention of pterygium recurrence. Ophthalmologica. 2008;222(6):391-6.
21. Fonseca EC, Rocha EM, Arruda GV. Comparison among adjuvant treatments for primary pterygium: a network meta-analysis. Br J Ophthalmol. 2018;102(6):748-56.
22. Hercules LA, Viveiros MM, Schellini SA, Candeias J, Padovani CR. Exposure of Tenon's capsule fibroblasts of pterygium to cyclosporin 0.05%. Arq Bras Oftalmol. 2006;69(6):831-5.
23. Viveiros MM, Kakizaki FY, Hércules LA, Padovani CR, Candeias JM, Schellini SA. In vitro study of cyclosporine A 0.05 % on primary and recurrent pterygium fibroblasts. Int Ophthalmol. 2016; 36(2):237-42.
24. Cornand G. Le ptérygion. Evolution et traitement. J Fr Ophtalmol. 1990;13(1-2):33-45.
25. Goodman LA. A simultaneous confidence intervals for contrasts among multinomial populations. Ann Math Stat. 1964;35(2):716-25.
26. Goodman LA. On simultaneous confidence intervals for multinomial propositions. Technometrics. 1965;7(2):247-54.
27. Fernandes M, Sangwan VS, Bansal AK, Gangopadhyay N, Sridhar MS, Garg P, et al. Outcome of pterygium surgery: analysis over 14 years. Eye (Lond). 2005;19(11):1182-90.
28. Borel JF. History of the discovery of cyclosporin and of its early pharmacological development. Wien Klin Wochenschr. 2002; 114(12):433-7.
29. Nakamura M, Nishida T. Differential effects of epidermal growth factor and interleukin 6 on corneal epithelial cells and vascular endothelial cells. Cornea. 1999;18(4):452-8.
30. Solomon AS. Immunologic basis for the pathogenesis of pterygium. Am J Ophthalmol. 1985;99(2):216-7.
31. Gündüz K, Ozdemir O. Topical cyclosporin treatment of keratoconjunctivitis sicca in secondary Sjögren's syndrome. Acta Ophthalmol (Copenh). 1994;72(4):438-42.