Original Article

Topical Use of Cyclosporine in the Treatment of Vernal Keratoconjunctivitis

Tahir Masaud Arbab, Manzoor A Mirza

Pak J Ophthalmol 2011, Vol. 27 No. 3

See end of article for authors affiliations

Correspondence to:
Tahir Masaud Arbab
Zamzama Medical Centre,
Plot No 144, 7th Neelum lane,
3rd Zamzama street,
Opp. Zamzama Park, Defence Housing Society, Phase V
Karachi

Submission of paper
August' 2010

Acceptance for publication
September' 2011

Purpose: To study the efficacy and safety of topical 2% cyclosporine in patients with vernal keratoconjunctivitis.

Material and Methods: This is a placebo-controlled, clinical trial to evaluate the effects of topical 2% cyclosporine on patients with vernal keratoconjunctivitis. Twelve patients were placed in the cyclosporine treatment group and eight patients were placed in the placebo group. All patients had a wash out period of one week in which they were advised not to instill any eye drop. After this period, patients underwent a detailed ophthalmic examination with specific note being made of itching, tearing, photophobia, mucous discharge and foreign body sensation. Specific signs looked for on slit lamp biomicroscopic examination included conjunctival hyperemia, punctuate keratitis, trantas dots, limbal edema and papillae.

Patients were assigned at random to one of the study groups, either cyclosporine 2% eye drops or placebo eye drops administered four times daily to the both eyes.

Patients were examined weekly for a total follow-up period of 6 weeks.

Results: There were 18 males and 2 females in the study. Patients had mean age of 11.6 years (range 7 to 19 years). There was a statistically significant decrease in symptoms and in the conjunctival hyperemia, punctate keratitis, and Trantas dots in the group of patients treated with cyclosporine. No adverse effects were noted in the cyclosporine treated group.

Conclusion: Topical cyclosporine appears to be safe and effective for treatment of vernal keratoconjunctivitis.

Vernal keratoconjunctivitis (VKC) is a chronic allergic conjunctivitis. The disease is usually bilateral and is more common among males. The signs and symptoms of VKC usually occur from April to August, although some patients have a perennial form of the disease[1]. The spectrum of disease differs in tropical and temperate countries[2]. The reported risk of visual loss is generally greater in tropical countries, which is about 10%[3,4].

The precise immunopathogenic mechanism is unknown but is thought to be more complex than a simple type 1 hypersensitivity reaction. The trophic changes are due to enhanced fibroblast proliferation and collagen deposition in epithelium and substantia propria caused by eosinophil and mast cell degranulation[5]. Therapy for VKC includes the use of topical vasoconstrictors, antihistamines, inhibitors of mast cell degranulation and Corticosteroids. The most effective treatment for VKC is topical Corticosteroids, but it carries considerable risk of complications. Corneal morbidity along with steroid related complications may lead to permanent visual impairment. Therefore there is need for an alternative, effective, safe drug that can decrease the morbidity from this potentially blinding disease.

Cyclosporine is a non steroidal immunomodulating agent, which has been used widely in the treatment of such ocular inflammatory conditions as

noninfectious, corticosteroid resistant, sight threatening uveitis and corneal graft rejection.

Cyclosporine can selectively suppress a variety of T lymphocyte function and has a unique ability to selectively suppress the synthesis and production of Interleukin 2[6-8].

In experimental animals, cyclosporine has been shown to suppress IgE production in mice by interfering with T cell-dependent mechanism[9].

Topical cyclosporine has been used in prevention of corneal graft rejection[10] and treatment of ligneous conjunctivitis[11]. Cyclosporine 2% eye drops has been used successfully in the treatment of patients with severe vernal keratoconjunctivitis[12-14].

We used topical cyclosporine in treatment of 20 patients with severe vernal keratoconjunctivitis. Many of the patients were sensitive to high dosages of topical Corticosteroids, with no other drug being effective in controlling their clinical signs and symptoms. The topical use of cyclosporine was assumed to be useful in these patients as a substitute or as a sparing factor for Corticosteroids.

MATERIAL AND METHODS

The study was undertaken at Sir Syed Hospital, Karachi, from April 2009 to June 2010. Twenty patients with a history of severe VKC who provided informed consent were included in the study. All cases had been previously treated with a variety of topical drops in the form of mast cell stabilizers, antihistamines, anti-inflammatory drugs and steroids for at least one year before enrollment. Patients with shield ulcer, epithelial defect, associated ocular or systemic diseases; those taking oral medicines were excluded from the study. All patients had a wash out period of one week in which they were advised not to instill any eye drop. Only commercially available saline was given to the patients to be instilled if needed. After this period, patients underwent a detailed ophthalmic examination with specific note being made of itching, tearing, photophobia, mucous discharge and foreign body sensation. Specific signs looked for on slit lamp biomicroscopic examination included conjunctival hyperemia, punctate keratitis, trantas dots, limbal edema and papillae.

Patients were assigned at random to one of the study groups, either cyclosporine 2% eye drops four times daily or placebo eye drops four times daily were administered to both eyes. A weekly record of their symptoms and signs was kept for a period of 6 weeks. All patients had a total follow-up period of 6 weeks.

The grading system was followed for categorizing symptoms and signs of VKC. These were graded on a scale of 0-3 using the method described by Bleik et al[14]. Patients subjectively graded their symptoms and the questionnaire was completed by the examiner, who also recorded the signs.

GRADING OF SYMPTOMS

Symptoms of itching, tearing, photophobia, discharge and foreign body sensation were recorded for a period of 6 weeks. The symptoms were recorded at a scale of 0 indicating no symptoms, 1+ = mild symptoms of discomfort noticed (mostly just noticeable), 2+ = moderate discomfort noticed most of the day but did not interfere with daily routine activities, 3+ = severe symptoms disrupting daily routine activities and patient staying at home most of the time.

GRADING OF SIGNS

Conjunctival Signs

Hyperemia was graded as follows: 0 = no evidence of bulbar hyperemia, 1+ = mild bulbar hyperemia, 2+ = moderate bulbar hyperemia, and 3+ = severe bulbar hyperemia.

Upper palpebral conjunctiva was graded as follows: 0 = no papillary hypertrophy of the palpebral conjunctiva, 1+ = mild papillary hypertrophy, 2+ = moderate papillary hypertrophy (edema of the palpebral conjunctiva with hazy view of the deep tarsal vessels), 3+ = severe papillary hypertrophy where the papillary hypertrophy was in more than 50% of the surface.

Corneal Signs

Punctate keratitis was graded as follows: 0 = no evidence of punctate keratitis, 1+ = one quadrant of punctate keratitis, 2+ = two quadrants of punctate keratitis, and 3+ = three or more quadrants of punctate keratitis.

Limbal Signs

Trantas dots were graded as follows: 0 = no evidence of dots, 1+ = 1 to 2 dots, 2+ = 3 to 4 dots, 3+ = more than 4 dots.

Limbal infiltration. Grading for limbal infiltration was as follows: 0 = no evidence of limbal infiltration,

1+ = less than 90^0 of limbal infiltration, 2+ = less than 180^0 of limbal infiltration but more than 90^0, and 3+ = more than 180^0 of limbal infiltration.

MEDICATIONS

One treatment regimen consisted of cyclosporine 2% eye drops, and the placebo eye drops. The bottles of cyclosporine and placebo eye drops were labeled appropriately. The cyclosporine used in this study was taken from Agha Khan hospital pharmacy.

PATIENT WITHDRAWAL

None of the patients had adverse reactions to the topical medications that required withdrawal of the patient from the study.

RESULTS

Age and sex distribution

There were 18 males and 2 females in the study. Patients had mean age of 11.6 years (range 7 to 19 years). Twelve patients were placed in the cyclosporine treatment group and eight patients were placed in the placebo group.

SYMPTOMS

Itching: Eleven patients (91.6%) who were administered cyclosporine had decrease in itching, compared with 2 in the control group (25%).
Tearing: Improved in 9 patients (75%) who were administered cyclosporine and 2 of the patients (25%) in the control group.
Photophobia: Ten patients (83%) reported marked improvement in photophobia in the cyclosporine group and no patient (0%) reported any improvement in photophobia in the placebo group.
Discharge: Decreased in 10 patients (83%) who were administered cyclosporine and 2 of the patients (25%) in the control group.
Foreign body sensation: Improved in 10 patients (83%) who were administered cyclosporine and 2 of the patients (25%) in the control group.

Conjunctival Signs

Conjunctival hyperemia: Bulbar conjunctival hyperemia improved in 10 of 12 patients (83%) who were administered cyclosporine and 2 out of the 8 patients (25%) in the control group.
Papillary Hypertrophy: Showed no improvement with the use of cyclosporine.

Corneal Signs

Punctate Keratitis: Eleven patients (91.6) out of 12 showed improvement with cyclosporine compared to1 of 8 patients (12.5%) treated with topical placebo drops.

Limbal Signs

Trantas dots: Showed decrease in number in 9 of 12 patients (75%) treated with cyclosporine compared with 1 of 8 patients (12.5%) in the group treated with placebo.

Limbal infiltration and edema improve in 9 patients (75%) treated with cyclosporine with 2 patients (12.5%) treated with placebo drops.

DISCUSSION

Vernal keratoconjunctivitis is a common disorder in our part of the world. Most of the patients show mild systems, usually relieved by over the counter medications. Some patients show severe form of disease that may lead to distress in patient life.

Management of VKC in tropical countries like ours is not easy because of the safety and cost as well as the easy availability of over the counter medicines. Mast cell stabilizers have not shown good results from Middle East and Africa[15,16]. Topical steroids are effective but unsupervised treatment leads to unsuspected steroid induced glaucoma and cataract[17].

Visual loss occurs because of corneal complications from the disease or because of the use and abuse of topical Corticosteroids, which may lead to steroid-induced glaucoma and steroid-induced cataract.

Because the condition eventually resolves, usually after adolescence, the treatment should be conservative and aimed at preventing potential complications.

Continuous search for safe and effective therapy for vernal keratoconjunctivitis is highly desirable.

In this short-term clinical trial, we demonstrated that topical administration of cyclosporine 2% eye drops is a safe and effective therapy for vernal keratoconjunctivitis. It was well tolerated by all of our patients and it is an effective therapeutic modality in controlling the symptoms and signs of both conjunctival tarsal and limbal forms of vernal keratoconjunctivitis. The symptoms responded more readily and in a more substantial way to the treatment.

Table 1. Effect of topical cyclosporine on symptoms in patients with vernal keratoconjunctivitis symptoms

S. N	Durg	Sex/Age	Itching		Tearing		Photophobia		Discharge		Foreign Body Sensation	
			Before	After	Before	After	Before	After	Before	After	Before	After
1	PLA	M (12 Yrs)	3+	2+	3+	3+	3+	3+	2+	3+	1+	2+
2	PLA	F (9 Yrs	3+	3+	2+	3+	2+	2+	3+	2+	1+	1+
3	CSA	M (8 Yrs)	3+	1+	3+	1+	2+	0	3+	1+	2+	0
4	CSA	M (13 Yrs)	3+	1+	3+	0	3+	0	3+	1+	2+	1+
5	PLA	M (14 Yrs)	3+	3+	2+	2+	2+	3+	2+	3+	1+	1+
6	CSA	M (17 Yrs)	3+	3+	3+	3+	3+	3+	2+	2+	2+	2+
7	PLA	M (8 Yrs)	3+	3+	3+	3+	3+	3+	3+	2+	3+	2+
8	PLA	M (15 Yrs)	3+	1+	3+	1+	2+	2+	3+	3+	3+	0
9	CSA	M (11 Yrs)	3+	1+	3+	1+	3+	1+	0	0	2+	1+
10	CSA	M (11 Yrs)	3+	2+	3+	2+	3+	2+	3+	1+	3+	0
11	CSA	M (9Yrs)	3+	1+	1+	1+	1+	1+	2+	2+	1+	1+
12	PLA	M (12 Yrs)	3+	1+	1+	0	0	0	0	0	0	0
13	CSA	M (13 Yrs)	3+	1+	3+	1+	3+	1+	0	0	0	0
14	CSA	M (14 Yrs)	3+	0	3+	0	3+	0	1+	1+	2+	0
15	PLA	M (7 Yrs)	2+	3+	3+	3+	3+	3+	1+	1+	2+	2+
16	CSA	M (19 Yrs)	3+	1+	3+	2+	2+	2+	3+	1+	2+	0
17	CSA	M (12 Yrs)	3+	0	2+	1+	1+	0	0	0	1+	0
18	PLA	M (11 Yrs)	3+	3+	2+	2+	1+	1+	3+	3+	1+	1+
19	CSA	F (11 Yrs)	3+	2+	2+	2+	2+	1+	1+	0	1+	0
20	CSA	M (7 Yrs)	3+	0	1+	2+	2+	0	3+	0	2+	0

CSA = Cyclosporine; PLA = Placebo
Before = Before treatment; After = 6 weeks after initiation of treatment

Cyclosporine had a remarkable effect on most of the signs of vernal keratoconjunctivitis. There was decrease in punctate staining of cornea, limbal infiltration and in number of Trantas dots. The number and size of giant papillae were not influenced by the use of topical cyclosporine and showed little change in the relatively short time of our trial, but a decrease in the conjunctival edema and hyperemia was noted in the group of patients treated with topical cyclosporine.

Similarly Jamal Bleik and Khalid Tabbara[14] in a placebo-controlled, clinical trial evaluated the effects of topical 2% cyclosporine on patients with vernal keratoconjunctivitis for period of 6 weeks. No adverse effects and no detectable levels of cyclosporine were noted in the blood in the cyclosporine treated groups. They reported marked improvement in symptom and signs in patients treated with topical cyclosporine and concluded that topical cyclosporine is safe and effective for the short-term treatment of vernal keratoconjunctivitis.

Ather Jameel et al[18] evaluated the effects of topical 2% cyclosporine eye drops in patients with active vernal keratoconjunctivitis. In his study all patients were treated with 2% cyclosporine eye drops for a period of 6 weeks. His results showed a statistically significant improvement in itching, photophobia, mucous discharge, conjunctival hyperemia, punctate keratitis and trantas' dots after 6 weeks treatment period.

Topical cyclosporine has been, in our patients, an excellent substitute for Corticosteroids. (91.6%) of patients had decrease in itching, 75% and 83% of patients had improvement in tearing and photophobia respectively. 83% of patients showed decreased in discharge.

Table 2. Effect of topical cyclosporine on signs in patients with vernal keratoconjunctivitis

S. No	Drug	Eye	Signs							
			Conjunctival Hyperemia		Punctate Keratitis		Trantas Dots		Limbal Edema	
			Before	After	Before	After	Before	After	Before	After
1	PLA	OS	2+	2+	1+	1+	3+	3+	3+	3+
	PLA	OD	2+	2+	1+	1+	2+	3+	2+	2+
2	PLA	OS	2+	2+	2+	2+	2+	2+	1+	1+
	PLA	OD	2+	2+	3+	3+	1+	1+	1+	1+
3	CSA	OS	2+	1+	3+	1+	3+	0	2+	1+
	CSA	OD	2+	1+	3+	1+	2+	0	2+	1+
4	CSA	OS	2+	1+	2+	0	3+	1+	3+	1+
	CSA	OD	2+	1+	2+	1+	3+	1+	3+	1+
5	PLA	OS	3+	3+	2+	2+	3+	3+	3+	3+
	PLA	OD	3+	3+	2+	2+	2+	2+	3+	3+
6	CSA	OS	2+	3+	3+	3+	3+	3+	3+	3+
	CSA	OD	2+	2+	3+	3+	3+	3+	3+	3+
7	PLA	OS	3+	2+	1+	2+	3+	0	3+	2+
	PLA	OD	3+	2+	1+	2+	3+	0	3+	2+
8	PLA	OS	3+	2+	3+	3+	3+	3+	3+	2+
	PLA	OD	3+	2+	3+	2+	3+	3+	3+	2+
9	CSA	OS	3+	2+	1+	0	3+	0	3+	1+
	CSA	OD	3+	2+	1+	0	0	0	2+	1+
10	CSA	OS	3+	3+	1+	0	0	0	1+	0
	CSA	OD	3+	3+	1+	0	0	0	1+	0
11	CSA	OS	2+	2+	2+	1+	3+	3+	3+	3+
	CSA	OD	2+	2+	3+	2+	3+	3+	3+	3+
12	PLA	OS	1+	1+	1+	1+	0	0	2+	1+
	PLA	OD	1+	1+	2+	1+	0	0	2+	1+
13	CSA	OS	2+	2+	3+	3+	0	0	3+	3+
	CSA	OD	2+	2+	3+	3+	2+	2+	3+	3+
14	CSA	OS	3+	0	3+	0	3+	0	3+	0
	CSA	OD	3+	0	3+	0	3+	0	3+	0
15	PLA	OS	1+	3+	3+	3+	0	0	1+	3+
	PLA	OD	1+	3+	0	3+	0	0	1+	3+
16	CSA	OS	2+	1+	3+	1+	0	0	3+	1+
	CSA	OD	2+	1+	3+	1+	0	0	3+	1+
17	CSA	OS	3+	0	3+	0	1+	0	2+	0
	CSA	OD	3+	0	3+	0	3+	0	3+	0
18	PLA	OS	3+	3+	3+	3+	1+	1+	3+	3+
	PLA	OD	3+	3+	3+	3+	3+	3+	3+	3+
19	CSA	OS	1+	2+	1+	3+	0	0	1+	2+
	CSA	OD	1+	2+	0	1+	0	0	1+	2+
20	CSA	OS	2+	1+	3+	0	3+	0	3+	0
		OD	2+	1+	3+	0	3+	0	3+	0

CSA = Cyclosporine; PLA = Placebo. Before = Before treatment; After = 6 weeks after initiation of treatment

Bulbar conjunctival hyperemia improved in 83% of patients and 91.6 of patients showed improvement in corneal punctuate keratitis. Trantas dots decreased in 75% patients and there was improvement in limbal infiltration and edema 75% of patients treated with cyclosporine.

Cyclosporine appears to be safe and effective for short-term treatment of vernal keratoconjunctivitis. Literature shows that topical cyclosporine is not absorbed into the systemic circulation in sufficient concentration to reach therapeutic or toxic dosages and therefore is not associated with any systematic side effects. Topical cyclosporine appears to carry none of the serious, sight threatening complications of topical steroids, such as glaucoma, cataract and exacerbation of corneal infection[19].

Cyclosporine an immunosuppressive agent, most commonly used in organ transplantation has a selective inhibitory effect on helper T-lymphocytes proliferation and production of interleukin-2. It is therefore inhibitory to many T-Cell dependent inflammatory mechanisms. Cyclosporine also has direct inhibitory effects on eosinophil activation and release of granule proteins and cytokines and both direct and indirect inhibitory effects on mast cell activation, cytokine, and mediator release, which are likely to be important to its role in the treatment of allergic inflammation[6-8].

Two types of mast cells have been recognized in humans based on neutral protease composition[20] and T-lymphocyte dependency[21]. The T-lymphocyte-dependent mast cells contain tryptase but not chymase whereas the T-lymphocyte independent mast cells contain both tryptase and chymase[22]. Patients with active VKC have a significant increase in the T-lymphocyte-dependent mast cells in the epithelial cells of conjunctival biopsy specimens[23]. The exact mechanism of action of cyclosporin on the mast cell is unknown but it may be postulated that cyclosporin modulates the local IgE production by the B cell via its effects on the T-helper cells and possibly by influencing the T-lymphocyte-dependent mast cells[9].

The current cost of cyclosporine may restrict its use to severe form of vernal keratoconjunctivitis. Other topical conservative therapy may be considered for mild forms of the disease. Topical cyclosporine represents an important addition to the therapeutic armamentarium for severe vernal keratoconjunctivitis, which until now was only sensitive to Corticosteroids.

Author's affiliation

Dr. Tahir Masaud Arbab
Sir Syed College of Medical Sciences
Karachi

Prof. Manzoor A Mirza
Sir Syed College of Medical Sciences
Karachi

REFERENCE

1. **Friedlaender MH.** Allergy and Immunology of the Eye. Harper and Row: Hagerstown; 1979; 185-8.
2. **Tuft SJ, Cree IA, Woods M, et al.** Limbal Vernal Keratoconjunctivitis in the Tropics. Ophthalmology. 1998; 105: 489-93.
3. **Sandford-Smith JH.** Vernal eye disease in North Nigeria. Trop Geogr Med.1979; 31: 321-8.
4. **Baryishak YR, Zavaro A, Monselise M, et al.** Venal keratoconjunctivitis in an Israeli group of patients and its treatment with sodium cromogylate. Br J Ophthalmol. 1982; 66: 118-22.
5. **Smolin G. O'Connor.** Ocular Immunology. 3rd ed. Little Brown: Boston. 1986; 135-92.
6. **Kaufmann Y, Chang AE, Robb RJ, et al.** Mechanism of action of Cyclosporine A: inhibition of lymphokine secretion studied with antigen-stimulated T cell hybridomas. J Immunol. 1884; 133: 3107-11.
7. **Larsson EL.** Cyclosporine A and dexamethasone suppress T cell responses by selectively acting at distinct sites of the triggering process. J Immunol. 1980; 124: 2828-33.
8. **Nussenblatt RB, Palestine AG.** Cyclosporine: immunology, pharmacology and therapeutic uses. Surv Ophthalmol. 1986; 31: 159-69.
9. **Okudaira H, Sakurai Y, Terado K, et al.** Cyclosporine A-induced suppression of ongoing IgE antibody formation in the mouse. Int Arch Allergy Appl Immunol. 1986; 79:164-8.
10. **Hunter PA, Wilhelmus KR, Jones BR.** Cyclosporin A applied topically to the recipient eye inhibits corneal graft rejection. Clin Exp Immunol. 1981; 45: 173-7.
11. **Holland EJ, Chan C-C, Kuwabara T, et al.** Immunohistologic finding and results of treatment with cyclosporine in ligneous conjunctivitis. Am J Ophthalmol. 1989; 107: 160-6.
12. **BenEzra D, Pe'er J, Brodsky M, Cohen E.** Cyclosporine eye drops for treatment of severe vernal keratoconjunctivitis. Am J Ophthalmology. 1986; 101: 278-82.
13. **Sechi AG, Tognon MS, Leonardi A.** Topical use of cyclosporine in the treatment of vernal keratoconjunctivitis. Am J Ophthalmology. 1990; 110: 641-5.
14. **Bleik JH, Tabbara KF.** Topical cyclosporine in vernal keratoconjunctivitis. Ophthalmology. 1991; 98: 1679-84.
15. **Abu el-Astar AM, Van den Oord JJ, Geboes K, et al.** Immunopathological study of vernal keratoconjunctivitis. Graefes Arch Clin Exp Ophthalmol. 1989; 227: 374-9.
16. **Easty D, Rice NS, Jones BR.** Disodium cromogylate in the treatment of vernal keratoconjunctivitis. Trans Ophthalmol. Soc UK. 1971; 91: 191-9.
17. **Khan MD, Kundi N, Saeed N.** A study of 530 cases of vernal conjunctivitis from the North Western Frontier Province of Pakistan. Pak J Ophthalmol. 1986; 2: 111-4.

18. **Jameel A, Moin M, Hussain M.** Role of cyclosporine eye drops in allergic conjunctivitis. Pak J Ophthalmol. 2009; 25: 104-9.
19. **Hoang-Xuan T, Prisant O, Hannouche D, et al.** Systemic Cyclosporin A in severe atopic keratoconjunctivitis. Ophthalmology. 1997; 104: 1300-5.
20. **Irani AA, Schechter NM, Craing SS, et al.** Two types of human mast cells that have distinct neutral protease composition. Proc Natl Acad Sci USA. 1986; 83: 4464-8.
21. **Craig SS, Schechter NM, Schwartz LB.** Ultra structural analysis of human T and TC mast cells identified by immunoelectronmicroscopy. Lab Invest. 1998; 58: 682-91.
22. **Irani AA, Craig SS, De Bois G, et al.** Deficiency of the tryptase-positive, chymase-negative mast cell type in gasto-intestinal mucosa of patients with defective T lymphocyte function. J Immunol. 1987; 138: 4381-6.
23. **Irani AM, Butrus SI, Tabbara KF.** Human conjunctival mast cells: Distribution of MCr and MCrc in vernal conjunctivitis and gaint papillary conjunctivitis. J Allergy Clin Immunol. 1990; 86: 34-40