
Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis

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Background: Corticosteroids have been the only effective topically administered treatment for severe vernal keratoconjunctivitis (VKC), but their prolonged use is often associated with complications. Topical cyclosporine therapy has been used in the past decade, but few controlled trials have been conducted, and conflicting results have been reported.

Objective: This study sought to evaluate the efficacy and safety of ocular administration of cyclosporine in VKC.

Methods: Twenty-four children with severe VKC were treated with cyclosporine 2% eyedrops. The treatment began in spring and lasted 4 months. One eye was treated with cyclosporine (Cs-eye); the fellow eye received the vehicle as placebo (Pl-Cs-eye) during the first 2 weeks in a double-blind, placebo-controlled trial and thereafter was treated with cyclosporine (open trial). Patients were instructed to protect their eyes against sunlight. Ocular symptoms and signs were scored at entry and at 2 weeks, 4 weeks, and 4 months after the beginning of treatment. All children underwent biochemical and immunologic evaluations.

Results: Compared with baseline, scores for ocular signs and symptoms at 2 weeks decreased significantly in the Cs-eyes ($P < 0.001$), and signs improved in the Pl-Cs-eyes ($P = 0.001$). A significant difference was noted between Cs-eyes and Pl-Cs-eyes at 2 weeks for both subjective ($P < 0.005$) and objective ($P < 0.001$) scores. At 4 weeks, scores for signs ($P < 0.001$) and symptoms ($P = 0.01$) were reduced in the Pl-Cs-eyes, with no further improvement in the Cs-eyes. At 4 months, clinical scores had declined further, and serum eosinophil cationic protein levels were significantly lower than at entry ($P = 0.009$). Most patients reported mild burning sensation and tearing after administration of cyclosporine. Four patients (17%) required an additional brief period of topical corticosteroid therapy.

Conclusions: Cyclosporine eyedrops were effective and safe for treating severe VKC, without causing major side effects. Most of the therapeutic effect was achieved after 2 weeks. The initial therapeutic effect was maintained during the next 3 months, with a further slow decrease in the symptoms.

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic and often severe form of bilateral tarsal or bulbar (or both) conjunctivitis. The term “keratoconjunctivitis” implies a possible involvement of the cornea and a subsequent compromise of vision.¹ VKC usually begins during the first decade of life and disappears during the second decade.^{2,3} It is widespread in predominantly warm climates such as Mediterranean areas.^{3,4} The intensity of the disease usually increases in the spring and, in contrast with seasonal allergic conjunctivitis, in the summer.

The major conjunctival signs include hyperemia, papillae, and giant papillae, which frequently are located in the upper tarsal conjunctiva and in corneal infiltrates (limbal Trantas' dots). Mixed tarsal and limbal forms are common. Punctate keratitis, corneal ulcers, and corneal neovascularization are possible complications. Recent studies have shown a prevalent local helper T-cell type 2 response in VKC, with the

presence of helper T-cell type 2-like cells in tears and conjunctival biopsy specimens.^{5,6} Increased numbers of activated mast cells and eosinophils have been found in the conjunctivae.^{2,7} Interleukin (IL)-3, IL-5, IL-6, and granulocyte-macrophage colony-stimulating factor are particularly expressed in conjunctival eosinophils.⁷ High levels of tear IL-5 and eosinophil cationic protein (ECP) have also been found in patients with VKC.^{8,9}

Topical corticosteroids are an effective treatment for VKC, but their prolonged use is often associated with complications such as glaucoma, cataracts, and bacterial infections. Other topical agents such as antihistamines, inhibitors of mast cell degranulation, and nonsteroidal anti-inflammatory drugs have been used in the treatment of VKC, but they are effective only in mild-to-moderate cases.^{2,3,10,11} Topical mitomycin-C has been used successfully in severe VKC but has been administered only for a limited period (4 weeks) to avoid potential side effects.¹² During the past decade, topical cyclosporine therapy has been used to treat a variety of ocular conditions such as corneal graft,¹³ atopic keratoconjunctivitis,¹⁴ ligneous conjunctivitis,¹⁵ and conjunctival lichen planus.¹⁶ Further, several studies have reported that topical cyclosporine is very effective in treating moderate and severe VKC.^{17–21} In three controlled trials, patients underwent followup for 2 weeks, 6 weeks, and 4 months.^{4,21,22}

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These studies reported only partial data about the efficacy of topical cyclosporine on scores for signs and symptoms of VKC, and the results were controversial.

In the current study, we evaluated the efficacy and safety of cyclosporine 2% eyedrops in 24 patients with VKC that was refractory to commonly used treatments. The study was a double-blind, placebo-controlled trial of 2 weeks followed by an open trial for up to 4 months. Immunologic and allergologic variables were also evaluated.

PATIENTS AND METHODS

Study Subjects

Twenty-four consecutive patients with tarsal or bulbar (or both) VKC were recruited into the study. To be included in the study, patients must have had signs and symptoms of VKC for at least 1 year before entering the study, with or without remission during cold seasons; patients must have a total objective ocular score of 8 or more; and patient levels of biochemical measurements and systemic blood pressure must be within normal range. In addition, patients must have experienced no substantial decrease in signs and symptoms of VKC with the use of at least two of the following topical drugs, each for 2 weeks: antihistamines, nedocromil, spaglumic acid, or ketorolac.

For all study participants, informed consent was obtained, and a complete washout period from any type of drug of at least 10 days was established. Seven healthy age-matched subjects without atopy also underwent evaluation for total serum immunoglobulin (Ig)E, serum ECP, and peripheral blood eosinophil counts (PBECS).

Clinical Scoring System

Each patient with VKC was evaluated for subjective ocular symptoms (itching, photophobia, tearing, foreign body sensation, and burning sensation), which were scored as previously reported,⁴ and objective ocular signs (conjunctival hyperemia, papillae, giant papillae, and corneal infiltrates). Each variable was graded as follows: 0 = absent; 1 = mild; 2 = moderate; or 3 = severe. In detail, papillae were graded according to the system described by Bonini et al² with a slight modification, depending on their number and size: 0 = absent; 1 = a few papillae <0.2 mm; 2 = papillae of 0.3 to 1 mm on the tarsal conjunctiva; or 3 = papillae of 1 to 3 mm throughout the tarsal conjunctival area. Giant cobblestone-like papillae (>3 mm) of the superior tarsal conjunctiva were also graded, depending on their number and size: 1 = a few giant papillae of 3 to 4 mm; 2 = giant papillae of 3 to 4 mm throughout the tarsal conjunctival area or a few papillae of 4 to 6 mm; or 3 = giant papillae of 4 to 6 mm throughout the tarsal conjunctival area or papillae >6 mm. The scoring of corneal infiltrates depended on the number and size of limbal Trantas' dots, as for papillae. Punctate keratitis, corneal ulcers, and corneal neovascularization were not scored because they were considered complications and were not thought to be a direct expression of VKC. Patients were included in the study when they had an objective score of 8 or more (as the

sum of both eyes), with a score of at least 3 for one eye; positive score data for each eye had to be distributed between a minimum of two variables.

Biochemical, Physical, and Immunologic Factors

Blood samples were collected at the time of the initial clinical evaluation, at 4 weeks, and at 4 months for determination of the leukocyte count, PBECS, serum ECP (UniCAP ECP; Pharmacia, Uppsala, Sweden), serum total IgE (UniCAP total IgE; Pharmacia), serum electrolytes, serum alanine aminotransferase and aspartate aminotransferase, serum creatinine, and blood cyclosporine levels. Systemic blood pressure was also determined at each visit.

All patients underwent skin prick tests for common inhalant and food allergens, including house dust mites, horse, cat, and dog dander, *Alternaria alternata*, *Cladosporium herbarium*, grass pollen, *Parietaria officinalis*, *Artemisia vulgaris*, plane (sycamore), cypress, and olive pollen, milk, egg, tomato, peanut, codfish, wheat, rice, and soybean. A wheal response of 3 mm in diameter or more was considered positive.²³ Serum-specific IgE was determined for the same allergens (UniCAP specific IgE; Pharmacia), and a result greater than 0.35 kU/L was considered positive.

Double-Blind, Placebo-Controlled Trial and Open Trial

Patients were randomly assigned to receive cyclosporine (Sandimmune), 2% in olive oil, in one eye (Cs-eye) and the vehicle (placebo) in the fellow eye (Pl-Cs-eye) during a 2-week double-blind, placebo-controlled trial. One drop of the study drug (0.8 mg) or vehicle was administered four times daily in each eye. The administration of other topically or systemically administered drugs (corticosteroids, antihistamines, and nonsteroidal anti-inflammatory drugs) was not allowed during this period. At entry patients were instructed to use dark glasses and caps, to open their eyes carefully in the morning, and to avoid sunlight in the morning and at midday. During the following 3 months and 2 weeks, one drop of cyclosporine 2% was given in both eyes (Cs-eye and Pl-Cs-eye) four times daily in an open trial. The administration of topically administered corticosteroids was allowed during this period in case of significant worsening. Signs and symptoms were recorded at entry into the study (at the time of vernal exacerbation) and at 2 weeks, 4 weeks, and 4 months (during summertime) after the beginning of the treatment. Blood studies were performed at entry, at 4 weeks, and at 4 months. Serum-specific IgE was determined, and skin prick tests were performed at entry. Adverse events were recorded, as reported by the children or by their parents.

Statistical Analysis

All data were analyzed with use of a commercially available statistical computer software package (SPSS, Chicago, IL). Student *t* tests for paired samples were used for the comparison of means. Student *t* tests for independent samples were used to compare mean values for serum total IgE, ECP, and PBECS between patients with VKC and control subjects. *P* values less than 0.05 were considered statistically significant.

RESULTS

The mean age ($\pm$ SD) of the 24 patients (16 boys and 8 girls) with VKC was 8.4 ± 1.6 years (range, 5.7 to 11.7). The mean age at onset of VKC, as reported by the parents, was 5.3 ± 2 years (range, 2 to 9). Of the 24 patients, 15 (62%) were from Tuscany, 5 (21%) were from other regions of central Italy, and 4 (17%) were from southern Italy.

Of the 24 children, 19 (79%) had a mixed tarsal-limbal VKC, 4 (17%) had a tarsal form, and 1 (4%) had a limbal form. Sixteen patients (67%) had seasonal VKC, which occurred from early spring to late summer, and 8 (33%) had perennial disease, although vernal-summer worsening was common.

Subjective symptom and objective sign scores are shown in Table 1 and Figure 1. During the double-blind, placebo-controlled trial, the mean score for severity of each subjective and objective variable showed a significant decrease in the Cs-eye, whereas only the scores for papillae and corneal infiltrates were significantly improved in the PI-Cs-eye (data not shown). At the 4-week visit, the mean score for each objective ocular sign reflected significant improvement from the initial evaluation at entry (data not shown). In contrast, however, severe giant papillae (score = 3), which was reported in six children at entry, showed only partial improvement. At 4 months, the score for giant papillae was unchanged in three study subjects, slightly improved in another three (score = 2), and strongly improved in one (score = 0).

The mean values ($\pm$ SD) of serum ECP at entry were significantly higher in children with VKC than in control children (28.1 ± 24.1 $\mu\text{g/dL}$ vs 6.4 ± 4.1 $\mu\text{g/dL}$, respectively; $P = 0.002$). The mean values for serum ECP, PBECS, and serum total IgE during the study period are presented in Figure 2.

In 8 of the 24 children (33%), atopy was diagnosed on the basis of a positive skin prick test or specific IgE levels for at least one common allergen; 1 patient had asthma and rhinitis associated with VKC. No significant differences were found between children with and those without atopy with regard to the severity of scores, efficacy of cyclosporine, and safety of treatment. At entry into the study, mean serum ECP was 47.0 $\mu\text{g/dL}$ versus 19.4 $\mu\text{g/dL}$ in children with and without atopy, respectively ($P = 0.02$). The mean serum total IgE level at

entry was 263 kU/L versus 106 kU/L in children with and without atopy (not significantly different). No significant difference between children with and without atopy was found at subsequent visits.

During the open trial, four children (17%) needed topically administered corticosteroid drugs for 1 week, and three patients (12%) required topical antibacterial therapy for 7 to 10 days. No additional treatment was necessary for 17 children (71%).

Several patients reported a mild-to-moderate burning sensation and associated tearing for 5 to 15 minutes (14 children, 58%) or for 15 to 40 minutes (6 children, 25%) immediately after administration of the eyedrops. These symptoms tended to diminish after the first 2 to 3 weeks and sometimes disappeared. Nevertheless, no patient discontinued the cyclosporine treatment, even temporarily. This side effect was also noted in both eyes during the double-blind, placebo-controlled trial. Four patients (17%) had no side effects.

At onset of the study, the concentrations of serum electrolytes, alanine aminotransferase, aspartate aminotransferase, and creatinine were in the normal ranges for age based on established guidelines. No significant variations were found during the treatment. Blood levels of cyclosporine were always less than the lower detectable limit (20 ng/L). The systemic blood pressure was always within the normal range for age.²⁴

DISCUSSION

Ocular allergic disorders have recently been reviewed.²⁵ These conditions include seasonal and perennial allergic conjunctivitis, atopic keratoconjunctivitis, VKC, and giant papillary conjunctivitis.

An effective and safe therapy for VKC is needed to alleviate signs and symptoms and to avoid ocular complications. In a review of 195 patients with VKC, corneal scarring caused reduction of vision in 12 cases (6%), and corticosteroid-induced glaucoma was found in 4 children (2%).² In another study, visual loss was attributable to corneal scars in 7 of 58 patients (12%) with severe VKC and to keratoconus in 3 patients (5%). Corticosteroid-induced glaucoma was reported in four patients (7%), and corticosteroid-associated cataract was noted in eight patients (14%).²⁶

Table 1. Symptoms and Signs of 24 Patients with VKC

Trial*	Subjective symptom score† (mean $\pm$ SD)		Objective sign score† (mean $\pm$ SD)	
	Cs-eye	PI-Cs-eye	Cs-eye	PI-Cs-eye
DBPC				
At entry	6.8 ± 3.78	5.7 ± 3.55	8.1 ± 1.63	7.8 ± 2.43
At 2 weeks	3.4 ± 3.43	5.0 ± 3.91	4.5 ± 2.25	6.7 ± 2.65
Open				
At 4 weeks	3.5 ± 3.24	3.0 ± 3.09	4.3 ± 2.64	4.1 ± 2.66
At 4 months	1.8 ± 1.68	1.7 ± 1.83	3.7 ± 2.36	3.6 ± 2.09

* DBPC, double-blind placebo-controlled trial (first 2 weeks of study); open, the following 3 months and 2 weeks (see text for details).

† Cs-eye = eye treated with cyclosporine 2% eyedrops; PI-Cs-eye, the other eye treated with placebo eyedrops during the first 2 weeks and with cyclosporine 2% eyedrops thereafter; SD, standard deviation.

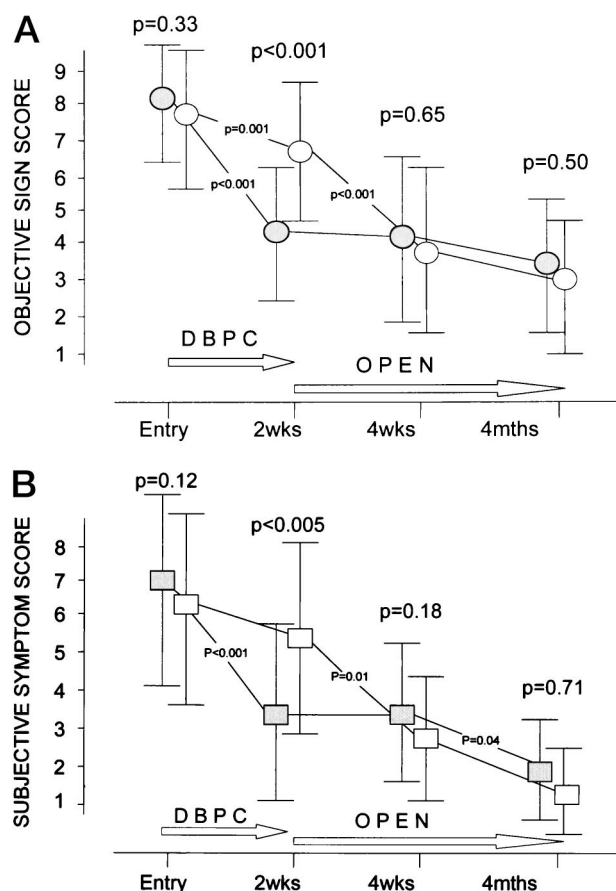


Figure 1. (A) Mean scores for objective signs in 24 patients with vernal keratoconjunctivitis. ●, Cyclosporine-treated eyes; ○, placebo-treated eyes in double-blind placebo-controlled trial (DBPC) and, after 2 weeks, cyclosporine-treated eyes in open trial (OPEN); vertical bars, standard deviation. (B) Mean scores for subjective symptoms in 24 patients with VKC. ■, Cyclosporine-treated eyes; open squares = placebo-treated eyes in double-blind placebo-controlled trial (DBPC) and, after 2 weeks, cyclosporine-treated eyes in open trial (OPEN); vertical bars = standard deviation.

Cyclosporine is an immunosuppressive drug most commonly used in the prevention of organ graft rejection. It blocks helper T-lymphocyte proliferation and IL-2 production.^{15,27} Further, cyclosporine inhibits histamine release from human mast cells and basophils,^{28,29} and through a reduction in IL-5 production, it may reduce the presence and effects of eosinophils on the conjunctiva.²⁶ In contrast with corticosteroids, cyclosporine does not produce lens changes or increase intraocular pressure.³⁰

For 15 years, cyclosporine 2% eyedrops have been used for the treatment of VKC. In five uncontrolled studies, 35 children were treated during a period of 3 weeks to 24 months, and substantial improvement was noted.¹⁷⁻²¹

Three double-blind, placebo-controlled trials have been reported. In the first study, 11 patients (mean age, 12.4 years; range, 7 to 27) received cyclosporine 2% for 2 weeks in one

	Entry	4 weeks	4 months
s-ECP (μg/dL)	28.1 (± 24.1)	29.8 (± 25.1)	13.7 (± 8.9)
	NS		
PBECs (mm ³)	405 (± 210)	330 (± 110)	190 (± 68)
	NS		
Tot s-IgE (kU/L)	153 (± 212)	253 (± 445)	295 (± 483)
	NS		

Figure 2. Mean values (±SD) for serum eosinophil cationic protein (s-ECP), peripheral blood eosinophil counts (PBECs), and total serum IgE (Tot-s-IgE) at various times in 24 patients with vernal keratoconjunctivitis treated with cyclosporine eyedrops during 4-month trial. NS = no significant difference.

eye, and the control eye was treated with the vehicle (castor oil) during the same period.²¹ The results showed a significant decrease in sign and symptom scores of cyclosporine-treated eyes compared with placebo-treated eyes and showed significant clinical improvement in signs and symptoms from study entry to day 15 in the cyclosporine-treated eyes but not in the placebo-treated eyes. Details about the score for each variable were not reported. In the second study, 11 patients (mean age, 9.7 years; range, 5 to 19) with VKC were treated with cyclosporine for 6 weeks; 9 control patients received the vehicle.⁴ At the end of the study, a statistically significant difference between the two groups was noted in the ocular objective signs, even if the number and size of the giant papillae were not influenced by the topical use of cyclosporine. The subjective symptoms (except photophobia) were not significantly decreased.

In a recent study, 12 children between 5 and 16 years of age were successfully treated with cyclosporine 2% eyedrops for 4 months. Only partial data about the patients are reported, and clinical sign and symptom scores at the beginning of the study are completely lacking.

In our current study, we confirmed the efficacy of cyclosporine eyedrops in 24 children with VKC in a 2-week double-blind, placebo-controlled trial. To take into account environmental variables such as wind, sunshine, and other climatic factors, which have a crucial role in the clinical manifestations,³¹ we used the fellow eyes as controls. Accordingly, we ensured that the actively treated and placebo-treated eyes were exposed to the same climatic conditions. An objective score for giant papillae was used, which was a slight modification of a scoring system recently applied in a large series of patients.² Sex and age distribution of our patients corresponded to findings in other reports.^{2,4,21} The presence of atopy in our study (in 8 of 24 children or 33%) did not differ from that in a normal pediatric population.³² Other investigators have found that up to 50% of their patients with VKC have atopy.² Type I, IgE-mediated mecha-

nisms, however, do not seem to be implicated in the pathogenesis of VKC.

We found a statistically significant difference between the Cs-eyes and the Pl-Cs-eyes for both signs and symptoms at 2 weeks. At 2 weeks, we also noted a significant improvement over entry in the subjective and objective scores in the Cs-eye. The Pl-Cs-eyes likewise showed a significant improvement in the objective signs during the double-blind, placebo-controlled trial (Table 1 and Fig 1). An explanation for this finding may be that all patients at entry had been actively instructed to protect their eyes and to use caps and dark glasses. The subjective symptoms in the Pl-Cs-eyes, however, showed relatively less improvement, probably because of the burning sensation and tearing reported by most of the patients soon after administration of the eyedrops. We have ascribed this effect to the vehicle (olive oil) because symptoms were present in both eyes during the double-blind, placebo-controlled trial.

At 2 weeks, we stopped the double-blind, placebo-controlled trial and continued the study in an open manner, treating both eyes with cyclosporine. The Pl-Cs-eyes showed a significant decrease in scores for both signs and symptoms during the following 2 weeks, as expected; however, no further effects were obtained in the Cs-eyes (Fig 1). At 4 months, there was a further nearly significant improvement only for symptoms, especially for photophobia and tearing; however, overall maintenance of the initial therapeutic effect was evident.

At 4 months, the effect of cyclosporine on the giant papillae was poor in those children who had had a high score for this sign at entry. In these patients, however, further improvement of the score for giant papillae was noted when the treatment was prolonged over the 4-month study period. This late effect of cyclosporine on giant papillae depended on the prolonged exposure of the tarsal infiltrates to the action of the immunosuppressive drug.

A few children required an additional brief treatment with topically administered corticosteroids during the open trial, but none had a further relapse. Serum ECP levels and PBECs were significantly higher in our patients with VKC than in the control subjects, without showing a correlation with the severity of ocular symptoms, as was reported in a recent study.³³ We found, however, a significant decrease in serum ECP levels and PBECs after 4 months of treatment (Fig 2). This probably reflected a reduction of eosinophil recruitment and activation. To our knowledge, this is the first report identifying a serologic marker of disease activity in VKC. Tear ECP levels, however, seem to be a more useful measure in monitoring the disease.⁹

CONCLUSION

In this study, topical cyclosporine 2% was effective and safe in the treatment of severe VKC. Most of its effects on signs and symptoms were achieved after 2 weeks of treatment. Further slow improvement resulted at 4 months, together with a significant decrease in serum ECP levels. A brief period of

topical corticosteroid treatment was occasionally required. The only side effects reported were a burning sensation and tearing soon after the administration of the eyedrops, which affected the subjective evaluation during the first 2 to 3 weeks of treatment.

The use of cyclosporine eyedrops for treatment of VKC should be encouraged in an attempt to prevent complications associated with the natural course of the disease and the prolonged topical use of corticosteroids.

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