

Efficacy of 1.25% and 1% topical cyclosporine in the treatment of severe vernal keratoconjunctivitis in childhood

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Cyclosporine eyedrops 2% have been used for treatment of corticosteroid-resistant vernal keratoconjunctivitis (VKC) cases. The purpose of our study was to verify the efficacy of 1.25% vs. 1% topical cyclosporine in improving severe form of VKC in childhood. Twenty children with severe VKC, were enrolled in a double-blind, placebo-controlled study and received cyclosporine 1.25% in one eye for 2 wk. Then an open trial was conducted during the next 3 months and 2 wk. Thirty-two more patients were recruited the next year into a new open trial and they received cyclosporine 1% for 4 months. Ocular subjective symptoms and objective signs were scored in all children at entry, 2 wk and 4 months. Skin prick tests and conjunctival scraping tests were also performed; serum immunological and biochemical markers were assessed. The mean score values for severity of subjective symptoms and objective signs were significantly decreased after 2 wk, and 4 months, compared with those at entry ($p < 0.001$), in both groups of children who received cyclosporine eyedrops 1.25% and 1%, respectively. Serum markers did not differ from the beginning to the end of treatment. Conjunctival eosinophils and cyclosporine serum levels were not detectable at the end of therapy, nor were endothelial corneal cells damaged. Our findings suggest that 1% cyclosporine concentration might be the minimal effective treatment regimen to control symptoms and local inflammation in severe forms of VKC.

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Vernal keratoconjunctivitis (VKC) is a seasonal chronic ocular disease, which usually affects boys during the first decade of life, and spontaneously disappears during the second decade. Typical clinical signs and symptoms of the disease include itching, photophobia, burning, tearing, foreign body sensation, sticky mucous discharge, giant papillae on the upper tarsal conjunctiva or at the limbus (often leading to palpebral ptosis), bulbar nodules and superficial keratitis that can evolve into corneal shield ulcers. From 5 to 30% of cases, permanent changes to the ocular surface, such as keratoconus, corneal ulcers

and/or steroid-induced glaucoma or cataract, may occur and be accompanied by permanent visual impairment (1, 2). Vernal keratoconjunctivitis is widespread in warm regions, such as the Mediterranean areas, the Arabic Peninsula, Pakistan, India and Equatorial Africa.

Based on a different corneal involvement, it is possible to distinguish a tarsal form, a limbal form and a mixed form of VKC. The corneal epithelium damage is because of an activated eosinophilic degranulation and the toxic effect of the major basic proteins (MBP) and of the eosinophil cationic protein (ECP) (3–5).

Eosinophils are constantly detectable in conjunctival and lacrimal cytological analysis, together with some basophils. (6, 7). Continual palpebral rubbing increases mast cells degranulation and histamine concentration, causing itching and inflammation. Frequent ocular foreign body sensation is because of the irregular conjunctival surface and mucus secretion; pain, instead, is a consequence of corneal damage. In tarsal form, giant cobblestone-like papillae are characteristics, while in limbar form the diagnosis can be easily made based on the observation of gelatinous infiltrates on the limbus, the circumference of which might appear thickened and opaque, with a superficial neovascularization (8).

The pathogenesis of the disease is not completely known. A Th₂-driven mechanism has been suggested. Several studies have documented the presence of the Th₂ lymphocytes subtype (9–11) in tears and in conjunctival biopsy samples of patients with VKC. High levels of IL5 and ECP have also been found in patient's tears (5, 12). The role of features such as personal history of atopy and specific immunoglobulin (Ig)E-allergen sensitization, usually ascribed to VKC pathogenesis, is now controversial. An Italian survey documented low levels of serum total and specific IgE in patients with VKC especially in those with the bulbar localized form (13). Other studies suggest that non-IgE-dependent mechanisms might play a role in the pathogenesis of VKC. In fact, some researchers have demonstrated the possible involvement of neural factors, sex hormones and conjunctival histaminase deficiency in the pathogenesis of the disease (7, 14).

Vernal keratoconjunctivitis should be distinguished mainly from allergic conjunctivitis, which can be either seasonal or perennial, usually associated with high total serum IgE levels, IgE-mediated sensitization to aero-allergens, and other atopic diseases, such as asthma and rhinitis (8, 15).

Symptoms of allergic conjunctivitis are less serious than those of VKC. Moreover, allergic conjunctivitis usually never leads to ocular complications; it is successfully treated with systemic and topic therapies and it may be prevented by using environment prophylaxis measures. The diagnosis is easily made in patients showing high serum total and specific IgE, positive skin prick tests to common allergens, and in presence of acute exacerbation of ocular symptoms during the season of pollination (16).

The therapy of mild and moderate forms of VKC is based on the use of topical and systemic antihistamines, mast-cell stabilizing agents and anti-allergic/anti-inflammatory compounds

(17–21). Topical administration of corticosteroids is used in severe cases but is associated with an increased risk for the development of cataracts and glaucoma (22, 23). Thus there is a worldwide search for new biotargets for the treatment of these diseases. Recently, cyclosporine 2% eyedrops have been used successfully for the treatment of VKC (7, 24–27).

The objective of this study was to compare the clinical efficacy of cyclosporine 1.25% and 1% eyedrops, respectively, in young patients with severe VKC, usually responding to high-risk topical steroids therapy.

Methods

Between January 2002 and December 2003 a total of 20 out of 189 consecutive children, 16 males and four females (age range 5–14 yr), with severe VKC, who came for the out-patient scheduled appraisal at the Department of Pediatrics, Division of Immunology and Allergology, University of Bari, were enrolled. Patients were selected according to two disease severity scales, one based on objective signs (conjunctival hyperemia, giant papillae, papillae hypertrophy and bulbar nodules), and the other one based on subjective ocular symptoms (itching, photophobia, tearing, foreign body sensation and burning sensation), both graded from zero 'absent' to two 'severe'. Children were classified as having severe VKC if the score was ≥ 3 points for one eye for each scale. Signs and symptoms were recorded at entry into the study, at 2 wk and 4 months. Data about subjective ocular symptoms occurred during the entire enrolment period were also collected using a questionnaire filled-out by the parents of children.

Moreover, pictures of the ocular front segment from each patient were taken by an oculist at the time of the first visit and recorded for further objective evaluations.

Quantitative and qualitative abnormalities of the corneal endothelium were both examined by the same observer using a clinical automatic non-contact specular microscope (Konan Noncon Specular Microscope SP/9000, Hyogo, Japan).

At enrolment, all children underwent skin prick tests to common aero- (cypress, olive tree, grass, parietaria, dermatophagoides pteronyssinus, dermatophagoides farinae, alternaria, dog and cat dandruff) and food- (cereals, egg, fish, meat, fruits, legumes, solancee, milk and soy) allergens. Children were defined 'atopic' in presence of positive skin prick tests and/or elevated specific and total IgE. Total and specific serum IgE, serum ECP levels and peripheral blood

eosinophil counts (PBEs) were determined at the beginning and at the end of the study. A conjunctival scraping on the upper tarsal conjunctiva was also performed at the time of enrolment and 4 months later. All cells were evaluated under light microscopy and the number of eosinophils per 10 high-power field (HPF) was assessed.

All children were treated with cyclosporine 1.25% eyedrops (Sandimmun® galenical collyrium Chemistry Service Institute, University of Bari, Italy), prepared strictly respecting sterility criteria, by the Chemistry Service Institute at the University of Bari, following a formulation including one part of commercially available cyclosporine solution for intravenous infusion (Sandimmun), diluted in aqueous vehicle (Lacrimart®, Baif, Italy). Parents were asked to keep refrigerated, shielded from light, the vial with the eyedrops, and to use it within 15 days from the opening.

We conducted a double-blind, placebo-controlled study for 2 wk. During this period, all patients received, four times daily, one drop of cyclosporine 1.25% in one eye, and the vehicle (placebo vial called 'Lacrimart') in the fellow eye. Then, a clinical assessment of ocular subjective symptoms (SS) and objective signs was carried-out in all children. During the following 3 months and 2 wk, patients received one drop of cyclosporine 1.25% in both eyes, at the same dose schedule.

Serum cyclosporine levels were assessed 4 months after the beginning of treatment.

Between April and December 2004, 32 severe VKC patients, 27 males and five females (age range 5–14 yr) were also recruited into a new open trial. Ten of them had received cyclosporine 1.25% the previous year. This group of patients received one drop of cyclosporine 1% (Sandimmun galenical collyrium), prepared following the same conditions of the 1.25% formulation, in both eyes, four times daily, for 4 months. They underwent the same follow-up examination than that of subjects who received cyclosporine 1.25% except for the assessment of serum markers.

An informed consent was obtained from parents. Children were instructed to use dark glasses and caps, to avoid sunlight in the morning and eye contact with sea water and chlorine in swimming pools. Environment prophylaxis measures against house dust mite and pollens were adopted. The use of systemically administered drugs was not allowed during the entire study period.

We obtained approval for the study from the local Ethics Committee.

Statistical analysis

Data are expressed as mean with standard deviation. The statistical analysis was performed using SPSS program (Version 11.0). Student's *t*-tests for paired samples were used for the comparison of means. Sperman's rho correlation test was used to investigate the relationship between continuous variables. A $p < 0.05$ was considered statistically significant.

Results

A significant improvement of the disease status in all children was documented at the ocular examination after only 2 wk and after 4 months of treatment with both concentration of cyclosporine eyedrops (1.25% and 1%) as shown by a strong reduction of mean score for severity of each subjective and objective variable (Tables 1 and 2, Fig. 1). There were no significant differences in means of SS and objective sign scores (OS) at 2 wk and 4 months between children treated with cyclosporine eyedrops 1.25% and those who received cyclosporine eyedrops 1%

Table 1. Symptoms and signs of 20 patients (first group) treated with cyclosporine 1.25%

Trial†	Subjective symptom score (SS) (mean ± s.d.)	Objective sign score (OS) (mean ± s.d.)
DBPC		
At entry	6.9 ± 2.47	5.2 ± 2.07
At 2 wk	1.7 ± 1.97*	2.0 ± 1.52***
Open		
At 4 months	0.65 ± 1.09**	1.00 ± 0.97****

s.d., standard deviation.

* $p < 0.001$ vs. the average of SS at entry.

** $p < 0.001$ vs. the average of SS at entry and at 2 wk.

*** $p < 0.001$ vs. the average of OS at entry.

**** $p < 0.001$ vs. the average of OS at entry and at 2 wk.

†DBPC, double-blind placebo-controlled trial (first 2 wk of study); open, the following 3 months and 2 wk.

Table 2. Symptoms and signs of 32 patients (second group) treated with cyclosporine 1%

Open trial	Subjective symptom score (SS) (mean ± s.d.)	Objective sign score (OS) (mean ± s.d.)
At entry	4.9 ± 2.28	3.8 ± 1.70
At 2 wk	2.4 ± 1.68*	1.9 ± 1.59***
At 4 months	0.21 ± 0.46**	0.17 ± 0.47****

s.d., standard deviation.

* $p < 0.001$ vs. the average of SS at entry.

** $p < 0.001$ vs. the average of SS at entry and at 2 wk.

*** $p < 0.001$ vs. the average of OS at entry

**** $p < 0.001$ vs. the average of OS at entry and at 2 wk.

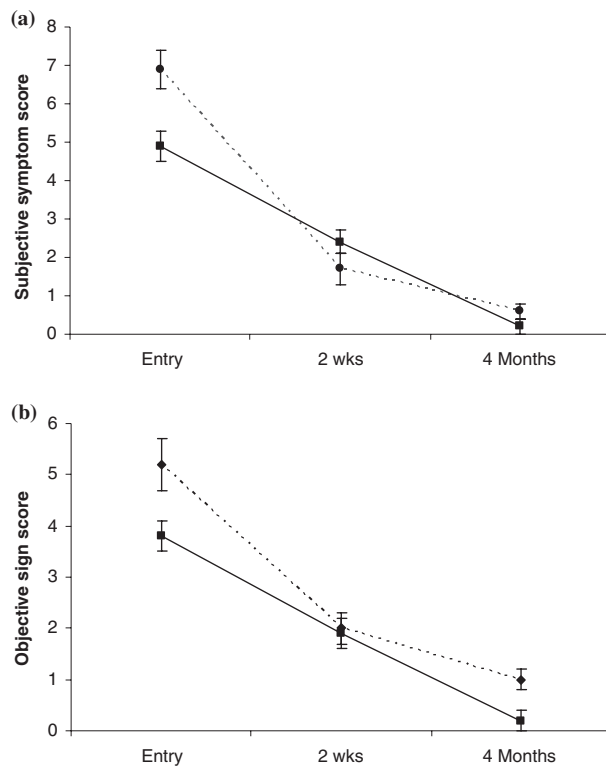


Fig. 1. (a) Mean score $\pm$ standard error mean (vertical bars) for subjective symptoms in 20 patients with vernal keratoconjunctivitis (VKC) treated with topical cyclosporine 1.25% (circles) in double-blind placebo-controlled trial and, after 2 wk in open trial (dotted line), and in 32 patients treated in open trial (continuous line) with cyclosporine 1% (squares). (b) Mean score $\pm$ standard error mean (vertical bars) for objective signs in 20 patients with VKC treated with topical cyclosporine 1.25% (circles) in double-blind placebo-controlled trial and, after 2 wk in open trial (dotted line), and in 32 patients treated in open trial (continuous line) with cyclosporine 1% (squares).

Table 3. Biochemical and immunological serum markers (first group)

	Entry	Four months	p-Value
PBECs (mmc)	388 ($\pm$ 175)	316 ($\pm$ 88)	ns
s-ECP (μ g/dl)	27.4 ($\pm$ 16.6)	28.9 ($\pm$ 22.3)	ns
Tot s-IgE (kU/l)	193 ($\pm$ 351)	299 ($\pm$ 473)	ns

Mean values ($\pm$ s.d.) for serum eosinophil cationic protein (s-ECP), peripheral blood eosinophil counts (PBECs), and total serum IgE (Tot s-IgE) at the beginning and at the end of the study in 20 patients with severe VKC treated with cyclosporine 1.25% eyedrops during four-month trial.

ns, no significant difference.

(SS: 1.75 vs. 2.38 and 0.65 vs. 0.21; OS: 2.00 vs. 1.90 and 1.00 vs. 0.17, respectively; $p = \text{ns}$).

The clinical improvement of treated eyes was also documented by comparing pictures of the ocular front segment from the beginning to the end of the study for each patient. Children who had a second cycle of treatment with cyclospo-

rine eyedrops the following year showed a faster and more lasting clinical improvement. Even four patients with corneal ulcers corrected their visual acuity after 4 months therapy with cyclosporine 1% eyedrops.

Twenty-two of 42 (52%) examined subjects showed positive skin prick tests and/or high levels of total and specific IgE to aeroallergens. There were no differences in mean subjective and objective score levels between atopic and non-atopic children at each observation time (SS: 5.19 vs. 6.14, 1.95 vs. 2.25 and 0.28 vs. 0.25; OS: 4.38 vs. 4.36, 1.81 vs. 2.03 and 0.43 vs. 0.57, respectively at entry, 2 wk and 4 months; $p = \text{ns}$). Furthermore, we found that the mean values of serum total IgE, serum ECP and PBECs did not differ from the beginning to the end of treatment with cyclosporine collyrium (Table 3) in the group of children in whom they were tested.

Eosinophils were detectable by scrapings test in the conjunctival epithelium of all enrolled patients during the acute phase of the ocular disease, and they normalized by the end of the therapy. The mean number of eosinophils at the beginning of the two studies was 11.57 with a range of 1–35 per HPF; following treatment, the mean number of eosinophils was 3.22 per HPF with a range of 0–10 ($p < 0.01$).

Patients do not experienced side effects during the treatment, except for a mild ocular burning sensation immediately after administration of eyedrops. Endothelial corneal cells damage was not reported after ophthalmological examination in each child. It was interesting to notice that cyclosporine levels in serum did not arise during treatment confirming that the observed clinical improvements were only because of its local effect.

Discussion

Several studies have reported the effectiveness of cyclosporine 2% eyedrops in improving signs and symptoms of VKC in children (24–27). To our knowledge, in our current study, for the first time, we report an experience with the use of 1.25% and 1% topical cyclosporine in the treatment of severe VKC in Caucasians. Recently, authors from Thailand documented a good response to low-concentrated topical cyclosporine to relieve symptoms of VKC in patients with different severity grade of the disease (28). According to our experience, few cases of severe VKC complicated with shield ulcers have also been successfully treated with cyclosporine 1% concentration (29). Akpek et al. (30) had successfully tested very much lower

concentration of topically administered cyclosporine in related conditions, such as atopic keratoconjunctivitis.

We verified that selected Italian children with a severe form of VKC were successfully treated with cyclosporine 1.25% and 1% eyedrops for 4 months. We noted that both concentrations of topical cyclosporine remarkably improved the mean scores of signs and symptoms of VKC in children after 2 wk of controlled trials (Fig. 1). Then we continued the study and we documented a further decrease of the ocular disease status (Fig. 1). Moreover, there were no statistically significant differences in mean scores of subjective and objective variables at 2 wk and 4 months between children treated with cyclosporine eyedrops 1.25% and those who received cyclosporine eyedrops 1%. This suggests that the lowest concentration of tested cyclosporine was effective for the almost complete recovery of severe forms of VKC. This is an important finding considering that cyclosporine is an immunosuppressive drug and that the use of low concentrated eyedrops might avoid systemic effects. It is noteworthy that after 4 months of study, serum levels of cyclosporine were not detectable.

At entry, the second group of enrolled children showed lower mean scores of both ocular subjective and objective variables, compared with those of the patients who first entered the study. This might be explained by the fact that 10 subjects treated with cyclosporine 1% eyedrops, completed one cycle of treatment the previous year, with long-term ocular improvements.

The clinical improvement in VKC after topical cyclosporine therapy has been related to its immunomodulating effect on the components of cell-mediated and humoral immune (31), which may explain our findings on the reduction of the presence and the effects of eosinophils on the conjunctiva.

According to other studies (24, 31), we demonstrated that the immunological and biochemical serum markers tested in the first group of enrolled patients with VKC were unaltered after cyclosporine topical therapy (Table 3). So, we did not measure the same markers in the second group of enrolled children. Our result was expected considering that we did not find detectable levels of systemic cyclosporine by the end of the study.

According to other Italian reports on patients with VKC (13, 17), we have found that up to 50% of our patients were atopic. There were no differences in mean subjective and objective score levels between atopic and non-atopic children at each study time, confirming the controversial role of atopy in the pathogenesis of the disease.

The treatment was well tolerated, patients did not discontinue the therapy; major side effects were not noted, nor was required additional therapy with topically administered corticosteroids. However, a follow-up study is needed to assess if long-term local therapy with cyclosporine may improve the prognosis of the disease or cause visual acuity damages.

In conclusion, we tested a new treatment regimen with topical cyclosporine in severe forms of a major ophthalmic condition. The results are satisfactory, considering that after 2 wk of treatment with low concentration of cyclosporine topically administered, patients experienced significant improvements of their ocular disease status. Thus, both cyclosporine 1.25% and 1% might represent a valid alternative to the use of steroids for treatment of severe VKC cases.

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