Efficacy of topical 0.05% cyclosporine treatment in children with severe vernal keratoconjunctivitis

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We aimed to determine the efficacy of topical cyclosporine in children with vernal keratoconjunctivitis refractory to topical mast cell stabilizer and antihistamine therapy. Thirty-one patients, 24 boys and 7 girls younger than 16 years of age, were included in the study. All patients were scored on a four-point scale from 0 to 3 for symptoms and signs. Each patient received topical cyclosporine 0.05% emulsion (Restasis, Allergan Inc., Irvine, CA, USA) four times daily in addition to preservative-free artificial tears and was followed for 6 months. The data was recorded before the initiation of treatment (day 0) and at the 1st, 3rd, and 6th months following treatment. After six months of treatment, severity of all symptoms and signs showed a statistically significant decrease ($p<0.05$). Patients did not report any serious adverse effects. Topical cyclosporine 0.05% emulsion treatment is a safe and effective treatment option for controlling the symptoms and signs of vernal keratoconjunctivitis in children.

***Key words:** child, adverse effects, vernal keratoconjunctivitis, topical cyclosporine.*

Vernal keratoconjunctivitis (VKC) is a severe form of ocular allergic disease, with exacerbations during the spring and summer seasons, that particularly affects children and young adults.[1] VKC symptoms and signs usually begin during the first decade of life and disappear during the second decade.[2] The symptoms can prevent a child from engaging in normal activities and are of great concern to the parents. Typical symptoms and signs of the disease include photophobia, tearing, discomfort, discharge, cobblestone papillae, superficial keratitis, Trantas' dots, bulbar conjunctival hyperemia and chemosis, limbal edema, corneal shield ulcers and corneal neovascularization.[3] In addition to steroid-induced glaucoma and cataract, permanent changes of the ocular surface, such as scarring, keratoconus and corneal shield ulcers, may occur during the active disease and may cause severe visual impairment.[4] Histopathological studies have proven the presence of local helper T-cell type 2 and helper T-cell type 2-like cells in tears and conjunctival biopsy specimens in VKC patients.[5,6] Increased numbers of activated mast cells and eosinophils have been reported to be found in the conjunctiva. Interleukin IL-3, IL-5, IL-6 and granulocyte-macrophage colony-stimulating factor are expressed in conjunctival eosinophils in particular.[7]

Corticosteroids are well known to be the most effective topically applied medication in the treatment of VKC[3], inducing a generalized anti-inflammatory and immunosuppressant effect and decreasing phagocyte response.[8] However, serious side effects, including

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secondary glaucoma, posterior subcapsular cataract formation, the risk of delayed wound healing and superinfection with viruses and bacteria may occur with long-term topical steroid treatment.[3] Therefore, corticosteroids are not preferred therapeutic agents in the long-term therapy of VKC. Topical mast cell stabilizers, topical antihistamines and non-steroidal anti-inflammatory agents are other treatment modalities that are generally effective in the treatment of mild-to-moderate cases. But they are not adequate in severe cases.[9,10]

Cyclosporine is an immunosuppressive drug that blocks helper T-lymphocyte proliferation and interleukin-2 production. Furthermore, cyclosporine inhibits histamine release from human mast cells and basophils.[11-13] In contrast to corticosteroids, cyclosporine does not have severe ocular side effects such as changes in the lens or increased intraocular pressure.[14] Recently, several reports studied the efficacy of topical cyclosporine therapy in VKC cases in different dosages.[15-21] In this study, we aimed to investigate the long-term efficacy of topical cyclosporine 0.05% emulsion in children with VKC who are refractory to topical mast cell stabilizers and antihistamine therapy.

Material and Methods

We retrospectively evaluated 31 consecutive cases of VKC in children and adolescents who were given topical cyclosporine 0.05% emulsion treatment for at least 6 months at the Pediatrics and Ophthalmology Unit of Baskent University, Adana Hospital (Adana, Turkey), between January 2010 and January 2013. Patients with ocular diseases such as glaucoma, uveitis, corneal disease, ocular infection, presence of systemic diseases other than coexisting allergic rhinitis, asthma and atopic dermatitis and reported hypersensitivity to FK-506 or cyclosporine were excluded. There were 24 boys and 7 girls, with a mean age of 10.0 ± 3.3 years. All patients had previously been treated with either mast cell stabilizers or topical dual action agents (mast cell stabilizers and antihistamines) for at least one month before starting the medication and were refractory to these therapeutic regimens. The parents of all patients were informed about the possible side effects and signed informed consent forms before starting the medication.

Patients underwent a complete ophthalmic examination, including best-corrected visual acuity, slit lamp examination and indirect ophthalmoscopy. A questionnaire including inquiry about subjective symptoms such as itching, discomfort, photophobia, tearing and discharge was filled out by the parents for younger children and by the patient him/herself if older than 11 years of age. Patients were asked to grade their symptoms on a four-point scale, with 0 being no complaints and 3 severe. Also, a spreadsheet for signs was routinely filled out for each patient in our clinic at each visit by the same examiners (MCK, SMD). The objective signs, such as palpebral conjunctival hyperemia, edema, papillary hypertrophy, cobblestone papillae, conjunctival hyperemia and chemosis, Trantas' dots, limbal swelling and corneal neovascularization, were scored according to severity from 0 to 3 (Table I). We undertook a retrospective medical record review to determine the symptoms and signs of vernal keratoconjunctivitis. The questionnaire summarized in Table I was prepared by modifying previously described methods.[22] Each patient received topical cyclosporine 0.05% emulsion (Restasis, Allergan Inc., Irvine, CA, USA) four times a day in addition to preservative-free artificial tears. The data concerning the symptoms and signs were recorded during the first visit before the initiation of treatment (baseline) and at the 1st, 3rd, and 6th months following treatment (Month 1, Month 3 and Month 6, respectively). All data were evaluated using statistical software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc., Chicago, IL, USA). Baseline, 1-month, 3-month and 6-month data measures were compared using the Wilcoxon test. Values of p less than 0.05 were considered statistically significant.

Results

Table II shows the subjective clinical scoring of the 31 patients at day 0 and at each follow-up visit (Month 1, Month 3 and Month 6). All patients tolerated the treatment well. Mild burning was considered normal. Other side effects, such as severe burning, hyperemia, tearing and pain, were not observed during the 6-month treatment period. Scoring of all subjective symptoms, including itching, tearing, discomfort, discharge and photophobia, decreased significantly compared to baseline at each follow-up during 6 months of cyclosporine

A treatment ($p<0.0001$, for each) (Table II).

Table III shows that all of the objective signs, including palpebral conjunctival hyperemia, edema, papillary hypertrophy, cobblestone papillae, conjunctival hyperemia and chemosis, Trantas' dots, limbal swelling and corneal neovascularization, also showed statistically significant improvement during the 6 months of follow-up ($p<0.05$). Although limbal Trantas' dots showed improvement, the comparison of baseline with first-month values was not statistically significant ($p=0.052$). In the third and sixth months, the improvement was statistically significant ($p=0.011$ and $p=0.007$ respectively).

Discussion

Vernal keratoconjunctivitis is a sight-threatening inflammatory disease of the conjunctiva and cornea. Although VKC is classified as an allergic eye condition, the role of allergens as an inciting factor is not clear. The pathogenesis of VKC involves roles for IgE, cytokines, chemokines and inflammatory cells (T and B lymphocytes, mast cells, basophils, neutrophils, and eosinophils), with the release of their granular proteins, the proliferation of fibroblasts and the laying down of exuberant amounts of collagen fibers in the conjunctival tissue. Mild cases of VKC tend to remit with nonspecific and supportive therapy. On the other hand, severe cases are usually more protracted, with remission/relapse occurring for a prolonged period of time[23].

In patients with severe vernal conjunctivitis, treatment with topical antihistamines and mast cell stabilizers is usually inadequate. These patients may require topical corticosteroid therapy during exacerbations of the disease. However, due to their well-known side effects, topical corticosteroids are not preferred agents for long-term treatment, particularly in children. In the present study, we used topical 0.05% cyclosporine in 31 patients for 6 months. To evaluate the outcome of this treatment, a four-point scale was used. All patients had significant improvement in their symptoms as well as their clinical signs.

Several studies have shown that topical cyclosporine 2% is beneficial in the treatment of VKC, producing a reduced need for topical steroids[1,15-21]. Cyclosporine A(CsA) is an immunomodulatory agent that primarily inhibits the proliferation and action of T cells.

Ben Ezra et al.[17] treated 21 children with severe vernal conjunctivitis who were refractory to corticosteroids and 2% disodium cromoglycate with cyclosporine 2% eye drops in oil solution. Subjective parameters like redness, itching, photophobia, tearing, pain, mucous discharge and inability to participate in normal daily activities were recorded. Eighty-six percent of the children responded favorably and rapidly to this treatment. Additionally, local or systemic treatment with corticosteroids was avoided in most cases, at least during the period of cyclosporine treatment.[17]

Gupta et al.[1] randomly treated 24 children between 5 and 16 years of age with 2% cyclosporine A 4 times daily, or a placebo, for 3 months. The subjective and objective assessment was performed via a five-point scale. Of the 12 patients treated with cyclosporine A, 11 showed symptomatic improvement 7 days after starting the treatment, whereas in the placebo group, only 3 patients showed mild symptomatic improvement.

In a double-blind, placebo-controlled trial, 2% cyclosporine was used to treat 24 children with severe VKC.[18] Most of the effects of topical cyclosporine 2% on ocular symptoms and signs were achieved after 2 weeks of treatment. A brief period of topical corticosteroid treatment was occasionally required. It was concluded that cyclosporine 2% was safe and effective in the treatment of severe VKC.

In a more recent study, topical cyclosporine 1% was used in 197 children with severe VKC for 4 months. Ocular subjective symptoms and objective signs were scored in all children at entry, and at 2 weeks and 4 months post-treatment. The mean score values for severity of subjective symptoms and objective signs were significantly decreased after 2 weeks and 4 months. Cyclosporine serum levels were not detectable at the end of therapy, nor was any endothelial corneal cell damage seen.[19]

Spadaveccia et al[20] compared the efficacy of 1.25% topical cyclosporine versus 1% cyclosporine in patients with severe VKC. In both groups, the mean score values for severity of subjective symptoms and objective signs were significantly decreased at 2 weeks and

Table I. Grading of Symptoms and Signs of Vernal Keratoconjunctivitis

	0	1	2	3
Symptoms				
Itching	No desire to rub or scratch the eye	Occasional desire to rub or scratch	Frequent need to rub or scratch the eye	Constant need to rub or stretch the eye
Tearing	Normal tear production	Positive sensation of fullness of the conjunctival sac without tears spilling over	Intermittent, infrequent spilling of tears over the lid margin	Constant, or nearly constant spilling of tears over the lid margin
Discomfort (burning, stinging and foreign body sensation)	None	Slight	Moderate	Severe
Discharge	No abnormal discharge	Small amount of discharge noted in the lower cul-de-sac	Moderate amount of discharge noted in the lower cul-de-sac and in the marginal tear strip; presence of crust upon awakening	Eyelids tightly matted together upon awakening; warm soaks necessary to clean eyelids during the day
Photophobia	No difficulty experienced	Slight difficulty with light causing squinting	Moderate difficulty, necessitating dark glasses	Extreme photophobia causing the patient to stay indoors; cannot stand natural light even with dark glasses
Signs				
Palpebral conjunctival hyperemia	None (Findings absent)	Slight (several vessels dilated)	Moderate (numerous vessels dilated)	Severe (individual blood vessels indistinguishable)
Swelling	None (Findings absent)	Slight infiltrate	Moderate infiltrate	Severe infiltrate with turbidity
Papillae	None (Findings absent)	Slight (diameter 0.1-0.2)	Moderate (diameter 0.3-0.5 mm)	Severe (diameter >0.6 mm)
Cobblestone papillae	None (Findings absent)	Slight (papillae flattened)	Moderate(papillae protuberant in <1/2 of palpebra)	Severe (papillae protuberant in >1/2 of palpebra)
Bulbar conjunctival				
Hyperemia	None (Findings absent)	Slight (several vessels dilated)	Moderate (numerous vessels dilated)	Severe (all blood vessels dilated)
Chemosis	None (Findings absent)	Slight swelling	Moderate swelling	Severe swelling
Limbus				
Trantas dots	None (Findings absent)	Slight (1-4)	Moderate (5-8)	Severe (>9)
Swelling	None (Findings absent)	Slight (<1/3 of circumference)	Moderate (1/3-2/3 of circumference)	Severe (>2/ 3 of circumference)
Corneal				
Epithelium	None (Findings absent)	Slight (superficial punctuate keratitis)	Moderate (Desquamatory superficial punctuate keratitis)	Severe (Shield ulcer or epithelial erosion)
Neovascularization (new vessel crossing the limbus onto the clear cornea by ≥2 mm)	No evidence of new vessel	Slight (Presence of neovascularization in 1 quadrant of cornea)	Moderate (Presence of neovascularization in 2 quadrants of cornea)	Severe (Presence of neovascularization in ≥3 quadrants of cornea)

Table II. The Distribution of Patients According to the Score of Clinical Symptoms

	0 (n)	1 (n)	2 (n)	3 (n)	p
Itching					
Baseline	-	-	11	20	Ref.
1.month	-	6	25	-	0.0001*
3.month	2	25	4	-	0.0001*
6.month	14	17	-	-	0.0001*
Tearing					
Baseline	1	4	9	17	Ref.
1.month	4	7	20	-	0.0001*
3.month	10	21	-	-	0.0001*
6.month	28	3	-	-	0.0001*
Discomfort					
Baseline	-	2	14	15	Ref.
1.month	3	12	16	-	0.0001*
3.month	6	25	-	-	0.0001*
6.month	25	6	-	-	0.0001*
Discharge					
Baseline	3	6	14	8	Ref.
1.month	12	16	3	-	0.0001*
3. month	25	6	-	-	0.0001*
6. month	31	-	-	-	0.0001*
Photophobia					
Baseline	2	5	17	7	Ref.
1. month	8	20	3	-	0.0001*
3.month	25	6	-	-	0.0001*
6.month	30	1	-	-	0.0001*

n: Number of patients; values of p: Probability value; * statistically significant, ref.: reference value.

at 4 months with the treatment. The authors suggest that 1% cyclosporine concentration might be the minimal effective dose to control symptoms and local inflammation in severe forms of VKC.

The most common side effects with 2% cyclosporine were reported as redness and stinging of the eyes a few minutes after administration of the medication[1,17,18]. Yet, these side effects were not reported to be severe enough for any patient to discontinue the medication. A burning sensation and tearing soon after the administration of 1.25% cyclosporine were also reported in a few cases.[20]

Topical cyclosporine has also been shown to be an effective treatment in the management of shield ulcers in patients with VKC.[21] Four patients with shield ulcers not responding to medical treatment with topical steroids, antihistamines and mast-cell stabilizers were treated with 0.05%-2% topical cyclosporine 4 times a day. The concentration was adjusted according to the clinical status, starting with 2%. The minimal effective concentration in such cases seemed to be 1%.

Ozcan et al[22] used cyclosporine in 0.05% concentration 2 or 4 times daily in 7 children with severe allergic conjunctivitis who were not responding to topical steroids. Six patients had VKC, and 1 patient had atopic keratoconjunctivitis. In this study, all patients

Table III. The Distribution of Patients According to the Score of Clinical Signs

	0 (n)	1 (n)	2 (n)	3 (n)	p
Palpebral conjunctival hyperemia					
Baseline	-	-	15	16	Ref.
1.month	-	15	15	1	0.0001*
3.month	10	15	6	-	0.0001*
6.month	22	9	-	-	0.0001*
Conjunctival edema					
Baseline	-	6	16	9	Ref.
1.month	5	15	10	1	0.0001*
3.month	14	15	2	-	0.0001*
6.month	28	3	-	-	0.0001*
Papillary hypertrophy					
Baseline	-	1	11	19	Ref.
1.month	-	11	19	1	0.0001*
3.month	5	20	5	1	0.0001*
6.month	12	18	1	-	0.0001*
Cobblestone papillae					
Baseline	1	6	9	15	Ref.
1.month	2	6	23	0	0.0001*
3. month	9	18	3	1	0.0001*
6. month	22	8	1	-	0.0001*
Bulbar conjunctival hyperemia					
Baseline	1	4	20	6	Ref.
1.month	2	19	10	-	0.0001*
3.month	12	16	3	-	0.0001*
6.month	29	2	-	-	0.0001*
Bulbar conjunctival chemosis					
Baseline	4	12	11	4	Ref.
1.month	15	10	6	-	0.0001*
3.month	25	6	-	-	0.0001*
6.month	31	-	-	-	0.0001*
Trantas dots					
Baseline	22	2	3	4	Ref.
1.month	23	4	4	-	0.052
3.month	26	5	-	-	0.011*
6.month	28	3	-	-	0.007*
Limbal edema					
Baseline	15	7	3	6	Ref.
1.month	21	6	4	-	0.002*
3.month	27	3	1	-	0.001*
6.month	28	3	-	-	0.001*
Neovascularization					
Baseline	25	3	3	-	Ref.
1.month	25	5	1	-	0.006*
3.month	28	3	-	-	0.002*
6.month	30	1	-	-	0.003*

n: Number of patients; values of p: Probability value; * statistically significant; ref.: reference value.

were still symptomatic at the time of enrollment despite treatment with topical steroids. The authors concluded that, with the addition of topical cyclosporine 0.05% emulsion, a significant beneficial effect was observed in all patients. Moreover, the need for steroids was reduced or even eliminated.[22]

Recent studies revealed that severe VKC responds promptly to topical cyclosporine A and tacrolimus, generally within one month of therapy. Prolonged use of cyclosporine A and tacrolimus in VKC is safe and tolerated by most patients without significant side effects.[23] Cyclosporin eye drops, at either 1% or 2% concentrations, were shown to be safe and effective for long-term treatment of VKC in 156 children. Systematic ocular examination and both liver and kidney function investigation allowed researchers to exclude the possibility of local or systemic side effects over a period of 7 years.[24]

Additionally, in a case report, a 6-year-old child with severe vision-threatening vernal keratoconjunctivitis was treated successfully with oral cyclosporine. It was not possible to control the patient's symptoms with topical steroids, cyclosporine and mast cell stabilizers. The patient showed a dramatic improvement and stabilization with oral cyclosporine treatment.[25]

In our study, we used topical 0.05% cyclosporine 4 times a day in 31 children with VKC for 6 months. The objective signs and subjective symptoms improved significantly with cyclosporine treatment, and none of the patients needed additional topical steroid treatment. None of the patients complained of any significant side effects that might preclude continuing the treatment. This may be related to the lower concentration of cyclosporine used in this study. Also, in this dosage the drug is commercially available as a sterile ophthalmic solution that is easy to use.

In conclusion, topical cyclosporine 0.05% emulsion was found to be safe and effective in the treatment of VKC. It was effective in alleviating ocular symptoms and signs without resulting in significant side effects. Cyclosporine A ophthalmic emulsion (0.05%) seems to be of value in the treatment of severe VKC patients who are resistant to topical antihistamine and mast cell stabilizer therapy. The shortcoming of this study is the lack of a control group. Thus, prospective controlled clinical trials are necessary to support our findings.

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