Original Research Article

Efficacy and safety of topical cyclosporine 0.05% in vernal keratoconjunctivitis: Aggarwal Eye Hospital, Hyderabad

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Abstract

Introduction: While corticosteroids are an effective choice of treatment for severe vernal keratoconjunctivitis (VKC), their long-term use is restricted due to side effects. This study was conducted to evaluate the efficacy and safety of topical cyclosporine A (CsA) 0.05% in the treatment of VKC. **Methods**: A total of 40 patients with VKC that was resistant to topical corticosteroids, antihistamines, and mast cell stabilizers were treated with topical CsA 0.05%. Patients were evaluated at weeks 4, 8, and 12 after the initiation of therapy. Symptoms and signs observed before and after treatment were recorded and scores were assigned. Scores were assigned to symptoms and indicators, as well as the requirement for topical corticosteroids and ocular side effects. **Results**: Symptoms and indicators were graded on a four-point scale from 0 to 3 for all patients. Each patient was given topical cyclosporine 0.05 percent emulsion (Restasis, Sun Pharmaceutical Industries Ltd, India) four times a day, along with preservative-free artificial tears, and was followed for 12 weeks. The data was collected before the start of therapy (day 0) and at Weeks 4, 8, and 12 after treatment. The severity of all symptoms and indicators decreased statistically significantly ($p<0.05$) after 12 weeks of therapy. There were no significant side effects reported by the patients. **Conclusion:** Topical cyclosporine 0.05% emulsion treatment is a safe and effective treatment option for controlling the symptoms and signs of vernal keratoconjunctivitis in children.

Keywords: vernal keratoconjunctivitis, cyclosporine A, allergic conjunctivitis, topical.

Introduction

Vernal keratoconjunctivitis (VKC) is a severe form of ocular allergy illness that primarily affects children and young adults during the spring and summer seasons[1]. Symptoms and indications of VKC generally develop in the first decade of life and go away in the second[2]. The symptoms might make it difficult for a kid to participate in typical activities, which is a source of concern for parents. Photophobia, tearing, pain, discharge, cobblestone papillae, superficial keratitis, Trantas' spots, bulbar conjunctival hyperemia and chemosis, limbal edema, corneal shield ulcers, and corneal neovascularization are all common symptoms and indications of the illness[3]. Permanent alterations of the ocular surface, including scarring, keratoconus, and corneal shield ulcers, may occur during the active disease and cause significant vision impairment[4]. In tears and conjunctival biopsy specimens from VKC patients, histopathological investigations have revealed the presence of local helper T-cell type 2 and helper T-cell type 2-like cells[5, 6]. The conjunctiva has been shown to have an increased amount of activated mast cells and eosinophils. Conjunctival eosinophils express interleukin-3, IL-5, IL-6, and granulocyte-macrophage colony-stimulating factors in particular[7].

Corticosteroids are the most effective topically applied drug for the treatment of VKC[8], causing a broad anti-inflammatory and immunosuppressive impact as well as lowering phagocyte response[9]. Long-term topical steroid therapy, however, can cause significant adverse effects such as secondary glaucoma, posterior subcapsular cataract development, the risk of delayed wound healing, and superinfection with viruses and bacteria[10].

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As a result, corticosteroids are not recommended as a long-term treatment for VKC. Other therapeutic techniques that are typically helpful in the treatment of mild-to-moderate instances include topical mast cell stabilizers, topical antihistamines, and nonsteroidal anti-inflammatory drugs. However, they are insufficient in extreme instances[11, 12].

Topical cyclosporine A (CsA) is an immunosuppressive medication that inhibits the growth of helper T lymphocytes and the generation of interleukin-2. In addition, cyclosporine suppresses the release of histamine by human mast cells and basophils[13]. Cyclosporine, unlike corticosteroids, does not cause serious ocular adverse effects such as lens alterations or elevated intraocular pressure[14]. CsA is a fungal metabolite that inhibits Th2 lymphocyte proliferation, interleukin-2 synthesis, and histamine release from mast cells and basophils, which decreases ocular inflammation[15, 16]. The goal of this study was to look at the long-term effectiveness and safety of topical CsA 0.05 percent in treating severe VKC that was resistant to traditional antiallergic therapy.

Material and methods

Between January 2020 and January 2021, we prospectively examined 40 instances of VKC in children and adolescents who had topical cyclosporine 0.05 percent emulsion therapy for at least 12 weeks at the Pediatrics and Department of Ophthalmology, Aggarwal Eye Hospital, Hyderabad, Telangana, India. Patients with glaucoma, uveitis, corneal illness, ocular infection, systemic disorders other than concomitant allergic rhinitis, asthma, or atopic dermatitis, and history of cyclosporine hypersensitivity were excluded. With a mean age of 11.6 2.3 years, there were 28 boys and 12 girls. Before commencing the drug, all patients had been treated with either mast cell stabilizers or topical dual-action medications (mast cell stabilizers and antihistamines) for at least one month and were resistant to these treatments. Patients that were included had been diagnosed with VKC, had been attending follow-up sessions for at least a year, and had not responded to topical corticosteroids, antihistamines, or mast

cell stabilizers. During the enrollment period, all of the patients had an active illness. Patients who did not satisfy the criteria or were under the age of five years were not included in the study. The patients were assessed four weeks, eight weeks, and twelve weeks after starting treatment. Symptoms and symptoms were documented before and after therapy at four-week intervals, with ratings ranging from 0 to 3. Itching, discomfort (such as a foreign body sensation, stinging, and burning), tearing, discharge, and photophobia were all graded to determine symptom ratings. Conjunctival hyperemia, tarsal papillae, limbal papillae, keratopathy, and corneal neovascularisation were graded to determine sign scores. When evaluating the tarsal conjunctival and limbal papillae, the extent and size of the papillae were taken into account. The extent of punctate epithelial keratitis and/or the presence of ulceration were used to grade corneal symptoms. Corneal neovascularization was evaluated using corneal quadrants and the distance between the limbus and the central cornea as a measurement (Table 1).

Table 1: Scoring method for the signs and symptoms of severe vernal keratoconjunctivitis

Variable	Score			
	0	1	2	3
Symptom				
Itching	None	Occasional	Frequent	Constant
Discomfort	None	Mild	Moderate	Severe
Tearing	Normal	Impression of wet eyes, without tears on the face	Intermittent tears on the face	Constant tears on the face
Discharge	None	Small amount	Moderate amount	Constant
Photophobia	None	Mild	Moderate	Severe
Sign				
Conjunctival hyperemia	None	Mild	Moderate	Severe
Tarsal papillae	None	< 1 mm	1–3 mm	> 3 mm
Limbal papillae	None	< 90° or < 2 mm	90°–180° or 2–4 mm	> 180° or > 4 mm
Keratopathy	Normal cornea	Mild and localized punctate epithelial keratitis	Two quadrants of epithelial keratitis	Three or more quadrants of epithelial keratitis and/or a corneal ulcer
Corneal neovascularisation	None	< 90° or < 1 mm	90°–180° or 1–3 mm	> 180° or > 4 mm

Topical CsA 0.05% (Restasis, Sun Pharmaceutical Industries Ltd, India) four times a day was added to each patient's treatment regimen. Although topical drugs that the patients were taking were not ceased, topical corticosteroid doses were reduced or stopped when possible (i.e. if clinical recovery was observed) during clinic visits. Scores for symptoms and signs, the need for topical corticosteroids, and ocular side effects were evaluated. All data were analyzed using origin pro 8.5. Data on symptom and sign scores that did not have a normal distribution were compared using the wilcoxon test and compared with the baseline value and a p-value < 0.05 was considered statistically significant. Baseline, 4-week, 8-week, and 12-week measures were compared using the Wilcoxon test. Values of p less than 0.05 were considered statistically significant.

Results

The subjective clinical scoring of the 40 patients at day 0 and each follow-up visit is shown in Table 2. (4-week, 8-week, and 12-week). The therapy was well tolerated by all of the patients. Mild burning was thought to be typical. During the 12-week therapy period, no further adverse effects such as severe burning, hyperemia, tearing, or discomfort were noted. At each follow-up during the 12 weeks of cyclosporine treatment, scoring of all subjective symptoms, including itching, tearing, discomfort, discharge, and photophobia decreased considerably compared to baseline. For each, a therapy (p=0.0001) was used (Table 2).

Table-2: The Distribution of Patients According to the Score of Clinical Symptoms (n = 40)

Variable	0 (n)	1(n)	2 (n)	3 (n)	P
Itching					
Baseline	-	-	16	24	
Week 4	-	9	31	-	< 0.001
Week 8	4	28	8		< 0.001
Week 12	18	22			< 0.001
Tearing					
Baseline	1	4	10	25	
Week 4	8	12	20	-	< 0.001
Week 8	10	30	-	-	< 0.001
Week 12	35	5	-	-	< 0.001
Discomfort					
Baseline		3	17	20	
Week 4	5	13	22	-	< 0.001
Week 8	7	33	-	-	< 0.001
Week 12	32	8	-	-	< 0.001
Discharge					
Baseline	5	9	16	10	
Week 4	15	20	5	-	< 0.001
Week 8	32	8	-	-	< 0.001
Week 12	39	1	-	-	< 0.001
Photophobia					
Baseline	5	7	22	6	
Week 4	10	25	5	-	< 0.001

Week 8	34	6	-	-	< 0.001
Week 12	38	2	-	-	< 0.001

n: Number of patients; values of p: Probability value; *Calculated using Wilcoxon test and compared with the baseline values. p < 0.008 considered statistically significant.

Table 3 shows that all objective signs improved statistically significantly during the 6-month follow-up period (p<0.05), including palpebral conjunctival hyperemia, edema, papillary hypertrophy, cobblestone papillae, conjunctival hyperemia, and chemosis, Trantas' dots, limbal swelling, and corneal neovascularization. Although the Trans dots in the limbal region improved, the difference between baseline and first-month values was not statistically significant (p=0.05). The improvement was statistically significant in the third and sixth months (p=0.01 and p=0.008, respectively).

Table-3. The Distribution of Patients According to the Score of Clinical Signs (n = 40)

Variable	0 (n)	1(n)	2 (n)	3 (n)	P
Palpebral conjunctival hyperemia					
Baseline	-	-	19	21	
Week 4	-	-	-	-	< 0.001
Week 8	-	19	18	3	< 0.001
Week 12	28	12			< 0.001
Conjunctival edema					
Baseline	-	15	16	9	
Week 4	6	17	12	5	< 0.001
Week 8	12	19	9	-	< 0.001
Week 12	29	11	-	-	< 0.001
Papillary hypertrophy					
Baseline	-	9	15	16	
Week 4	-	12	23	5	< 0.001
Week 8	9	22	7	2	< 0.001
Week 12	36	4	-	-	< 0.001
Cobblestone papillae					
Baseline	5	7	10	18	
Week 4	5	10	25	-	< 0.001
Week 8	16	20		4	< 0.001
Week 12	25	10	5	-	< 0.001
Bulbar conjunctival hyperemia					
Baseline	5	15	13	7	
Week 4	14	17	9	-	< 0.001
Week 8	29	11	-	-	< 0.001
Week 12	39	1		-	< 0.001
Trans dots					
Baseline	25	4	6	5	
Week 4	26	8	6	-	0.052
Week 8	28	12	-	-	0.011
Week 12	36	4	-	-	0.056
Limbal edema					
Baseline	15	9	11	5	
Week 4	25	9	6	-	< 0.001
Week 8	29	4	7	-	< 0.001
Week 12	32	8	-	-	< 0.001
Neovascularization					
Baseline	27	9	4	-	
Week 4	29	8	3	-	< 0.001
Week 8	32	8	-	-	< 0.001
Week 12	34	6	-	-	< 0.001

n: Number of patients; values of p: Probability value; *Calculated using Wilcoxon test and compared with the baseline values. p < 0.008 considered statistically significant.

When compared with the baseline scores, the reductions in the symptom and sign scores at Weeks 4, 8, and 12 of treatment were statistically significant (p < 0.05). There was no significant improvement in symptom scores between Weeks 4 and 12, while the sign scores continued to improve (p < 0.008). No other side effects were reported.

Discussion

Vernal keratoconjunctivitis is a long-term allergy condition with complex immunopathogenic processes. VKC is an inflammatory condition of the conjunctiva and cornea that can cause blindness. Even though VKC is categorized as allergic eye disease, the function of allergens as an initiating cause is unknown. IgE, cytokines, chemokines, and inflammatory cells (T and B lymphocytes, mast cells, basophils, neutrophils, and eosinophils) all play a role in the pathogenesis of VKC, with the release of granular proteins, fibroblast proliferation, 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[17].Treatment with topical antihistamines and mast cell stabilizers is typically ineffective in individuals with severe vernal conjunctivitis. During exacerbations of the illness, some individuals may require topical corticosteroid treatment. Topical corticosteroids, on the other hand, are not recommended for long-term therapy, especially in youngsters, due to their well-known adverse effects. We utilized topical 0.05 percent cyclosporine in 40 individuals for 12 weeks in this research. A four-point scale was

employed to assess the treatment's success. The symptoms and clinical indications of all of the patients improved significantly.

Several studies have demonstrated that topical cyclosporine 2% is effective in treating VKC and reduces the requirement for topical steroids[18-24]. Cyclosporine A (CsA) is an immunomodulator that primarily prevents T lymphocytes from proliferating and acting. Ben Ezra et al.[20] used cyclosporine 2 percent eye drops in an oil solution to treat 21 children with severe vernal conjunctivitis who were resistant to corticosteroids and 2 percent disodium cromoglycate. Redness, itching, photophobia, tears, discomfort, mucous discharge, and incapacity to participate in regular daily activities were all reported as subjective characteristics. Eighty-six percent of the kids reacted positively and quickly to the therapy. Additionally, local or systemic treatment with corticosteroids was avoided in most cases, at least during the period of cyclosporine treatment[20].Gupta et al.[25] gave 24 youngsters aged 5 to 16 years old either 2 percent cyclosporine A or a placebo four times a day for three months. A five-point scale was used to measure both subjective and objective factors. Only three patients in the placebo group exhibited minor symptomatic improvement 7 days after commencing cyclosporine A therapy, whereas 11 patients in the cyclosporine A group showed mild symptomatic improvement.2 percent cyclosporine was used to treat 24 children with severe VKC in a double-blind, placebo-controlled study[21]. After two weeks of therapy, the majority of the benefits of topical cyclosporine 2 percent on ocular symptoms and signs were accomplished. It was occasionally necessary to use a topical corticosteroid for a short length of time. Cyclosporine 2 percent was shown to be both safe and effective in the treatment of severe VKC. In more recent research, 197 children with severe VKC were given 1% topical cyclosporine for four months. All children were assessed for ocular subjective symptoms and objective indicators at the start of the study, as well as two weeks and four months afterward. The mean score values for the 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[22].

Spadaveccia et al[23] compared the efficacy of 1.25% topical cyclosporine versus 1% cyclosporine in patients with severe VKC. In both groups, the mean score values for the severity of subjective symptoms and objective signs were significantly decreased at 2 weeks and 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[20, 21]. 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[23].

In individuals with VKC, topical cyclosporine has also been found to be a successful therapy for shield ulcers[24]. Four patients with shield ulcers who had not responded to topical steroids, antihistamines, or mast-cell stabilizers were given 0.05 percent -2 percent topical cyclosporine four times a day. Starting at 2%, the concentration was modified according to the clinical condition. In such situations, the lowest effective concentration appeared to be 1%.

In 7 children with severe allergic conjunctivitis who were not responding to topical steroids, Ozcan et al[26] administered cyclosporine in a 0.05 percent concentration 2 or 4 times daily. Six individuals were diagnosed with VKC, while one was diagnosed with atopic keratoconjunctivitis. Despite therapy with topical steroids, all of the patients in this trial were still symptomatic at the time of enrolment. The authors found that adding topical cyclosporine 0.05 percent emulsion to the treatment had a substantial positive impact on all patients. Furthermore, the use of steroids was decreased, if not completely abolished[26].

Recent research has found that severe VKC responds quickly to topical cyclosporine A and tacrolimus, usually within a month after starting treatment. Long-term treatment of cyclosporine A and tacrolimus in VKC is safe and well-tolerated by the majority of patients[27]. In 156 children, cyclosporin eye drops at 1% and 2% doses were shown to be safe and effective for long-term therapy of VKC. Over seven years, researchers used a systematic eye examination as well as liver and kidney function tests to rule out the potential of local or systemic adverse effects[28]. A 6-year-old kid with severe vision-threatening vernal keratoconjunctivitis was also effectively treated with oral cyclosporine, according to a case study. Topical steroids, cyclosporine, and mast cell stabilizers failed to manage the patient's symptoms. With oral cyclosporine therapy, the patient's condition improved dramatically and stabilized[29].

In our study, we used topically 0.05% cyclosporine 4 times a day in 40 children with VKC for 12 weeks. 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.

Conclusion

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. To back up our findings, prospective controlled clinical studies are required.

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