

## Role of cyclosporin 0.1% in perennial vernal keratoconjunctivitis

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### Abstract

**Introduction:** To evaluate the efficacy of topical cyclosporin A 0.1% eye drops in management of moderate to severe perennial vernal keratoconjunctivitis.

**Methods:** Fourteen patients with moderate to severe perennial vernal keratoconjunctivitis, who were dependent on steroid eye drops for control of disease, were administered 0.1% cyclosporin A eye drops twice a day. Signs, symptoms and steroid score were calculated at start of study, and then at two monthly interval.

**Results:** Ten males and four females, between age of 3 – 17 years were enrolled in this study. Treatment with cyclosporin A 0.1% eye drops decreased the symptom, sign and steroid score at 12 months ( $p < 0.0001$ , paired t test). Steroid sparing effect was seen in five patients at the end of study period.

**Conclusions:** Topical cyclosporin A 0.1% eye drops can be used as a steroid sparing agent in the management of perennial vernal keratoconjunctivitis.

**Keywords:** Cyclosporin A, Perennial vernal keratoconjunctivitis

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**Website:**

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**DOI:**

10.5958/2395-1451.2016.00042.1

### Introduction

Vernal keratoconjunctivitis is a bilateral (96.7%)<sup>1,2</sup> recurrent inflammation of the conjunctiva, that frequently occurs in children and young adults with a positive history of seasonal allergy, asthma or eczema<sup>3</sup>. Disease is predominantly seen in warm temperate middle – east, Mediterranean region and Mexico. Male female ratio is 2:1 and peak incidence is between 11- 13 years. The disease is self-limited in children with an average duration of 4- 10 years. However adults suffer a severe disease which recurs indefinitely. VKC occurs in three clinical forms – palpebral, limbal and mixed; depending on which part of eye is predominantly involved. Symptom is predominantly itching, apart from photophobia, burning, watering, ropy discharge and rarely ptosis. Signs are – limbal or palpebral papillae, Horner – Tranta's dots, superficial pannus, punctate epithelial keratitis and shield ulcer.

Approximately 23% of patients had a perennial form of VKC from disease onset, and more than 60% had additional recurrences during winter<sup>4</sup>. These perennial VKC cases when in severe form, require steroid therapy for long term as maintenance therapy. Though highly effective drugs, they cause a myriad of complications on long term usage, e.g., raised intraocular pressure, cataract, delayed wound healing and increased chances of infection<sup>5</sup>. And most

importantly, few patients fail to respond even with high dose of topical steroids. Although steroid sparing efficacy of cyclosporine A eye drops is well known, but none of the studies has focused on perennial vernal keratoconjunctivitis patients. Histopathology in VKC is characterized by conjunctival infiltration with eosinophils, degranulated mast cells, basophils and plasma cells. CD4+ subset of T lymphocytes which are present in conjunctival papillae in patient of VKC are known to produce interleukin -2<sup>3,6</sup>. Cyclosporin is a non-steroidal immunomodulator that inhibits antigen dependent T cell activation. It also causes direct inhibition of eosinophil and mast cell, and release of their mediators<sup>7</sup>.

### Materials and Methods

All moderate to severe perennial VKC patients presenting to our outpatient department, were enrolled in this study from October 2014. All the study participants had their medication stopped for a week. After a week baseline visit was planned, and sign and symptom score were calculated. Medication was prescribed. Repeat examinations were done at 2, 4, 6, 8, 10 and 12 months. Since all the patients were of perennial VKC, moderate to severe grade, they received cyclosporin A emulsion 0.1% twice a day. Commercially available CsA 0.1% eye drops, from > 1 companies were used. According to manufacturers the eye drop should be used twice daily, as is the case in our study.

All patients who completed one year follow up were included in this study.

### Inclusion Criteria

1. Perennial VKC
2. Dependence on steroid drops (on and off/regular)
3. Tapering of steroids led to recurrence of disease

### Exclusion Criteria

1. Acute allergic conjunctivitis
2. Tapering of steroids did not lead to recurrence of symptoms
3. Keratopathy/ shield ulcer
4. Keratoconus or keratoconus suspect
5. Coexisting ocular disorder, e.g. corneal ulcer, optic atrophy, glaucoma, uveitis.
6. Patient on any oral medication e.g. antihistaminics, steroids
7. Patient already on cyclosporin eye drops
8. Periocular injection of steroids in last six months
9. Ocular surgery within last six months
10. Pregnant and lactating females
11. Poor compliance

With these criteria we enrolled sixteen patients of VKC for our study in the month of October 2014. We did not encounter any pregnant or lactating females. All patients had been treated with variety of topical medications before enrollment. The medications were discontinued for two weeks before the commencement of study. Consent was taken regarding the use of relatively new eye drop. Different scoring systems have been used by different observers<sup>8,9</sup>. But one of the study<sup>8</sup>, has devised common classification system for VKC and atopic keratoconjunctivitis. The other study<sup>9</sup> mentions cicatrization as one of the signs, which is a feature of atopic keratoconjunctivitis, not of VKC. Hence we made our own classification system, which is as mentioned below.

Symptoms (Total Score=12)				
Symptoms	Grade 0	Grade 1	Grade 2	Grade 3
Itching	Absent	Mild (occasional)	Moderate (frequent)	Severe (constant)
Watering	Absent	Occasional	Intermittent	Nearly constant
FB sensation	Absent	Mild	Moderate	Severe, gritty
Discharge	Absent	Minimal mucoid discharge at medial canthus in the morning	Moderate amount of mucoid discharge at medial canthus in the morning	Ropy discharge in morning, on and off discharge throughout the day

Signs (Total Score= 15)				
Signs	Grade 0	Grade 1	Grade 2	Grade 3
Superficial congestion	Absent	Mild	Moderate	Severe
Palpebral papillae	Absent	Micropapillae	Macropapillae	Giant papillary conjunctivitis
Limbal papillae	Absent	≤ 1 quadrant	> 1 but ≤ 2 quadrant	> 2 quadrant
Horner Tranta's Dots (numbers)	Absent	1 or 2	3 – 5	> 5
Neovascularisation	Absent	≤ 3 clock hours	> 3 but ≤ 6 clock hours	> 6 clock hours

### Steroid Score

We used two preparations of steroids in our study – prednisolone 1% eye drops and fluorometholone 0.1% eye drops. They had to be tapered according to the clinical response. So in order to compare them we devised steroid score. We ascribed multiplication factor of 2 to prednisolone acetate and 1 to fluorometholone. Steroid score was calculated by multiplying the number of drops used in a day by their respective multiplication factor.

Outcome of this study were – decrease in symptom score, decrease in sign score and decrease in steroid score.

### Observation

Sixteen patients were enrolled in this study. Out of which two patients had to be excluded. One of them developed cobblestone papillae during seasonal exacerbation and required supratarsal injection. The other patient has to be excluded due to poor compliance; he did not follow the instructions – even after explaining many times he forgot to instill the eye drops in the morning. So at the end of study period we had total fourteen patients.

### Age distribution

Age range of patients was 3 -17 years with mean of 10.85 years (SD = ± 4.62 years).

Age range	No. of patients	Percentage
0-5	2	14.29
6-10	4	28.57
11-15	5	35.71
16-20	3	21.43

### Sex Distribution

Male female ratio in our study was 5:2, commoner in males.

Sex	No. of patients	Percentage
Male	10	71.43
Female	4	28.57

Symptom Score			
Duration	Mean	±SD	Range
0 months	7.5	1.45	5 – 10
2 months	5.92	2.05	2 – 9
4 months	4.28	2.01	0 – 8
6 months	5.5	2.03	2 – 10
8 months	5.5	1.91	2 – 8
10 months	3.64	1.87	1 – 6
12 months	2.21	1.80	0 – 6

A gradual decrease in symptoms was noted. Slight exacerbation of symptoms was noticed after 6 – 8 months, which coincided with the seasonal reactivation of disease. p value was calculated between values of 0 and 12 months, using paired t test ( $p < 0.0001$ ).

Sign Score			
Duration	Mean	±SD	Range
0 months	9.79	2.04	7 – 13
2 months	8.29	2.27	6 – 12
4 months	6.64	2.56	3 – 11
6 months	7.79	2.91	4 – 13
8 months	6.79	3.07	2 – 12
10 months	4.93	2.73	1 – 10
12 months	3.21	2.36	1 – 8

As with symptoms, the signs also decreased gradually. Slight increase in signs was noticed at six months, which was in April – May, time of seasonal reactivation of disease. p value was calculated between values of 0 and 12 months, using paired t test ( $p < 0.0001$ ).

Steroid Score			
Duration	Mean	±SD	Range
0 months	10.35	3.63	6 – 14
2 months	8.29	3.43	3 – 12
4 months	6.29	3.20	2 – 10
6 months	7.43	3.78	3 – 14
8 months	6.00	3.23	2 – 12
10 months	3.71	2.78	0 – 8
12 months	2.00	2.08	0 – 6

The dependence on steroids gradually decreased. At 9 months, we could withdraw steroids in 3 out of 14 patients (21.43%), and at 12 months 5 out of 14 patients (35.71%). p value was calculated between values of 0 and 12 months, using paired t test ( $p < 0.0001$ ).

### Discussion

Vernal keratoconjunctivitis is a chronic allergic disease. Some patients only have seasonal reactivation of disease, while some have manifestations throughout the year. In approximately one quarter of VKC patients the disease smolders throughout the year, without any remission from the onset<sup>5</sup>.

Males are predominantly affected, with male female ratio being 4:1 to 2:1<sup>5</sup>. Our study also had male female ratio 2.5:1. The age range of patients was from 3-17 years, but maximum cases (35.71%) were in 11 - 15 years age, which is the age group to be predominantly affected. Symptom score showed a decline throughout the study period. There was slight exacerbation of symptoms in March – June period, which coincided with seasonal reactivation of disease. Similar pattern was seen with sign score. The difference between baseline symptom/sign score was highly significant ( $p < 0.0001$ ). These were the patients who had perennial VKC and were using steroids for many months/years. In these cases, the requirement of steroid decreased as well. Mean steroid score at 12 months decreased to less than 25% of original values, and the difference between baseline mean steroid score and final steroid score was highly significant ( $p < 0.001$ ). At nine months of study, we could withdraw steroids in 21.43% of patients, and at 12 months in 35.71%, which was not followed by any reactivation of disease. These fourteen patients were using steroid almost continuously for many months/years prior to enrollment in study. So this steroid sparing effect was believed to be due to 0.1% CsA eye drops.

VKC is a very common disease in India. It's management is aimed at controlling the symptoms and eliminating the signs, so any ocular morbidity can be avoided. Eye drops available for management of VKC are non-steroidal anti-inflammatory, antihistaminics, mast cell stabilizers and newer agents with dual antiallergic activity. But still the mainstay of management of moderate to severe cases is steroid eye drops. Improvement of signs and symptoms with steroids is highly gratifying. Problems associated with its long term use are serious potential adverse effects, and risk of reactivation of VKC whenever the drop is tapered or stopped, especially in perennial cases. Immunomodulators have lesser side effects on prolonged use. Many immunomodulators have been tried for these cases. A two week trial of topical mitomycin C 0.01%, four times daily was found to be effective in such cases<sup>10</sup>. Another recent study has reported topical interferon alpha 2b treatment to be safe and effective in cases of refractory VKC<sup>11</sup>.

The most widely studied drug in severe or refractory VKC is cyclosporin A. Being derived from soil fungus *Tolypocladium Inflatum*, it inhibits T- cell activation as well as eosinophilic infiltration into the conjunctiva and interferes with both late-phase and delayed-type allergic reactions<sup>12,13</sup>. Various concentrations of CsA in varying frequencies have been studied e.g. 2, 1.25, 1, 0.1 and 0.05 %. When the drug was not available commercially, drug was prepared in 2% concentration using olive oil, castor oil, maize oil or corn oil. It has been used most widely used for VKC, although it is associated with higher incidence of side effects e.g. more stinging, and even lid maceration have been reported. Commercial preparations (0.05 and 0.1%) have been designed for dry eyes. Out of these 0.05% is used for milder cases and 0.1% is reserved for moderate to severe cases in both dry eyes and VKC. Several studies have reported good response to 0.05% CsA<sup>8,9</sup> in cases of VKC, while some authors have failed to get similar results<sup>7</sup>.

Ebihara et al<sup>14</sup> evaluated the effectiveness and safety of 0.1% aqueous based cyclosporin A eye drops, in 594 patients of VKC and AKC. This prospective and observational study concluded that topical cyclosporin 0.1% is effective and safe for treatment of VKC and AKC. A recent systematic review and meta-analysis study suggests that topical cyclosporin is effective and safe for the treatment of VKC, irrespective of dosing<sup>15</sup>. A randomized controlled two year crossover study has demonstrated the safety and efficacy of CsA 0.05% for long term prevention of recurrences in VKC<sup>16</sup>. The steroid sparing effect of cyclosporin starts after long cycles of treatment<sup>16</sup>. Topical steroids can be added nevertheless, as and when required. These studies bear great impact, especially for children, who suffer maximum ocular morbidity – either due to steroid abuse or due to disease itself.

The only reported side effect of CsA with commercial preparations is mild stinging. Stinging is a well-known side effect of CsA, which limits its use<sup>17</sup>. Even on prolonged administration, systemic absorption and systemic side effects of the drug is nil<sup>18</sup>.

### Conclusions

As seen in this study, long term use of Cyclosporin A 0.1% eye drops led to drastic improvement in sign and symptoms of moderate to severe perennial VKC patients. We were able to withdraw steroids in 35.71 % of patients at the end of study period, and rest of the patients also had decrease in dependence on steroid eye drops. Perennial VKC is a common disease in India. In these cases, CsA eye drop is a very good choice for relief of disease, as well as to prevent them from steroid abuse and its disastrous complications.

### Acknowledgements

The author denies any conflicts of interest related to this study. None of the author has any financial interest in the product mentioned.

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