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A clinical study of Cyclosporine eye drops for refractory cases of Vernal Keratoconjunctivitis

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Abstract :
Purpose: *To evaluate the efficacy and safety of topical 0.05% Cyclosporine eye drops for treatment of refractory vernal keratoconjunctivitis (VKC).*
Methods: *This prospective study included 50 patients with refractory VKC, who had active symptomatic disease despite conventional medications including topical steroids. After discontinuing all other medications, patients were treated with topical 0.05% eye drops two times a day. Changes in subjective symptoms and objective signs after treatment were evaluated, and development of possible complications was assessed.*
Results : *Mean age of patients was16.56 years and mean duration of VKC was 8.4 years. After starting cyclosporine eye drops, patients were followed for a mean duration of 10 months (range of 6–12 months). All symptoms including itching, redness, photosensitivity, foreign body sensation, and mucus discharge improved after the treatment. In addition, there was improvement in objective signs including conjunctival hyperaemia, conjunctival papillary hypertrophy, giant papillae, limbal hypertrophy, corneal punctate epithelial erosions, and corneal pannus. Conjunctival hyperaemia was the first sign to show improvement. No patient required addition of other medications including steroids for further relief. Discontinuation of the cyclosporine eye drops was associated with recurrence of patients symptoms and signs, necessitating continued use of the medication during the entire follow-up time. Ocular complication related to cyclosporine was noted such as burning sensation and itching.*
Conclusion: *Topical 0.05% cyclosporine eye drops seemed to be a safe and effective treatment for steroid-resistant refractory VKC; however, long-term use was needed to control the disease.*

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I. Introduction:

Vernal conjunctivitis is a bilateral, recurrent inflammation of conjunctiva that tends to occur in children and young adults with a history of seasonal allergy, asthma, or eczema. Its onset is most common in the spring and summer, and the inflammation often goes into remission during the cooler months. The highest incidence of the disease is in the warm, temperate regions. Boys are affected twice as often as girls with a peak incidence between the ages of 11 and 13 years. The disease is self-limited in children, with an average duration of 4–10 years. In adults, a more severe form of the disease may recur indefinitely. The prominent symptom is intense pruritis. Other symptoms include photophobia, burning, tearing, mild ptosis, and a thick, ropy, yellow, mucoid discharge .

Treatment of all of the above conditions is based on the severity and chronicity of the disease in each patient. Medications then become necessary to control symptoms and any sequelae. The conventional medications include H1 receptor agonists, anti histamines with mast cell stabilizing properties, topical NSAIDS, vasoconstrictors, topical steroids and oral antihistamines.

Cyclosporine :

Cyclosporine is immunomodulatory agent, but with much higher potency (up to 100 times). It suppresses T-cell activation, T helper cell-mediated B-cell proliferation, and formation of cytokines, especially interleukin-2. In ophthalmology, tacrolimus has mainly been used to suppress immune reactions in corneal and limbal transplantations, uveitis, and allergic eye disease.

Mechanism of action:

Cyclosporine was discovered in 1987; it was among the first macrolide immunosuppressants discovered, preceded by the discovery of rapamycin (sirolimus) on Rapa Nui (Easter Island) in 1975. It is produced by a soil bacterium, *Streptomyces tsukubaensis* The name cyclosporine is derived from "Tsukuba macrolide immunosuppressant"[(2)]

Cyclosporine was first approved by the Food and Drug Administration in 1994 for use in liver transplantation; this has been extended to include kidney, heart, small bowel, pancreas, lung, trachea, skin, cornea, bone marrow, and limb transplants.

Cyclosporine is a macrolide calcineurin inhibitor. In T-cells, activation of the T-cell receptor normally increases intracellular calcium, which acts via calmodulin to activate calcineurin. Calcineurin then dephosphorylates the transcription factor nuclear factor of activated T-cells (NF-AT), which moves to the nucleus of the T-cell and increases the activity of genes coding for IL-2 and related cytokines. Cyclosporin prevents the dephosphorylation of NF-AT. FKBP12, the target protein of tacrolimus.

The most common adverse events associated with the use of topical cyclosporine eye drops, especially if used over a wide area, include a burning or itching sensation on the initial applications, with increased sensitivity to sunlight and heat on the affected areas. Less common are flu-like symptoms, headache, cough, and burning eyes. [(3)]

Patients and methods:

This prospective study included 44 patients with active VKC, which was refractory to conventional treatments of age groups from 10 to 25 years were considered. Both males and females were included. Patients who had received any form of immunosuppressive therapy including cyclosporine A eye drops were excluded. These patients were consecutively enrolled in the study from a tertiary eye care facility from June 2019 to Jan 2021.

VKC was diagnosed with a typical history of chronic, bilateral conjunctivitis, and with the patient exhibiting symptoms and signs of itching, redness, mucus discharge, papillae on the upper tarsal conjunctiva, and/or limbal changes. All these patients had active disease with no significant improvement despite being already treated with conventional medications such as anti-histamines, mast-cell stabilisers, non-steroidal anti-inflammatory drugs, and topical steroids. Despite all the medications, these patients still complained of persistent symptoms

Before starting treatment with cyclosporine eye drops and at each visit thereafter, all patients were given a questionnaire regarding the symptoms of itching, redness, photosensitivity, foreign body sensation, and mucus discharge. In addition, they underwent a detailed ophthalmic examination including measurement of best spectacle-corrected visual acuity (BSCVA), slit-lamp biomicroscopy. Before starting topical cyclosporine eye drops, all patients were asked to discontinue all other medications including steroids for 1 week.

Advantages and disadvantages of the treatment were fully explained for the patients and/or their parents and then informed consent was obtained from each participant or his/her parents. The treatment included topical 0.05% cyclosporine eye drops two times a day. In each visit after treatment, the above-mentioned questionnaire and ophthalmic examination were repeated; the patients were also specifically questioned about the discomfort associated with the use of cyclosporine eye drops.

II. Results :

Among 50 patients, 48 were males and 2 were females. The mean age group of the study is 16.56 years.

Age group	10-15 years	16-20years	21-25years	Total
No.of pts	18	26	6	50

The mean duration of years of disease was 8.4 years.

Duration of the disease	2-5 years	6-9 years	9-12 years
No. of pts	12	30	8

After starting 0.05% cyclosporine eye drops, the patients were followed for a mean duration of 10months (range, 6–12 months). Changes in symptoms and signs after treatment noted .All symptoms significantly improved after treatment with cyclosporine eye drops. Itching was the first symptom to show dramatic relief; while before treatment, 46 patients had severe itching and 4pts had moderate itching, 3 days after stating cyclosporine eye drops 48 patients had no itching and 2 other patients had only mild itching, which was relieved by 1 month. By 1 month after treatment, the residual symptoms included mild redness in seven patients, mild photosensitivity in three patients and mild foreign body sensation in two patients. The patients remained mostly symptom-free while under treatment during follow-up, with only mild symptoms of redness, photosensitivity, and foreign body sensation in 20, 4, and 8 patients, respectively, at the end of follow-up. Under

treatment with cyclosporine , no patient needed to use any additional medications such as topical anti-histamines, mast-cell stabilizers, or topical steroids to have more relief.

Change of symptoms:

SYMPTOM	DURATION OF RESPONSE	PRECENTAGE OF REDUCTION OF INTENSITY
Itching	1 month	100%
Redness	3 months	70%
Photosensitivity	3 months	80%
Foreign body sensation	2 months	60%
Mucus discharge	1 month	100%

Response to signs:

Sign	Duration of response	% of reduction
Conjunctival hyperemia	3 months	70%
Papillary hypertrophy	4 months	40%
Giant papillary conjunctivitis	1 month	100%
Limbal hypertrophy	1 month	100%
Corneal punctate lesions	1 month	100%
Pannus	2 months	70%
Mucus discharge	1 month	100%

Discontinuation of therapy due to ocular side affects like burning sensation and itching is seen in 2 patients

III. Discussion:

Vernal keratoconjunctivitis is known to be one of the most severe forms of ocular allergy, with the potential to cause corneal damage and permanent visual loss. This study showed that 0.05% cyclosporine eye drops was a safe and effective treatment for patients with VKC refractory to conventional medications including topical steroids. All patients showed good improvement of inflammatory symptoms and signs without developing any significant adverse effect. No patient needed to use any additional medication including topical steroids, showing the role of this medication as a steroid-sparing agent. However, long-term use of the medication was necessary to control the disease.

Cyclosporine is a potent immunosuppressive agent, which inhibits several immune reactions involved in the pathogenesis of VKC[4]. In our study, 0.05%of topical cyclosporine was used as an eye drop to treat patients with refractory VKC. Previously, systemic cyclosporine in the form of oral preparation has successfully been used in refractory severe Allergic Keratoconjunctivitis[5] [6] Furthermore, to treat allergic disease, some studies have used either a commercially available 0.1% 'skin' ointment applied to eyelids[7] [8] [9] [10] or fornix[11]

With this use of the topical cyclosporine, rapid and dramatic improvement of symptoms was noted in patients with refractory VKC. By 3 days after the treatment, itching was mostly relieved in all patients and 80% had no itching at all. Most other symptoms were also remarkably relieved by 1 month after starting cyclosporine eye drop. Similar findings have also been noted in other studies. Vichyanond *et al*[12] applied topical 0.1% cyclosporine eye drops for 4 weeks in 10 patients with recalcitrant VKC. All patients responded rapidly to the treatment; severity of symptoms reached 31% of their baseline at the end of the first week and after 4 weeks the mean symptom score was 20% of baseline. In another study, Miyazaki *et al*[13] used 0.02% cyclosporine eye drops for five patients with AKC and one patient with VKC. They noticed marked improvement of their symptoms within 2–4 weeks. Furthermore, in a multicentre, randomised clinical trial, Ohashi *et al*[14] applied 0.1% ophthalmic suspension of cyclosporine twice-daily for 4 weeks in 21 patients with AKC and 7 patients with VKC. Compared with placebo group, the treated eyes showed marked improvement in symptoms after 4 weeks of treatment.

Parallel to improvement of symptoms, objective signs in our cases showed improvement soon after starting the treatment. Conjunctival hyperaemia was the first sign to show improvement with marked reduction of hyperaemia within 1 month of treatment, which continued to show improvement during the therapy course. In addition to improved conjunctival papillary hypertrophy in all eyes, giant papillae were found to have improvement after treatment as early as 2 weeks and by 1 month all these eyes had mild giant papillae, which disappeared in eyes by the end of follow-up. In one case report, Kymionis *et al* reported that 0.05% cyclosporine eye drops applied twice a day in a boy with giant papillary conjunctivitis due to VKC resulted in resolution of giant papillae within 15 days, with no evidence of these papillae after 1 month of treatment. Ohashi *et al* also showed significant improvement of the giant papillae after 4 weeks of treatment with 0.1% cyclosporine ophthalmic suspension. In addition to conjunctival signs, limbal hypertrophy and corneal signs such as corneal punctate epithelial erosions, corneal pannus, and to some degrees corneal stromal opacity showed improvement.

In our series, any attempt to discontinue the cyclosporine eye drop resulted in recurrence of allergic symptoms and signs. Therefore, patients needed to be under treatment for their entire course. Although burning

sensation upon application of topical cyclosporine has been reported before, only 2 patients in our study experienced any burning or discomfort. However, due to its local immunosuppressive effects, topical cyclosporine may potentially be associated with some complications. Activation of herpes simplex dendritic keratitis [(15)] and development of molluscum contagiosum[(9)] have been reported before. Further studies are required to evaluate the long-term safety of this medication.

IV. Summary:

Vernal conjunctivitis is a bilateral, recurrent inflammation of conjunctiva that tends to occur in children and young adults associated with a history of seasonal allergy, asthma, or eczema. Treatment of refractory vernal keratoconjunctivitis is challenging. Cyclosporine is immunomodulatory has previously been used to suppress immune reactions in allergic eye disease. The use of cyclosporine 0.05% eye drops seems to be safe and effective treatment for steroid resistant refractory vernal keratoconjunctivitis. Long term usage of medication is necessary for the control of the disease.

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