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Effect of topical 0.05% cyclosporine for the treatment of vernal keratoconjunctivitis

KEYWORDS

Dr. Dipali Satani
Associate Professor, NHL Municipal Medical College

Dr.Krupali Raol
Third Year Resident, NHL Municipal Medical College

Dr. Shwetambari Singh
Assistant Professor, NHL Municipal Medical College

ABSTRACT

BACKGROUND:
To evaluate the short-term efficacy and safety of topical 0.05% cyclosporine for patients with vernal keratoconjunctivitis.

METHODS:
Fifteen patients with severe vernal keratoconjunctivitis were included in the study. All were treated with 0.05% cyclosporine eye drops. Eyes that received cyclosporine eye drops did not receive any other eye drops except 0.5% lubricating (CMC) eye drops. Symptoms and signs were scored on the day of enrolment and at the end of days 1, 2, 7,14,30,60,90,120,150 and 180.

RESULTS:
At the end of 7 days, no statistically significant decrease was noted from baseline in mean scores of either signs ($p = 0.18$) or symptoms ($p = 0.50$) in the eyes that received cyclosporine. On the other hand, a statistically significant decrease was observed in both sign and symptom scores ($p < 0.001$, for both) of eyes that received cyclosporine at the end of 14 days. At days 30 and 90, statistically significant decrease in both sign scores and symptom scores were noted compared with baseline in the eyes that received cyclosporine eye drops ($p < 0.001$, for all).

INTERPRETATION:
Topical 0.05% cyclosporine is effective in alleviating signs and symptoms of patients with severe vernal keratoconjunctivitis and had no observed side effects over the course of the study. Most of the therapeutic effect was achieved after 14 days. The initial therapeutic effect was maintained during the next 180 days.

Introduction

Allergic conjunctivitis is a local allergic condition centered mainly in the ocular area, although sometimes it is also associated with rhinitis. The disease ranges in severity from mild to severe forms. Mild can still interfere significantly with quality of life, while severe cases are characterized by potential impairment of visual function, especially if the cornea is involved [1]. Vernal Keratoconjunctivitis (VKC) is one severe chronic form of seasonally exacerbated allergic conjunctivitis. It is more common in children and young adults having an atopic background. Aside from being one of the most severe forms of ocular allergy, VKC can be considered the childhood form of allergic conjunctivitis due to the fact that the condition affects mainly children in their first decade of life and young adults [1-3]. This ocular allergy is characterized by bilateral inflammation of the palpebral conjunctiva, itching, conjunctival hyperemia and chemosis among others signs and symptoms. This disorder is usually triggered by allergens in the air, especially plant pollen, leading to seasonal exacerbations during the spring and summer months [5]. Conventionally, VKC pathogenesis has been considered as a type 1 hypersensitivity reaction, which means that it is driven primarily by IgE-mediated mast cell activation. However, recent studies have broadened the knowledge about the pathophysiology of this disease and indicate that VKC is more complex than a mere type 1 hypersensitivity disease, as very complex inflammatory processes have been shown to occur on the ocular surface [2,6]. By itself, the IgE-mast cell mediated process does not explain the entirety of the clinical and histopathological changes associated with VKC; there are other mediators and cells involved in the initiation and perpetuation of the ocular allergic inflammation [2].

Therapeutic measures are required to control signs and symptoms of VKC and to avoid the initiation of longstanding permanent inflammatory sequela that may lead to fibro vascular reaction, new collagen deposition, tissue remodeling and permanent visual damage. There are a variety of drugs currently used to treat VKC, including anti-histamines, mast-cell stabilizers, dual acting agents, corticosteroids and immunomodulators or immunosuppressants, but none have been shown to be sufficient to treat all aspects of the complex pathophysiology of VKC [1,7].

Topical steroids are the conventional treatment for practically all severe kind of allergic conjunctivitis. They are also the most effective drugs to control the signs and symptoms of VKC [1,8]. However, the long term use of steroids has clinical limitations due to their side effects and may result in severe complications such as ocular hypertension, glaucoma, cataract and secondary infections [7]. Additionally, there is a subset of VKC patients that become refractory to the corticosteroids treatment over time. Consequently, the development of agents that could be used effective and chronically without serious adverse effects is very important, for the management of chronic ocular disorders such as VKC [1]. This is where immunomodulatory agents such as Cyclosporine A (CsA) may be important.

CsA inhibits T cells proliferation and prevents the release of proinflammatory cytokines by blocking the activity of calcinerurin, a ubiquitous enzyme found in cell cytoplasm that is implicated in the control of replication of the genes for IL-2 and other pro-inflammatory cytokines.

There is a body of evidence supporting the use of CsA as a treatment for VKC. Several basic and clinical trials have demonstrated that CsA in oleic emulsion decreases the signs and the symptoms of this allergic disease [9,10]. Topical CsA treatment also has an advantage in that it lacks the serious adverse ocular effects often seen with topical corticosteroids [11].

Nonetheless, currently available systems using oils to deliver CsA are poorly tolerated and provide low bioavailability of the drug. Patients treated using these formulations of CsA have reported moderated to intense stinging, tearing, redness and swelling of lids after drop instillation [7]. CsA is a lipophilic molecule that it must be regularly dissolved in an alcohol-oil base, which causes the ocular irritation mentioned above [12,13]. However, these difficulties may be

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overcome through formulations aimed at improving the water solubility of CsA, facilitating tissue drug penetration, or by using penetration colloidal carriers (micelles) [14].

In the present study, we evaluated the safety, efficacy and tolerability of a topical aqueous solution CsA in VKC.

Patients and Methods

This was a prospective clinical study. Written informed consent was obtained from each volunteer's parent.

Patients with moderate to severe steroid dependent VKC who met the inclusion criteria according to previously established definitions were included in the study (Table 1).

VKC was diagnosed based on the presence of itching, mucus discharge, papillae on the superior tarsal conjunctiva and changes in the limbal area. The eligibility approval for all the subjects was determined after concluding the clinical evaluation in the basal visit.

The patients received the CsA 0.05% aqueous ophthalmic solution in a dosage of one drop every 12 hours in both eyes (8:00 h and 20:00 h ±1 hour) during the 180 days of the study.

All patients were evaluated by the same investigator in the screening period, as well as in the subsequent programmed follow up visits (days 2, 7, 14, 30, 60, 90, 120, 150 & 180). Consequently, on each follow-up visit, a tolerance questionnaire was applied using a verbal analog scale starting from 0 to 3 with increasing intensity of symptoms (Table 2).

For the purpose of this study, six symptoms (ocular itching, red eye, burning sensation, photophobia, tearing, and ocular foreign body sensation) were evaluated and also eight clinical signs (conjunctival hyperemia, ocular surface condition, conjunctival discharge, chemosis, Bengal rose staining, fluorescein staining, papillaes and follicles) were charted. These signs are directly related to the presence and severity of vernal conjunctivitis. Other variables (anterior segment condition, posterior segment condition) that are related to ocular health were also evaluated. The investigators at each center used identical forms to evaluate and measure these variables (referred in Table 2).

Table 1

INCLUSION CRITERIA
Patients with a clinical diagnosis of Vernal Keratoconjunctivitis
Patients of either gender, 5 years or older.
EXCLUSION CRITERIA
Patients with one blind eye.
Patients with visual acuity of 20/40 or worst in any of both eyes without a justifying cause.
Patients who are in an active stage of any other ocular inflammatory disease besides of VKC.
Patients receiving medication through topical ocular route of administration or any other that can in a very determinant way interfere in the results of the study, up to 48 hours prior to day 1 of study or until a period of time in which there are still residual effects. Such medication as systemic NSAIDs, systemic steroidal anti inflammatory drugs, systemic immunosuppressants and ocular topical steroids.
Patients with history of hypersensitivity or any medical situation that contraindicates or makes risky the use of any of the study articles or their compounds under any route of administration as well as any drug or formulation derived from them or related to them.
Contact lenses users.
Patients who cannot comply with the medical appointments or with all the protocol requirements.
Patients who disagree to participate in this clinical trial.

Table 2: Grading Scale for Ocular Signs and Symptoms in VKC study.

SYMPTOMS	0	1	2	3
Itching	No desire to rub or stretch the eye	Occasional desire to rub or stretch the eye	Frequent need to rub or stretch 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 the lid margin	Intermittent, infrequent spilling of tears over the lid margin	Constant, or nearly constant, spilling of tears over the lid margin
Foreign body sensation	Absent	Mild, similar to fine dust sensation	Moderate, similar to sand sensation, with mild tearing and blinking	Severe, similar to big foreign body sensation, with constant tearing and blepharospasm
Photophobia	No difficulty experienced	Mild 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
Stinging	Absent	Mild	Moderate	Severe
Red eye	Absent	Mild, he/she cannot observe his red eye but is told he/she has it	Moderate, he/she can observe his red eye from 30 cms in a mirror	Severe, he/she can observe his red eye from more than 30 cms in a mirror
SIGNS	0	1	2	3
Conjunctival hyperemia	Absent	Mild, in an area less than 25% of total conjunctival surface, including tarsal and bulbar	Moderate	Severe, with hyperemia in all conjunctival surface
Conjunctival discharge	Absent	Small amount of translucent or whitish discharge in the lower cul-de-sac	Moderate amount of like yellow or green-yellowish discharge in the lower cul-de-sac and in the marginal tear strip	Severe, with blood traces in the lower cul-de-sac and in the marginal tear strip

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Tarsal conjunctival papillary hypertrophy	No evidence of papillary formation	Mild papillary hyperemia	Moderate papillary hypertrophy with edema of the palpebral conjunctiva and hazy view of the deep tarsal vessel	Severe papillary hypertrophy obscuring the visualization of the deep tarsal vessels
Chemosis	Absent	Mild, in an area less than 25% of total conjunctival surface, including tarsal and bulbar	Moderate	Severe, with volume augmentation in all conjunctival surface

Basal examination

The basal examination (day 0 of the study) was carried out 7 days previous to the day 1 of the study. In this visit, the patient and their parents were asked to sign the informed consent. Demographic information, clinical history and specific symptoms were obtained. A complete ophthalmic examination including visual acuity determination (Snellen chart), biomicroscopy, intraocular pressure (IOP) measurement (Goldmann aplanation tonometer) and funduscopy under pupilary dilation was conducted. Patients meeting eligibility criteria during the basal visit were included in the study.

Follow-up visits on days 1, 2, 7, 14, 30, 60, 90, 120, 150 and 180

On each follow-up visit, visual acuity, biomicroscopy, and IOP were obtained. Funduscopy under pupilary dilation was performed only on days 90 and 180.

Results

Demographics

The mean age of the 15 VKC patients (30 eyes) was 10.25 ± 3.83 years. 10 (66.67 %) were male and 5 (33.33%) were female children. All of the patients received a 0.05% CsA solution.

Efficacy

At the end of 7 days, no statistically significant decrease was noted from baseline in mean scores of either signs ($p = 0.18$) or symptoms ($p = 0.50$) in the eyes that received cyclosporine. On the other hand, a statistically significant decrease was observed in both sign and symptom scores ($p < 0.001$, for both) of eyes that received cyclosporine at the end of 14 days. At days 30 and 90, statistically significant decrease in both sign scores and symptom scores were noted compared with baseline in the eyes that received cyclosporine eye drops ($p < 0.001$, for all).

No serious adverse effects were reported in the patients during the follow-up period. In the case report forms we did not find reports of corneal involving, nor before starting or during the clinical trial.

Discussion

An effective and safe therapy for VKC is needed to improve signs and symptoms and to prevent ocular complications. Long-term use of steroids has effective results, but steroids should be carefully administrated, and only for brief periods, to avoid their well-known adverse effects, mainly the secondary development of glaucoma [16].

The results of the present study confirm the beneficial effect of topical CsA 0.05% aqueous solution in improving the symptoms and clinical manifestations of moderate to severe allergic conjunctivitis type VKC. Further, in previous clinical studies for the topical use of CsA for allergic conjunctivitis, the drug had been administered as an oil base emulsion, while the present study used a monodisperse, stable, micelle aqueous solution, previously characterized by Quintana-Hau et al. [15]. This aqueous CsA formulation was also able to improve tolerance and compliance to the treatment.

It has been demonstrated by the abundance of Th2 cytokines in tears and serum of VKC patients that T helper type 2 cells (Th2), and their cytokines, contribute in a very crucial way to the onset and perpetuation of this disease. An altered balance between T helper type 1 (Th1) and Th2 cells and between Th1-Th2-types of cytokines is thought to be responsible of the development of ocular allergic diseases. Furthermore, conjunctival mast cells, eosinophils and macrophages, along with a wide range of cytokines, chemokines, proteases and various growth factors, play an important role in the pathogenesis of the disease [17,18]. Th2 cytokines are responsible for both hyperproduction of IgE (IL-4) and for differentiation and activation of mast cells (IL-3) and eosinophils (IL-5) [12]. The mast cells are a key cellular component and play a pivotal role in initiating the inflammatory cascade of events in allergic eye disease. Mast cells cytokines are also responsible for the initiation of this inflammation by promoting the eosinophil recruitment that infiltrate the conjunctiva and cornea in VKC. Two subtypes of mast cell have been recognized in humans based in their neutral protease content and T lymphocyte dependency. The T lymphocyte –dependent mast cell (MCT), contains only tryptase in their granules which are characterized by lattice substructure. The other subtype is the mast cell that contains both enzymes tryptase and chymase (MCTC). Patients with active VKC have a significant increase in MCT mast cells in the epithelial cells of conjunctival biopsy specimens, while normal patients have the majority of subtype MCTC mast cells [16,17,18].

Cyclosporine A, more than merely a non-specific immunomodulator, is an immunosuppressive molecule with predominant inhibitory effects against Th2 lymphocyte proliferation that acts by blocking early activation of genes specifically related to cytokines, mainly IL-2. CsA interferes with mast cell and lymphocyte mediated cytokine production and thus it has an inhibitory effect on the development of allergic disease. It is able to inhibit histamine release through a reduction in IL-5 production [9] Recently, it has been shown that CsA diminishes mast cell degranulation avoiding the release of pro-inflammatory molecules and also suppressing mast cell-white cell cytokine cascades [17,18,19]. The exact mechanism of action of CsA on mast cells is unknown, but it may be postulated that the drug modulates local IgE production by B cell by means of its effects on Th2 cells or possibly by influencing T-lymphocyte dependent mast cells [12,13,17].

Although most studies reported in the literature have used high concentrations of CsA, up to 2% for example, we considered it beneficial to use an aqueous solution with a lower concentration. We believe that the present formulation used in this study could increase bioavailability and allow higher effective concentrations of the drug in the ocular tissue without having to raise the raw concentration. This work is not the first to show the efficacy of CsA in treating ocular disease. In fact, similar findings regarding efficacy have been reported with CsA eye drops but with different concentrations and vehicles [3,6,13,19,21-24]. The first studies from the years 1991 to 2002 show a certain consistency in using CsA 2%, the highest concentration for VKC treatment; however recently the concentration of CsA eye drops has been diminishing (to a current minimal of 0.05%). These data suggest a trend towards the lowering of the CsA concentration and to changes to other vehicles that are safer and better tolerated for VKC patient [25,26].

It is important to emphasize that, in the present study; it was evident that statistical improvements were seen in the 0.05% treatment. It seems that the positive effect in VKC could be due to the suppression of T lymphocytes proliferation and also to the drug's effect on mast

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cells and eosinophils [18].

According to our results, formulations of CsA was effective, safe and well tolerated; use led to improvements in the clinical manifestations of VKC.

We did not observe any complication in the administration of CsA in our patients during the clinical trial. Additionally, the fact that CsA has been formulated in an aqueous solution increases the bioavailability of the drug in the cornea and conjunctiva.

Most of the therapeutic effect was achieved after 14 days. The initial therapeutic effect was maintained during the next 180 days.

In conclusion, topical application of a 0.05% CsA aqueous solution has been shown to be safe, effective and well tolerated in the treatment of patients with VKC. Our results are consistent with the results that Ebihara found in VKC patients with a 0.1% CsA formulation with an aqueous vehicle [27]. The use of cyclosporine 0.05% eyedrops in aqueous solution for treatment of VKC should be considered in order to prevent complications associated with the natural history of the disease. CsA could be an important alternative to steroid treatment [28].

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