Vernal keratoconjunctivitis (VKC) is a chronic, bilateral inflammation of the conjunctiva. VKC mainly affects boys in their first decade of life and the sequelae of the disease may be responsible for permanent visual impairment. Diagnosis is based on symptoms and signs including itching, photophobia, sticky mucous discharge, giant papillae on the upper tarsal conjunctiva or at the limbus, Trantas' dots, superficial keratopathy, and corneal shield ulcer [1–3]. Recent studies have documented various alterations of cornea, conjunctiva and tear film in VKC patients [4–6]. The disease was bilateral in 96.7% of the cases; all unilateral cases involved the tarsal form of VKC [7, 8]. Approximately 23% of patients had a perennial form of VKC from disease onset, and more than 60% had additional recurrences during the winter [1]. In the Mediterranean area and other temperate regions, the intensity of the disease increases in spring and summer and decreases in fall and winter [9].

The pathogenesis of the disease is not completely known. Conventionally, VKC was considered primarily a type 1 hypersensitivity reaction. However, approximately 50% of the patients with VKC have no familial or personal history of atopy, and a large proportion have negative results on the Standard allergic diagnostic tests, confirming that it is not solely immunoglobulin E (IgE)-mediated [10]. Recent studies suggest a more complex non-IgE-dependent pathogenic mechanism.

* Parts of this study has been accepted as an electronic poster at the European Society of Ophthalmology Congress, Copenhagen, Denmark.
Several studies have documented the presence of the Th2 lymphocytes subtype in tears and in conjunctival biopsy samples of patients with VKC. Histopathologically, VKC is characterized by conjunctival infiltrations with eosinophils, degranulated mast cells, basophils, plasma cells, lymphocytes, and macrophages. T cell culture from conjunctival scraping of VKC patients yielded mainly Th2-type clones. Th2-derived cytokines such as IL-4, IL-5, IL-13, growth factors and enzymes are found in the conjunctiva of VKC patients [11]. In addition, some researchers have demonstrated the possible involvement of neural factors, sex hormones and conjunctival histaminase deficiency in the pathogenesis of the disease [2, 10, 11].

Several earlier reports indicate that topical anti-inflammatory and anti-allergic eye drops are the mainstay of treatment for VKC; however, a gold standard treatment has not yet been established for this disease [3]. Topical anti-allergic and topical antihistamines are effective in reducing signs and symptoms of the disease. Non-steroidal anti-inflammatory agents also produce a beneficial effect on the course of VKC [1]. Steroids can be highly effective, but may cause unwanted elevation of intraocular pressure in steroid responders and increase the risk of corneal infection through local immunosuppression. In addition, induction of cataract and delayed wound healing can be problematic. Cyclosporine A (CsA) is a non-steroidal immunomodulator that inhibits antigen dependent T cell activation. CsA also has a direct inhibitory effect on eosinophil and mast cell activation and release of mediators, which is likely to be important in allergic inflammation [12–15].

In this placebo-controlled, randomized prospective study, we investigated the effects of topical CsA 0.05% on the clinical signs and symptoms of patients with VKC.

**Material and Methods**

This is a randomized placebo-controlled trial, which comprises 62 patients with moderate or severe VKC admitted to the Department of Ophthalmology, Faculty of Medicine, Dicle University, between January 2010–January 2011. The diagnosis of VKC was made, based on the patients’ history and the presence of typical clinical signs and symptoms. The clinical forms of the disease was considered to be tarsal in 67.9% of cases, limbal in 19.8% of cases, mixed in 12.3% of cases. Scores of the signs and symptoms were obtained from each patient at the beginning and at the end of the study. A clinical score (0–3 – 0 = absent; 3 = severe) was given, considering the severity of the following eye symptoms and signs. Symptoms included itching, tearing, discomfort, mucous discharge, and photophobia. Signs, however, included bulbar conjunctival hyperemia, upper tarsal conjunctival papillae, punctate keratitis, corneal neovascularization, cicatrizating conjunctivitis, and blepharitis (Table 1). The patients were classified as having severe VKC if the score was 5 or more points for one eye for each scale, and as moderate if the score was between 3 and 5 points.

Patients were randomly selected according to their application to our clinic to receive either topical CsA 0.05% (Restasis, Allergan, Waco, TX, USA) or preservative-free artificial tears (Refresh Tears, Allergan, Waco, TX, USA) for a period of 4 weeks, 4 times daily. The two preparations, which were applied to the patients, were closed with the same cover by different number to be prevented from bias by the researcher. All patients had been treated with a variety of topical medications before enrollment. If patients were using topical corticosteroid, anti-allergic or anti-histaminergic eye drops, this medication was discontinued 1 week before the start of the trial. None of the patients had earlier taken systemic steroids and other anti-inflammatory or immunosuppressive drugs. The study was performed according to the guidelines of the Declaration of Helsinki; furthermore, we obtained approval for the study from the local Ethics Committee.

**Statistical Analysis**

In the study, Chi-square ($\chi^2$) test was used to compare sex and age rates between the two groups. In addition, Independent Student’s $t$ test was used to analyse the matched sample. Data was analysed by using SPSS 15.0 statistical package for Windows (SPSS Inc., Chicago, IL, USA) program. Two-sided $p$ values were considered statistically significant at $p \leq 0.05$.

**Results**

The characteristics of the patients in the two groups were compared in Table 2. Overall, 69.3% were males, and the mean age of patient was 9.8 years (range, 7–19). There was no statistically significant difference between the two groups in terms of sex or mean age ($p > 0.05$). Of the 62 patients with VKC, 31 patients were assigned to receive 0.05% topical CsA and 31 to receive placebo. The median severity grades for signs and symptoms as well as composite scores before and after the treatment period are shown in Table 3. When
Table 1. Grading of symptoms and signs of vernal keratoconjunctivitis

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td>no desire to rub or scratch the eye</td>
<td>occasional desire to rub or scratch</td>
<td>frequent need to scratch or rub the eye</td>
</tr>
<tr>
<td>Tearing</td>
<td>normal tear production</td>
<td>positive sensation of fullness of the conjunctival sac without tears spilling over the lid margin</td>
<td>intermittent, infrequent spilling of tears over the lid margin</td>
</tr>
<tr>
<td>Discomfort (including burning, stinging, and foreign body sensations)</td>
<td>absent</td>
<td>mild</td>
<td>moderate</td>
</tr>
<tr>
<td>Discharge</td>
<td>no abnormal discharge</td>
<td>small amount of mucoid discharge noted in the lower cul-de-sac</td>
<td>moderate amount of mucoid discharge noted in the lower cul-de-sac and in the marginal tear strip; presence of crust upon awakening</td>
</tr>
<tr>
<td>Photophobia</td>
<td>no difficulty experienced</td>
<td>mild difficulty with light causing squinting</td>
<td>moderate difficulty, necessitating dark glasses</td>
</tr>
<tr>
<td><strong>Signs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar conjunctival hyperemia</td>
<td>absent</td>
<td>mild</td>
<td>moderate</td>
</tr>
<tr>
<td>Tarsal conjunctival papillary</td>
<td>no evidence of papillary formation</td>
<td>mild papillary hyperemia</td>
<td>moderate papillary hypertrophy with edema of the palpebral conjunctiva and hazy view of the deep tarsal vessel</td>
</tr>
<tr>
<td>Punctate keratitis (superficial epithelial keratitis and punctate staining of the cornea with fluorescein)</td>
<td>no evidence of punctate keratitis</td>
<td>one quadrant of punctate keratitis</td>
<td>two quadrants of punctate keratitis</td>
</tr>
<tr>
<td>Neovascularization of cornea (new vessel formation, crossing the limbus onto the clear cornea by 2 mm)</td>
<td>no evidence of new vessel formation</td>
<td>presence of neovascularization in 1 quadrant of cornea</td>
<td>presence of neovascularization in 2 quadrants of cornea</td>
</tr>
<tr>
<td>Cicatrizing conjunctivitis (superficial scarring of the conjunctiva)</td>
<td>no evidence of cicatrization</td>
<td>presence of subepithelial fibrosis</td>
<td>presence of fornix foreshortening</td>
</tr>
<tr>
<td>Blepharitis (hyperemia and edema of eyelid skin with meibomian gland dysfunction)</td>
<td>no evidence of blepharitis</td>
<td>presence of mild redness and edema of the eyelid with meibomian gland dysfunction</td>
<td>moderate inflammation with hyperemia, scales, and scurf of eyelid skin and tooth-paste phenomenon</td>
</tr>
</tbody>
</table>
Discussion

VKC is a chronic, seasonally exacerbated allergic inflammatory disease of the ocular surface, affecting mainly children and adolescents. Males are typically more affected than females. In the present group of VKC patients, the male: female ratio was 2.2:1. This tendency is confirmed in the literature. In the studies reported earlier, at the time of diagnosis, 83% of patients were under 10 years of age and 4% were over 20 years of age [7, 16]. In the present study, however, we determined the mean age of the patients as 9.8.

Management of VKC is primarily aimed at reducing symptoms and preventing serious vision threatening sequelae. Steroids can be highly effective, but there are risks of glaucoma, superinfection with viruses and bacteria due to local immunosuppression, delayed wound healing, and cataract induction warrant cautious use of topical steroids [17–24]. Therefore, non-steroidal medications are desirable for the treatment of VKC as alternative, but new topical agents with dual anti-allergic activity (mast cell stabilizers and antihistamine) may also be used for long-term treatment of allergic inflammation to alleviate signs and symptoms of the disease [21, 25, 26]. A recent study has reported that topical interferon alpha 2b treatment seems to offer a safe and effective alternative for the treatment of refractory vernal keratoconjunctivitis for a brief period [27].

CsA, a macrolide antibiotic, has been isolated from the soil fungus Tolypocladium inflatum. CsA is effective in controlling ocular inflammation, blocking Th2 lymphocyte proliferation, and IL-2 production. It also inhibits histamine release from mast cells and basophils, and through a reduction of IL-5 production, it may reduce the recruitment and the effects of eosinophils on the conjunctiva [1, 15, 28, 29]. Moreover, the therapeutic efficacy of CsA in VKC, a conjunctival hyperproliferative disorder, seems to be related to the drug’s efficacy in reducing conjunctival fibroblast proliferation rate and IL-1β production. Multiple studies have reported a beneficial effect of topical cyclosporine to relieve symptoms of VKC in patients with different severity grades of the disease [2, 30–33]. In a recent study, both topical treatment of 0.1% FK-506 ophthalmic ointment and 2% CsA eye drops have been reported to be effective for VKC. They also reported that FK-506 ophthalmic ointment twice daily brought about an improvement of symptoms of VKC similar to that of CsA eye drop four times daily [32].

In the field of ophthalmology, topically applied CsA in various oil-based solvents was first used to inhibit experimental corneal allograft reaction in the early 1980s [34, 35]. Later, the drug was found

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Cyclosporine group (N:31) mean ± SD</th>
<th>Placebo group (N:31) mean ± SD</th>
<th>Difference X²/t p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9/31</td>
<td>10/31</td>
<td>0.147 0.713</td>
</tr>
<tr>
<td>Male</td>
<td>22/31</td>
<td>21/31</td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>9.9 ± 2.11</td>
<td>9.7 ± 2.63</td>
<td>-0.238 0.812</td>
</tr>
</tbody>
</table>

<p>| Table 3. Mean scores of symptoms and signs of patients before and after treatment period |
|----------------------------------------------|------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Cyclosporine group (N:31) mean ± SD</th>
<th>Placebo group (N:31) mean ± SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>At entry symptom score</td>
<td>8.96 ± 2.11</td>
<td>9.10 ± 2.01</td>
<td>0.247</td>
<td>0.807</td>
</tr>
<tr>
<td>At entry sign score</td>
<td>8.62 ± 1.53</td>
<td>8.72 ± 2.16</td>
<td>0.182</td>
<td>0.854</td>
</tr>
<tr>
<td>At end of the study symptom score</td>
<td>4.87 ± 1.17</td>
<td>8.43 ± 2.08</td>
<td>6.139</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At end of the study sign score</td>
<td>5.56 ± 1.27</td>
<td>8.28 ± 2.16</td>
<td>4.422</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
useful in patients with various inflammatory ocular surface disorders [2, 22, 36–38]. Topical CsA 2% dissolved in maize oil has been shown to be beneficial for many years in the management of severe allergic eye disease [39]. However, side effects, whether related to the oil solvent or the CsA itself, were common. Lid skin maceration, allergic reaction, and marked blurring of vision after drop instillation were attributed to the vehicle; however, intense stinging was a side effect of the CsA. Indeed, this is a well-known side effect that limits its clinical use [22]. Topical CsA has been effective in treating patients with severe resistant VKC since 1986 [40]. Several studies have reported the effectiveness of CsA 2% eyedrops in improving signs and symptoms of VKC [30, 41, 42]. In recent years, several studies have reported a good response to low-concentrated topical cyclosporine to relieve symptoms of VKC [2, 22, 33, 43]. The mechanism(s) of the beneficial effect of topical CsA in VKC patients, however, is not clear. In vitro studies have demonstrated that CsA inhibits activation and proliferation of T lymphocytes via blockage of IL-2 gene expression. Topical CsA treatment has also been shown to reduce the T lymphocyte population in conjunctival biopsy specimens of VKC and atopic keratoconjunctivitis (AKC) patients. Both studies concluded that topical CsA treatment either in VKC or AKC patients significantly reduced the number of total lymphocytes infiltrating the conjunctiva and reduced the CD4+ subset only slightly and insignificantly [28]. Akpek et al., [22] in their placebo-controlled study, reported that CsA 0.05% had a steroid sparing and beneficial effect on the scores of symptoms and signs during treatment, without any side effects in patients with AKC. However, Daniell et al., [15] in their placebo-controlled trial, failed to show any beneficial effect in terms of final clinical score with the addition of topical CsA 0.05% in patients with steroid-dependent allergic eye disease. Nevertheless, they found that patients in the CsA treated group showed significantly greater improvement over time in lid margin thickening, inferior conjunctiva papillae, inferior and superior conjunctival hyperemia, and corneal tearfilm deficiency. In our study, there was a significant improvement for post-treatment scores of signs and symptoms in CsA group with respect to placebo group. We verified that VKC was successfully treated with cyclosporine 0.05% for 4 weeks, 4 times daily. No side effects attributed to topical CsA 0.05% treatment were encountered, suggesting that low-concentrated topical CsA is of benefit in the treatment of patients with VKC. Spadavecchia et al., [2] in their placebo-controlled study, reported that a lower concentration of CsA (1.25% and 1%) was safe and well tolerated as well as significantly improved the ocular signs and symptoms of VKC. This also suggests that lower concentration of tested cyclosporine was effective for almost complete recovery of severe forms of VKC. This is an important finding, considering that cyclosporine is an immunosuppressive drug and that the use of low concentrated eyedrops might avoid systemic effects. Similarly, Ozcan et al. [43] showed that topical CsA 0.05% had a significant beneficial effect on patients with VKC and AKC. In our study, topical low concentrated cyclosporine was found to be effective in treatment of VKC, and no systemic effects were observed. The results of earlier studies are compatible with our findings [2, 30, 43, 45]. For instance, in a recent randomized controlled study, it was shown that topical 0.05% cyclosporine was safe and effective for the long-term prevention of VKC relapses [44].

In conclusion, we used cyclosporine A 0.05% eyedrops in the treatment of patients with VKC. Topical CsA 0.05% was found to be effective in the treatment of patients with VKC. No side effects that can be attributed to topical CsA 0.05% treatment were encountered.

References


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