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Original Article

Cyclosporine 0.05% Ophthalmic Emulsion for Dry Eye in Korea: A Prospective, Multicenter, Open-Label, Surveillance Study

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Purpose: To assess the effectiveness and tolerability of cyclosporine ophthalmic emulsion (CsA) 0.05% in patients with moderate to severe dry eye disease in Korea.

Methods: This was a prospective, multicenter, open-label, surveillance study of 392 Korean patients with moderate to severe dry eye disease who were treated with CsA 0.05% for three months. An assessment of effectiveness was performed at baseline, and after 1, 2, and 3 months. The primary effectiveness outcomes were changes in ocular symptoms and Schirmer score. The secondary effectiveness outcomes were a change in conjunctival staining, use of artificial tears, global evaluation of treatment, and patient satisfaction. The primary safety outcome was the incidence and nature of adverse events.

Results: A total of 362 patients completed the study. After three months, all ocular symptom scores were significantly reduced compared to the baseline values, while the Schirmer scores were significantly increased relative to baseline ($p < 0.0001$). After three months, there were significant reductions from baseline in conjunctival staining ($p < 0.01$) and use of artificial tears ($p < 0.0001$). According to clinicians' global evaluations, most patients (>50%) experienced at least a 25% to 50% improvement in symptoms from baseline at each follow-up visit. The majority of patients (72.0%) were satisfied with the treatment results, and 57.2% reported having no or mild symptoms after treatment. The most common adverse events were ocular pain (11.0%).

Conclusions: Our findings indicate that CsA 0.05% is an effective and tolerable treatment for dry eye disease in Korean clinical practice.

Key Words: Cyclosporine, Dry eye syndromes, Ophthalmic solutions

Dry eye disease is a common condition that is particularly prevalent in Asia and that has a high burden of disease for patients. Indeed, dry eye disease is one of the most common conditions encountered by ophthalmologists [1] and accounts for 15% to 40% of cases at eye clinics across Asia [2-4]. Asian populations may experience a higher prevalence of dry eye disease [5-9] than do Caucasian populations [10-12]. Further, there is evidence suggesting that the incidence of dry eye disease in Asia may be increasing [13]. This increasing incidence is concerning as dry eye disease poses many significant burdens for patients, including direct and indirect costs [14,15], reduced quality of life [16], limitations to daily activities, reduced social and physical functioning, and decreased workplace productivity [15]. Given the high prevalence of dry eye disease in Asia and the potential burden of this disease on patients, it is important to clinicians that approved treatments meet expectations in clinical practice.

Dry eye disease is a multifactorial disease for which there are several treatments. Ocular inflammation and changes in tear osmolarity are the two factors that underlie dry eye disease and can cause ocular discomfort, visual disturbance, tear film instability, and damage to the ocular surface [17]. The recommended treatments for mild dry eye disease are lifestyle changes and the use of artificial tears [18,19]. However, patients with moderate to severe disease may require anti-inflammatory medications or surgery [20]. Cyclosporine ophthalmic emulsion (CsA) 0.05% is a topical antiinflammatory that has been approved by the United States Food and Drug Administration for treatment of moderate to severe dry eye

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disease. Several clinical trials have investigated the efficacy and tolerability of CsA 0.05% for treatment of dry eye disease in the United States [21-23] and in Korea [24,25]. While these clinical trials have established the efficacy of CsA 0.05% in select patient populations, only two, small-scale (less than 30 patients) Korean studies [26,27] have investigated the clinical effectiveness of CsA 0.05% for treatment of dry eye disease. Additional evidence from a larger population is needed to verify whether CsA 0.05% is effective and tolerable in clinical practice. The aim of our study was to assess the effectiveness and tolerability of CsA 0.05% in patients with moderate to severe dry eye disease in a Korean clinical practice setting.

Materials and Methods

Study design and setting

This prospective, multicenter, open-label, surveillance study was conducted between August 2006 and March 2009 at 26 clinical practice sites in Korea. At the time this study was conducted, there was no local requirement for ethics approval. All patients provided voluntary, signed informed consent before the commencement of any study-related procedures.

Study participants

The main inclusion criteria for enrollment were age >18 years; a diagnosis of moderate to severe dry eye disease (based on clinicians' standard clinical practices); symptomatic dry eye disease; and nonresponsiveness to conventional treatment such as artificial tear drops, gels, ointments, and punctal plugs.

The main exclusion criteria were use of systemic or topical CsA in the previous 90 days; anticipated use of any temporal punctal plugs during the study; women who were pregnant, planning a pregnancy, or lactating; end-stage lacrimal disease or dry eye disease caused by destruction of goblet cells; active ocular infections; and suspected hypersensitivity to any of the ingredients in the CsA formulation.

Study protocol

The study comprised a baseline visit and three follow-up visits after 1, 2, and 3 months of treatment. One drop of CsA 0.05% (Restasis®; Allergan Inc., Irvine, CA, USA) was applied every 12 hours to each eye as monotherapy or adjunct therapy. The use of artificial tear substitutes was continued in all applicable patients. New treatments, including any eyedrops or punctal plug, were not added after enrollment.

At each study visit, patients were examined according to the clinicians' standard clinical practices. In addition, symptoms of ocular discomfort (i.e., stinging/burning, itching, sandiness/grittiness, blurred vision, light sensitivity, pain, and soreness), Schirmer scores, use of artificial tears, global evaluation of improvement, and adverse events were recorded at each visit. There was an optional measurement of conjunctival staining (Oxford score) performed at baseline and after three months of treatment. Clinicians' also assessed global evaluation of improvement in symptoms of dry eye disease from baseline at each follow-up visit according to the following categories; >90% improvement, 75% to 90% improvement, 25% to 75% improvement, condition unchanged, and condition worsened. Patient satisfaction was assessed through the completion of a four-question survey at the final study visit. The exit survey comprised the following questions: How are your chronic dry eye symptoms?; With Restasis®, how does your chronic dry eye condition now affect your normal daily activities?; Overall, how satisfied are you with Restasis®?; How quickly did Restasis® start working to relieve your chronic dry eye symptoms? Scoring for each question was based on a scale bar from 0 (no symptom) to 10 (maximum symptom experienced).

Outcome measures

The primary effectiveness outcome measures included changes in symptom scores (rated on a scale of 0 [no symptoms] to 4 [always have symptoms]) and Schirmer scores (mm, with or without anesthesia [28]). The secondary effectiveness outcome measures included change in conjunctival staining (rated on a scale of 0 to 5), use of artificial tears, global evaluation of the treatment, and patient satisfaction with the treatment. The primary safety outcome measure was the incidence and nature of adverse events.

Statistical analysis

All data are summarized using frequency distributions and/or descriptive summary statistics (mean and standard deviation [SD]). The effectiveness analysis population included all patients who completed the study. The tolerability analysis population included all patients who were enrolled in the study. All statistical analyses included data for the treated eye or the mean data for both eyes (if patients received treatment for both eyes). Schirmer scores (with or without anesthesia) for all visits were compared using a repeated measures analysis of variance. For all other effectiveness variables, the changes from baseline data were compared using a paired sample *t*-test. Patients with missing baseline values were excluded from the analyses, and missing post-treatment data were inferred by carrying forward the subsequent observation. For all analyses, statistical significance was set at $p \leq 0.05$. Statistical analyses were performed using SAS ver. 9.1.3 (SAS Inc., Cary, NC, USA).

Results

A total of 392 patients were enrolled in the study and in-

cluded in the safety and tolerability analysis; 362 (92.3%) patients completed the study and were included in the effectiveness analysis. The main reasons for study discontinuation were loss to follow-up (n = 21 patients) and adverse events (n = 6 patients). Patients were predominantly female, and slightly less than half were 50 years of age or older (Table 1). Most patients had been diagnosed with moderate to severe dry eye disease for one to five years, and approximately one-quarter had undergone a previous ocular surgery.

Treatment with CsA 0.05% significantly improved symptom, Schirmer, and staining scores and reduced the use of artificial tears. There were significant reductions from baseline in all mean ocular symptom scores (stinging/burning, itching, sandiness/grittiness, blurred vision, light sensitivity, pain or soreness) after one month of treatment ($p < 0.0001$) (Table 2) and which persisted for up to three months of treatment ($p < 0.0001$). There were significant increases from baseline in mean Schirmer scores both with and without anesthesia at each study visit ($p < 0.0001$) (Fig. 1). There were no significant differences between Schirmer scores with and without anesthesia. The baseline conjunctival staining score (Oxford score ± SD) was 3.2 ± 2.2, while the corresponding score after three months of treatment was 2.8 ± 2.8. After three months of treatment, the mean percentage (±SD) reduction from baseline in conjunctival staining score was -12.8 ± 64.7% ($p < 0.01$), and there was a significant reduction from baseline in mean (± SD) use of artificial tears (5.6 ± 5.7 and 4.0 ± 4.5 drops/day for baseline and three months, respectively; $p < 0.0001$).

According to clinicians' global evaluations of treatment with CsA 0.05%, the majority of patients experienced an at least 25% to 50% improvement at each visit (Fig. 2). A greater percentage of patients experienced a 75% to 90% improvement after three months of treatment than after either one or two months of treatment. Dry eye disease worsened in three, five, and two patients after one, two, and three months of treatment, respectively.

According to the exit survey findings, patients generally reported that CsA 0.05% treatment provided relief from dry eye symptoms, and that their experience with the treatment was positive (Fig. 3). Specifically, most patients (57.2%) reported that they had no or mild symptoms of dry eye disease (score of 0 to 4 out of 10, 214 / 374 patients) (Fig. 3A). Most patients (55.2%) also reported that their dry eye disease had no or little effect on their normal daily living (scores 0 to 4 out of 10; 206 / 373 patients) (Fig. 3B). The majority of patients (72.0%) were satisfied or very satisfied with CsA 0.05% treatment (scores of 5 to 10 out of 10; 270 / 375 pa-

Table 1. Baseline demographics and disease characteristics of patients with dry eye disease

Characteristic, n (%)	n = 392
Female*	279 (73.8)
Age ≥50 yr†	174 (45.2)
Duration of disease‡	
Newly diagnosed	14 (3.6)
<1 yr	84 (21.9)
1-5 yr	197 (51.3)
6-10 yr	55 (14.3)
>10 yr	34 (8.9)
Previous ocular surgery§	97 (26.0)

*Data not available for 14 patients; †Data not available for 7 patients; ‡Data not available for 8 patients; §Data not available for 19 patients.

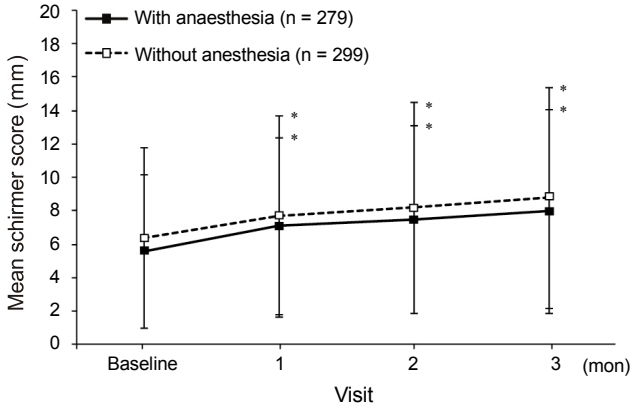

Fig. 1. Schirmer scores for patients with dry eye disease who were treated with cyclosporine ophthalmic emulsion 0.05% for three months. Schirmer scores (change from baseline, mm) were assessed with and without anesthesia. Data are presented as mean ± standard deviation. *$p < 0.0001$ compared with baseline (both with and without anesthesia).

Table 2. Symptom scores* for patients with dry eye disease who were treated with cyclosporine ophthalmic emulsion 0.05% for three months

Symptom	Baseline	1 mon	2 mon	3 mon
Stinging/burning (n = 331)	2.2 ± 1.4	1.6 ± 1.2†	1.3 ± 1.1†	1.1 ± 1.1†
Itching (n = 312)	1.2 ± 1.3	0.8 ± 1.0†	0.6 ± 0.9†	0.5 ± 0.8†
Sandiness/grittiness (n = 338)	2.4 ± 1.2	1.7 ± 1.1†	1.3 ± 1.0†	1.0 ± 0.9†
Blurred vision (n = 325)	2.0 ± 1.4	1.4 ± 1.2†	1.0 ± 1.1†	0.8 ± 1.0†
Light sensitivity (n = 312)	2.0 ± 1.5	1.4 ± 1.4†	1.1 ± 1.3†	0.9 ± 1.2†
Pain or soreness (n = 323)	2.0 ± 1.3	1.5 ± 1.1†	1.1 ± 1.1†	0.9 ± 1.0†

All data are presented as mean ± standard deviation.
*A score of 0 = no symptoms, a score of 4 = always have symptoms; †$p < 0.0001$ for the study visit compared with baseline.

tients) (Fig. 3C). For most patients, relief from dry eye symptoms began three to five weeks after commencing CsA 0.05% treatment (209 / 356, 58.7%) (Fig. 3D).

Treatment with CsA 0.05% was well-tolerated, and very few patients discontinued the study because of adverse events. There were a total of 97 adverse events during the study. The most common adverse events (incidence >5%) were ocular pain (43 / 392 patients, 11.0%) and ocular irritation (23 / 392 patients, 5.9%). Six patients (1.5%) discontinued the study due to adverse events, including three patients (0.8%) with ocular irritation, two patients (0.5%) with ocular pain, and one patient (0.3%) with ocular hyperemia. There were no serious adverse events during the study.

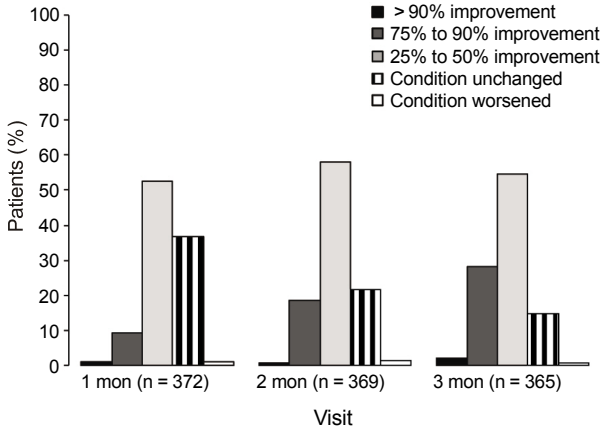

Fig. 2. Clinicians' global evaluations of improvement in patients with dry eye disease who were treated with cyclosporine ophthalmic emulsion 0.05% for three months. Data are presented as the percentage of patients with >90% improvement, 75% to 90% improvement, 25% to 50% improvement, condition unchanged, or condition worsened.

Discussion

Our study findings suggest that CsA 0.05% is an effective and tolerable treatment for moderate to severe dry eye disease in Korean clinical practice. We found that treatment with CsA 0.05% for three months led to improvements in both objective (Schirmer and conjunctival staining scores) and subjective (symptom scores and artificial tear use) measures of dry eye disease. Favorable tolerability was indicated by the very low percentage of patients who discontinued the study, the absence of serious adverse events, and high patient satisfaction with treatment. The results of our study extend the efficacy findings of earlier clinical trials [24,25] and clinical practice studies [26,27] of CsA 0.05% in Korean patients with moderate to severe dry eye disease and support the use of CsA 0.05% for treatment of moderate to severe dry eye disease in Korean clinical practice.

Consistent with previous studies, we found that CsA 0.05% was an effective treatment for dry eye disease as indicated by changes in symptom, Schirmer, and conjunctival staining scores, artificial tear use, and clinicians' global evaluations of treatment. The statistically significant reductions in symptom scores in our study are similar to those found in phase II [22] and phase III [21] clinical trials of CsA 0.05%. Likewise, the significant improvements in mean Schirmer scores in our study are similar to those found in Korean patients after short-term (six to eight weeks [25]) and lon-

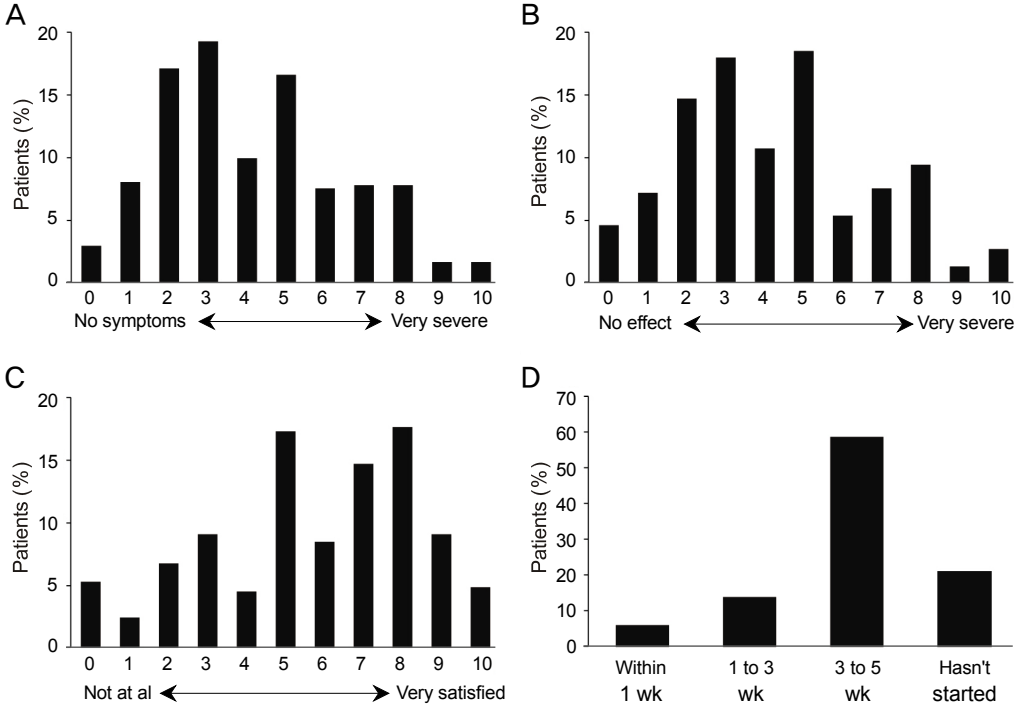

Fig. 3. Exit survey results for patients with dry eye disease who were treated with cyclosporine ophthalmic emulsion 0.05% (Restasis®) for three months. Data are presented as percentage of patients responding to the following questions: 'How are your chronic dry eye symptoms?' (A); 'With Restasis®, how does your chronic dry eye now affect your normal daily activities? (B); 'Overall, how satisfied are you with Restasis®?' (C); and 'How quickly did Restasis® start working to relieve your chronic dry eye symptoms?' (D).

gerterm (up to three months [24,26,27]) CsA 0.05% treatment. Importantly, our study included a much larger number of patients (n = 362) in the effectiveness analyses compared with those in the two previous clinical practice studies performed in Korea (n = 23 [27] and n = 26 [26]). The improvements in Schirmer scores (with and without anesthesia), conjunctival staining score, artificial tear use, and the clinicians' global evaluations of treatment in our study are in agreement with those determined in a randomized controlled trial of CsA 0.05% [21]. The significant reduction in artificial tear use in our study is also consistent with findings from a previous study, in which the majority (>60%) of patients reported decreased artificial tear use after 60 days of CsA 0.05% treatment [29]. Together, these findings confirm that CsA 0.05% reduces the symptoms of dry eye disease. Therefore, we speculate that CsA 0.05% partially resolves the pathophysiological changes that cause dry eye disease. However, additional studies are needed to confirm this conclusion.

We found that treatment with CsA 0.05% was generally well-tolerated, and that most patient experiences with CsA 0.05% were positive. The most common adverse events in our study (ocular irritation and pain) are known adverse reactions to CsA 0.05% [20-22]. The proportion of patients who discontinued treatment because of adverse events (1.5%) in our study is similar to the proportion (2.2%) in a phase II trial of CsA 0.05% [21]. Moreover, the patient-reported experience with CsA 0.05% in our study is similar to that in clinical practice studies performed in the United States [29,30]. Our findings regarding patientreported rating of symptoms (i.e., no or mild symptoms) and the effect of dry eye on daily activities after three months of CsA 0.05% treatment are similar to those of a clinical practice study in which patients reported a 30% reduction in symptom severity and improvement in their abilities to perform daily activities after two months of treatment with CsA 0.05% [29]. Likewise, our patientreported satisfaction findings are similar to those of a self-reported compliance study in which compliant patients had a mean satisfaction score of 7.7 (0 = not at all satisfied, 10 = very satisfied) after two months of treatment with CsA 0.05% [30].

Our study has a number of limitations that must be acknowledged. First, interpretation of our findings is limited by the single-arm, open-label study design. However, the clinical practice setting enhances the external validity of our findings, as does the prospective, multicenter, surveillance design. Second, as our patients were not grouped according to the cause of dry eye disease, we were unable to determine which patients may (or may not) respond to CsA 0.05% treatment. Third, we cannot exclude the possibility that improvements in dry eye disease were caused by the emulsion vehicle or that subjective improvements were a reflection of patients' providing socially desirable answers. However, the results of two randomized controlled trials have shown that CsA treatment results in significantly greater improvements in dry eye disease than does treatment with the emulsion vehicle [21,22]. In addition, the fact that there was agreement between clinician and patient evaluations of treatment (i.e., treatment resulted in improvement) would argue against the possibility that patients provided socially desirable answers. Finally, we did not assess patient adherence to study medication, document the type of artificial tear use, or use a validated questionnaire for assessing patient satisfaction with treatment. Despite these limitations, the use of multiple objective (i.e., Schirmer and conjunctival staining scores) and subjective measures (i.e., symptom scores and artificial tear use) has enabled us to provide clinically relevant evidence of the effectiveness of CsA 0.05% for treatment of dry eye disease.

In conclusion, the effectiveness and tolerability findings of our study support the use of CsA 0.05% for the treatment of moderate to severe dry eye disease in the Korean clinical practice setting.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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