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Topical Cyclosporine 0.05% for the Prevention of Dry Eye Disease Progression

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Abstract

Purpose: To assess the prognosis of dry eye in patients treated with cyclosporine 0.05% or artificial tears by using the International Task Force (ITF) guidelines.
Methods: This was a single-center, investigator-masked, prospective, randomized, longitudinal trial. Dry eye patients received twice-daily treatment with either cyclosporine 0.05% (Restasis®; Allergan, Inc., Irvine, CA; $n = 36$) or artificial tears (Refresh Endura®; Allergan, Inc., Irvine, CA; $n = 22$) for 12 months. Disease severity was determined at baseline and month 12 according to the consensus guidelines developed by the ITF. Dry eye signs and symptoms were evaluated at baseline and months 4, 8, and 12.
Results: Baseline sign and symptom scores and the proportion of patients with the disease severity level 2 or 3 were comparable in both groups ($P > 0.05$). At month 12, 34 of 36 cyclosporine patients (94%) and 15 of 22 artificial tear patients (68%) experienced improvements or no change in their disease severity ($P = 0.007$) while 2 of 36 cyclosporine patients (6%) and 7 of 22 artificial tears patients (32%) had disease progression ($P < 0.01$). Cyclosporine 0.05% improved Schirmer test scores, tear breakup time, and Ocular Surface Disease Index scores throughout the study, with significant ($P < 0.01$) differences compared with artificial tears being observed at months 8 and 12.
Conclusions: Treatment with cyclosporine 0.05% may slow or prevent disease progression in patients with dry eye at severity levels 2 or 3.

Introduction

Patients with dry eye disease suffer from ocular irritation often accompanied by vision impairment, which limits important daily activities and negatively impacts quality of life (QoL).[1–3] The prevalence of dry eye disease is estimated to be from 5% to >30%.[4,5] The largest US cross-sectional survey studies, the Women's Health Study (WHS) and the Physician Health Study (PHS), indicated that the prevalence of dry eye disease among women and men aged over 50 years is 7.8% and 4.3%, respectively. Using this prevalence data, ~4.9 million Americans aged over 50 years are estimated to be affected by dry eye disease.[6,7]

The diagnosis and treatment of dry eye is challenging.[8] The Wilmer Eye Institute at Johns Hopkins University recently invited the International Task Force (ITF) of 17 dry eye experts to create guidelines for the diagnosis and treatment of dry eye disease by using a Delphi consensus technique.[9] The ITF panel categorized dry eye disease severity into 4 levels (Table 1), with increasing severity from 1 to 4, and developed consensus treatment guidelines. The level of disease severity was considered the most important factor in determining the appropriate range of therapeutic options.[9] While counseling, education, and preserved artificial tears were recommended for the management of patients diagnosed at severity level 1, unpreserved artificial tears, topical cyclosporine, and/or corticosteroids were recommended for patients at severity level 2. Punctal plugs, oral tetracyclines, systemic immunomodulators, and surgery were reserved for the management of dry eye patients diagnosed at severity levels 3 and 4.[9]

A key recommendation of the ITF panel was the use of topical anti-inflammatory therapy in patients with clinically apparent ocular surface inflammation.[9] This recommendation stemmed from the recent evidence indicating that inflammation plays a major role in the disease etiology and may be a unifying mechanism that underlies dry eye

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Table 1. Criteria Used to Determine the Levels of Dry Eye Severity According to ITF Guidelines[8]

	Symptoms	*Signs*	*Staining*
Level 1	Mild to moderate	Mild/moderate conjunctival signs	None
Level 2	Moderate to severe	Tear film signs, visual signs	Mild punctate corneal and conjunctival staining
Level 3	Severe	Corneal filamentary keratitis	Central corneal staining
Level 4	Severe	Corneal erosions, conjunctival scarring	Severe corneal staining

Disease severity is categorized into 4 levels based on the severity of symptoms and signs. At least one sign and one symptom of each category should be present to qualify for the corresponding level assignment.

disease.[10–12] Therefore, it was suggested that the chronic use of safe anti-inflammatory therapies that normalize tear film composition early in the disease process may have the potential to slow, prevent, or reverse dry eye progression.[13]

Ophthalmic cyclosporine 0.05% emulsion (Restasis®; Allergan, Inc., Irvine, CA) is the only anti-inflammatory medication approved by the Food and Drug Administration to increase tear production in dry eye patients.[14] In T lymphocytes, cyclosporine binds to cyclophilin A and inhibits calcineurin-catalyzed dephosphorylation of the nuclear factor for T-cell activation.[15,16] Cyclosporine thereby inhibits IL-2 transcription, which upon secretion stimulates T-cell division by a self-propagating autocrine and paracrine loop.[16] In humans, topical administration of cyclosporine 0.05% has been shown to decrease the number of activated T cells and expression of inflammatory markers in the conjunctiva of dry eye patients.[17,18] These findings suggest that topical cyclosporine 0.05% targets the underlying inflammatory processes in dry eye disease. Therefore, chronic treatment with cyclosporine 0.05% may offer the potential to alter the course of dry eye disease.

Wilson and Stulting recently evaluated the clinical applicability of the ITF guidelines.[13] Physicians participating in that study successfully implemented the ITF guidelines for diagnosis and treatment of dry eye patients.[13] Using the ITF guidelines, this study was designed to assess the prognosis of dry eye disease in patients treated with cyclosporine 0.05% or artificial tears.

Methods

Study design

This was a single-center, investigator-masked, randomized, prospective, longitudinal clinical trial. The study was approved by the Western institutional review board in Olympia, WA, and was registered with ClinicalTrials.gov (identifier # NCT00567983). Inclusion criteria were of age 18 years or older, diagnosis of dry eye without lid margin disease or altered tear distribution and clearance, and a disease severity of level 2 or 3 as defined by the ITF guidelines (Table 1).[9] Primary exclusion criteria were prior use of topical cyclosporine 0.05% within the last year, topical or systemic use of anti-inflammatory or anti-allergy medications, active ocular infection or inflammatory disease, or uncontrolled systemic disease that can exacerbate dry eye disease. Patients who wore contact lenses were also excluded from the study. All participating patients signed a written consent form before initiation of the study-specific procedures.

Patients were randomly assigned in a 3:2 ratio to twice-daily treatment with either cyclosporine 0.05% or artificial tears (Refresh Endura®; Allergan, Inc., Irvine, CA) in both eyes for 12 months. The randomization ratio was an empirical estimation due to lack of adequate epidemiological information to conduct power calculations prior to initiating the study. Randomization was performed by a statistical program and was overseen by the research coordinator. Patients were enrolled in the study and initiated therapy after screening and randomization on the same day at the baseline visit (month 0). All patients were allowed to utilize rescue artificial tears as needed if discomfort was experienced. The primary objective of this study was to assess the potential of topical cyclosporine 0.05% therapy to halt or slow disease progression relative to control at month 12 based on the ITF severity categorization (Table 1). The secondary outcome variables were the changes in dry eye signs and symptoms. The study was conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

Disease severity and dry eye signs and symptoms

Disease severity was assessed according to the ITF consensus guidelines at baseline and month 12 (Table 1).[9] Patients were evaluated for signs and symptoms of dry eye by Schirmer test with anesthesia, tear breakup time (TBUT), ocular surface staining, and Ocular Surface Disease Index (OSDI) at baseline (month 0) and after receiving the study treatments at months 4, 8, and 12. In each study visit, TBUT was evaluated first, followed by ocular surface staining and Schirmer test, respectively. The TBUT was measured using fluorescein dye. Ocular surface damage was assessed by the Oxford method using sodium fluorescein to stain the cornea and lissamine green to stain the nasal and temporal bulbar conjunctiva.[19] The scoring scale for ocular staining was 0 to 5 in cornea, 0 to 5 in temporal conjunctiva, and 0 to 5 in nasal conjunctiva, with 0 representing no staining and 5 representing severe staining. These individual scores were then summed for the total Oxford score, which ranged from 0 to 15. The change from baseline was calculated by subtracting the baseline score from the months 4, 8, and 12 scores. The symptoms of ocular irritation and their impact on visual functioning was assessed by OSDI, a validated 12-item questionnaire, on a scale of 0 to 100 with 0 representing asymptomatic and 100 representing severe debilitating dry eye disease.[20]

Goblet cell density

The density of goblet cells in bulbar conjunctiva was evaluated at baseline and month 12. Impression cytology was performed in both eyes after evaluation of TBUT, ocular staining, and Schirmer test. Goblet cells were collected on cellulose acetate filters (HAWP 304 FO; Millipore Corp., Billerica, MA). The filters were fixated in glacial acetic acid, formaldehyde, and 70% ethanol and subsequently stained with a modified periodic acid–Schiff Papanicolaou stain. Goblet cells were counted in 5 (400 × 400 mm) representative microscopic fields on each filter.[21]

Statistical analyses

Patients who completed 12 months of treatment were included in the analyses. The results were presented as mean ± SD. Intergroup comparisons of categorical variables were performed using the chi-square or Fisher's exact test. Continuous variables were analyzed using nonparametric tests (Mann–Whitney tests for between-group comparisons and Wilcoxon signed rank tests for within-group comparisons). A P value < 0.05 was considered a statistically significant difference. Statview software (SAS Institute, Cary, NC) was used for all analyses.

Results

Patient disposition and disease characteristics

Of 74 patients enrolled between February 2006 and January 2007, 58 patients completed the 12-month study and were included in the analyses (Table 2). Forty-one patients were female and 17 patients were male. The distribution of patients with disease severity of level 2 or 3 was similar in both treatment groups at baseline. Approximately two-thirds of dry eye patients in both groups were diagnosed at severity level 2, while one-third of patients was diagnosed at severity level 3 (Table 2). There were no significant between-group differences in the mean age ($P = 0.667$) or distribution of gender ($P = 0.800$).

Sixteen patients discontinued the study. The number of discontinuations was significantly higher among patients treated with artificial tears compared with those treated with cyclosporine 0.05% (11 vs. 5; $P = 0.028$; Table 2). Of 11 discontinuations in the artificial tear group, 9 patients discontinued the study because of discomfort upon instillation, and 2 patients were lost to follow-up or moved. Seven of these patients had a disease severity of level 2, and 4 patients had a disease severity of level 3. Of the 5 discontinuations in the cyclosporine group, 2 patients discontinued the study because of discomfort upon instillation while 3 were lost to follow-up or moved. Three of these patients had a disease severity of level 2, and 2 patients had a disease severity of level 3.

Disease severity

At month 12, significantly more patients treated with artificial tears had more severe signs and symptoms of disease than did those treated with cyclosporine 0.05% and, therefore, were categorized as progressing to a higher disease severity level (7 of 22 [32%] patients vs. 2 of 36 [6%], respectively; $P < 0.007$; Fig. 1). In contrast, a greater percentage of patients treated with cyclosporine 0.05% had less severe signs and symptoms of disease and were categorized as improving to a lower disease severity level (14 of 36 [39%] patients vs. 4 of 22 [18%] patients, respectively). This difference, however, was not statistically significant ($P = 0.098$). When combined with those who did not have a change in the disease severity levels at month 12, significantly more patients treated with cyclosporine 0.05% had either improvements or no change in disease severity than did those treated with artificial tears (34 of 36 [94%] patients vs. 15 of 22 [68%] patients, respectively; $P = 0.007$).

Schirmer test scores

The mean baseline Schirmer test score was 7.7 ± 0.6 mm in patients randomized to artificial tears and 7.9 ± 1.2 mm

Table 2. Patients' Disposition and Disease Characteristics

	Artificial Tear	*Cyclosporine 0.05%*
Patients (*n*)		
Enrolled in study	33	41
Discontinued study	11[a]	5[b]
Completed study	22	36
Mean age[c] ± SD, years	48.2 ± 6.3	47.5 ± 5.9[d]
Range	39–59	30–57
Gender[c], *n* (%)		
Female	16 (73)	25 (69)[e]
Dry eye severity at baseline,[c] *n* (%)		
Level 2	15 (68)	24 (67)
Level 3	7 (32)	12 (33)

[a]Nine patients discontinued the study because of discomfort upon instillation. Two patients were lost to follow-up or moved. $P = 0.028$ compared to patients who received cyclosporine 0.05%.

[b]Two patients discontinued the study because of discomfort upon instillation. Three patients were lost to follow-up or moved.

[c]For patients who completed 12-month study.

[d]$P = 0.667$ compared to the mean age of patients who received artificial tears.

[e]$P = 0.800$ compared to the artificial tear group.

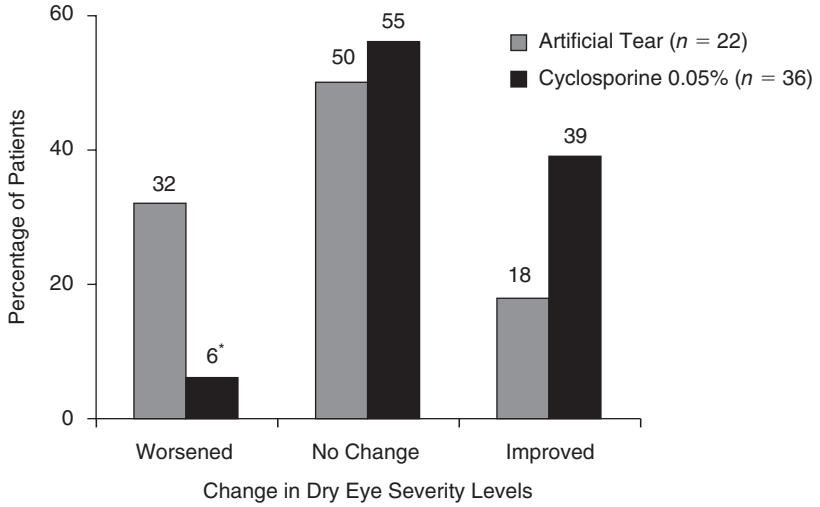

FIG. 1. Changes in dry eye severity at month 12 compared with baseline. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Disease severity was assessed according to the International Task Force (ITF) consensus guidelines at baseline and month 12. The changes in disease severity levels were categorized as worsened, no change, or improved when a patient had a, respectively, higher, same, or lower disease severity level at month 12 compared with baseline. *$P < 0.007$ compared with the treatment with artificial tears.

in patients randomized to cyclosporine 0.05% ($P = 0.625$). Patients treated with artificial tears did not have a significant change in their Schirmer test scores throughout the study, whereas those treated with cyclosporine 0.05% had increasingly higher mean Schirmer test scores at each follow-up visit. The mean Schirmer test scores of patients treated with cyclosporine 0.05% were significantly greater than those of patients treated with artificial tears at month 8 (9.1 ± 1.0 mm vs. 7.5 ± 1.1 mm; $P < 0.001$) and month 12 (9.8 ± 1.0 mm vs. 7.6 ± 1.1; $P < 0.001$; Fig. 2).

TBUT

The mean baseline TBUT was 5.0 ± 0.8 s in patients randomized to artificial tears and 4.9 ± 0.8 s in patients randomized to cyclosporine 0.05% ($P = 0.550$). The mean TBUT of patients treated with artificial tears slightly decreased throughout the study, whereas patients treated with cyclosporine 0.05% had increasingly longer mean TBUT at each follow-up visit (Fig. 3). The mean TBUT of patients treated with cyclosporine 0.05% was significantly longer than those of patients treated with artificial tears at months 8 (6.2 ± 1.4 s vs. 4.6 ± 0.6 s; $P = 0.001$) and 12 (6.5 ± 1.1 s vs. 4.6 ± 0.7 s; $P < 0.001$).

Ocular surface staining scores

At baseline, patients randomized to cyclosporine 0.05% or artificial tears had similar mean Oxford staining scores

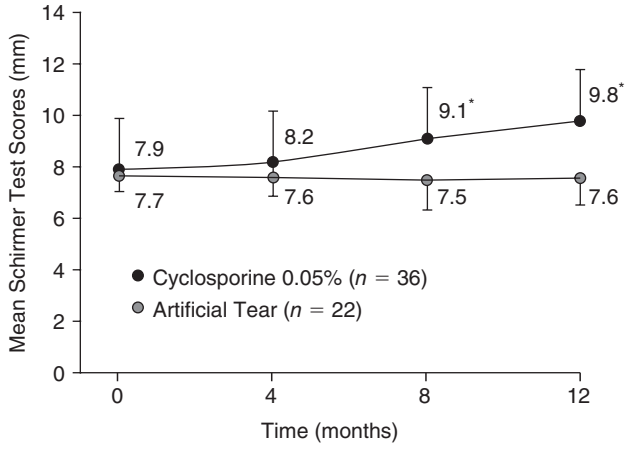

FIG. 2. Schirmer test scores. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Schirmer I test was performed with anesthesia at indicated study visits. *$P < 0.001$ compared with patients treated with artificial tears.

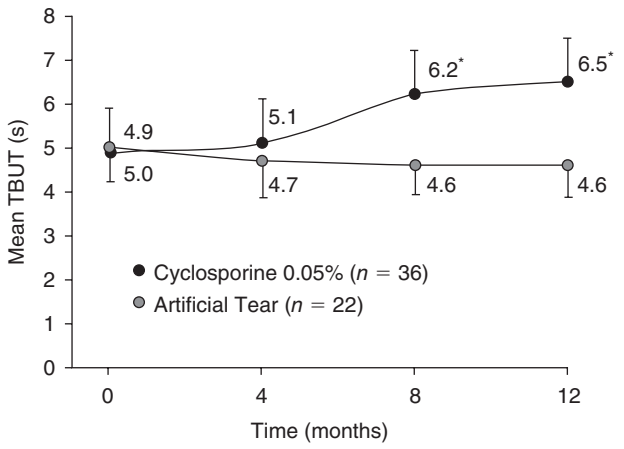

FIG. 3. TBUT. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Tear breakup time Tear breakup time (TBUT). was measured with fluorescein dye at indicated study visits. *$P \leq 0.001$ compared with patients treated with artificial tears.

Table 3. Mean Ocular Surface Staining Scores

	Artificial tear (n = 22)	*Cyclosporine 0.05% (n = 36)*	*P*
Baseline	7.86 ± 1.13 (NA)	8.44 ± 0.94 (NA)	0.056 (NA)
Month 4	7.73 ± 0.99 (–0.12 ± 0.64)	8.31 ± 0.95 (–0.13 ± 0.35)	0.036 (0.787)
Month 8	7.53 ± 1.01 (–0.25 ± 0.94)	7.78 ± 0.93 (–0.64 ± 0.63)	0.576 (0.087)
Month 12	7.54 ± 0.91 (–0.32 ± 0.94)	7.28 ± 1.28 (–1.19 ± 1.36)	0.223 (0.011)

Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Ocular surface damage was assessed at indicated times by the Oxford method. The mean changes from baseline and corresponding *P* values are indicated in brackets.[a] The change from baseline was calculated by subtracting the baseline score from the month 4, 8, or 12 scores.

NA = not applicable.

[a]The changes form baseline were paired comparisons. If a data point was missing, the baseline was also excluded from that calculation.

(8.4 ± 0.9 vs. 7.9 ± 1.1; $P = 0.056$; Table 3). At month 4, patients treated with cyclosporine 0.05% had significantly higher mean staining scores than those treated with artificial tears (8.3 ± 1.0 vs. 7.7 ± 1.0; $P < 0.036$). There was no between-group difference in ocular staining at months 8 and 12 (Table 3). Nonetheless, the mean improvement from baseline in the ocular staining scores of patients treated with cyclosporine 0.05% was significantly greater than of those treated with artificial tears at month 12 (1.2 ± 1.4 vs. 0.3 ± 0.9, respectively; $P = 0.011$; Table 3). These findings indicate that cyclosporine 0.05% improved ocular surface staining significantly more than did artificial tears at month 12 compared with baseline.

OSDI Scores

Patients randomized to artificial tears or cyclosporine 0.05% had similar OSDI scores at baseline (19.1 ± 1.9 and 18.9 ± 2.9, respectively; $P = 0.571$). The mean OSDI scores of patients treated with artificial tears remained unchanged throughout the study (Fig. 4). Patients treated with cyclosporine 0.05%, however, had increasingly lower OSDI scores at each study visit, with the scores at months 8 and 12 being significantly lower than those of patients treated with artificial tears (17.4 ± 3.4 vs. 19.6 ± 1.6 at month 8; $P = 0.011$ and 14.9 ± 4.2 vs. 19.7 ± 2.0 at month 12; $P < 0.001$).

Goblet cell density

At baseline, patients randomized to artificial tears or cyclosporine 0.05% had similar mean goblet cell density in bulbar conjunctiva (95.8 ± 12.5 cells and 93.6 ± 9.4 cells, respectively; $P = 0.446$; Fig. 5). By month 12, goblet cell density was significantly higher in patients treated with cyclosporine 0.05% than those treated with artificial tears (116.8 ± 14.8 cells vs. 92.7 ± 11.0 cells; $P < 0.001$).

Safety

No adverse events attributable to the study medications were reported other than discomfort upon instillation during the study.

Discussion

Dry eye is a multifactorial disorder of the tears and the ocular surface that results in tear film instability and symptoms of discomfort and visual disturbance.[22] Traditionally, treatment of dry eye has been palliative and largely based on over-the-counter artificial eyedrops and lubricating ointments.[23] The vast majority of patients seek new therapies after using several over-the-counter products over years.[23] However, it is not known if dry eye severity progresses through the course of disease during the years. Recently developed ITF guidelines provide a clinical standard for

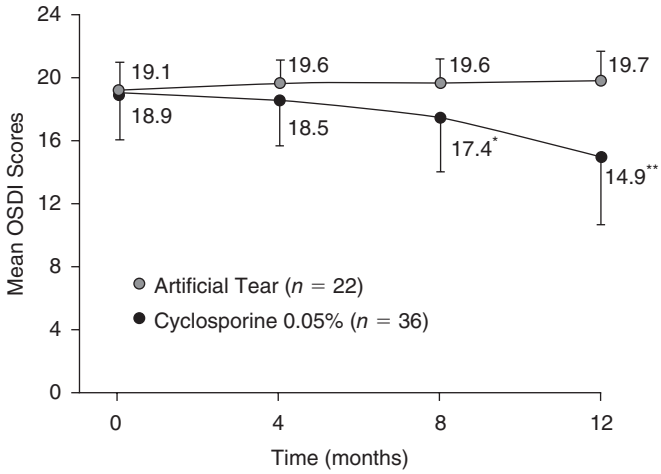

FIG. 4. Ocular Surface Disease Index (OSDI) scores. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Dry eye signs and symptoms were assessed by the self-reported OSDI questionnaire at indicated study visits. *$P < 0.011$ and **$P < 0.001$ compared with patients treated with artificial tears at months 8 and 12, respectively.

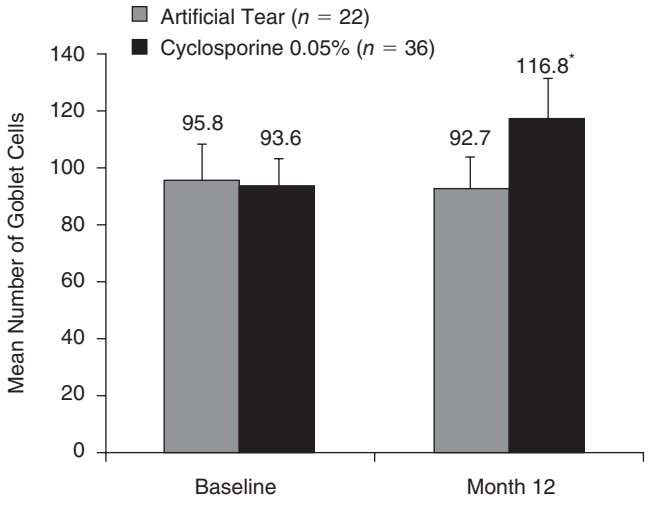

FIG. 5. Conjunctival goblet cell density at baseline and month 12. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Conjunctival goblet cells were collected by impression cytology and counted following staining with modified periodic acid–Schiff Papanicolaou at baseline and month 12. *$P < 0.001$ compared with artificial tears at month 12.

categorization of dry eye patients based on the disease severity and thereby allow longitudinal studies to evaluate the progression of dry eye disease. This study not only sought to assess the progression of dry eye disease in patients treated with artificial tears, but also evaluated the impact of cyclosporine 0.05% therapy in modulating the course of dry eye disease.

Treatment of dry eye patients with cyclosporine 0.05% improved Schirmer test scores, TBUT, conjunctival goblet cell density, ocular surface staining scores, and OSDI scores throughout the study. Treatment with artificial tears was not effective in improving the signs and symptoms of dry eye disease. Similar to these findings, several other studies demonstrated that cyclosporine 0.05% significantly increased tear production, decreased the intensity of ocular staining, and decreased the severity of symptoms in patients with moderate to severe dry eye.[24,25] A recent prospective study indicated that cyclosporine 0.05% therapy significantly improved signs and symptoms in patients at all stages of dry eye disease: mild, moderate, and severe.[26] Other studies have shown that treatment with cyclosporine 0.05% also increased conjunctival goblet cell density in patients with dry eye disease.[21,27]

Physicians participating in a study to develop treatment regimens based on the ITF consensus guidelines for newly diagnosed dry eye patients chose to treat over 40% of patients at severity level 1 with the severity level 2 treatments (ie, unpreserved tears and topical cyclosporine 0.05%).[13] Hence, the use of ITF guidelines resulted in greater focus on treatment of the disease at early stages. This shift in the patterns of anti-inflammatory therapy use stems from the notion that early interruption of inflammatory cycles may be instrumental in preventing disease progression.[13] The impact of dry eye in limiting daily activities and causing discomfort is known to become clinically more significant as the disease progresses from mild to moderate in severity.[2]

In addition to alleviating dry eye signs and symptoms, topical cyclosporine 0.05% therapy appears to be capable of slowing the rate of disease progression. Reassessment of patients at the end of the study period (month 12) indicated that a greater number of cyclosporine patients compared with the artificial tear patients (94% vs. 68%) had improvements or no change in their disease severity status, and far fewer (6% vs. 32%) experienced disease progression. These findings suggest the progressive nature of dry eye disease and indicate that dry eye patients may benefit from cyclosporine 0.05% therapy by achieving disease stabilization or a slower rate of progression. A recent retrospective study provided evidence that cyclosporine 0.05% therapy may change the course of dry eye disease. In that study, 8 chronic dry eye patients diagnosed at severity level 2 or 3 were free of signs and symptoms of dry eye disease for a minimum of 1 year after completing a 6- to 72-month course of cyclosporine 0.05% therapy.[28]

In some patients, dry eye is a difficult-to-treat disease that requires long-term anti-inflammatory therapy. The safety profile of a topical anti-inflammatory agent and its suitability for long-term use is, therefore, a key factor in successful management of dry eye disease. Topical corticosteroids have been effective in alleviating the signs and symptoms of dry eye following short-term use (2–4 weeks).[29,30] Prolonged administration of topical corticosteroids is complicated by the associated adverse events including elevation of intraocular pressure, defects in visual acuity and fields of vision, cataract formation, and increased risk of ocular infections.[29,31] Topical cyclosporine 0.05%, however, appears to be safe for a long-term use. Several clinical studies demonstrated that cyclosporine 0.05% was well tolerated for up to 3 years with most adverse events being transient in nature and mild to moderate in severity.[24,25,32]

The present study had a number of limitations. The sample size was small, as this was a pilot study to assess the feasibility of the study design. It should also be noted that the differences between the treatment groups reported in this study can be applied only to the use of Refresh Endura® as the artificial tears. Other artificial tears may have variable efficacies in alleviating the signs and symptoms of dry eye.

Strategies to treat dry eye disease are evolving as our understanding of dry eye as a tear volume insufficiency condition is changing to a disease of abnormal tear film composition with proinflammatory characteristics.[10,33,34] The findings of the current study are the first evidence indicating that dry eye can be progressive in patients treated with artificial tears alone, whereas topical anti-inflammatory therapy with cyclosporine 0.05% may slow or prevent the disease progression in patients with dry eye at severity level 2 or 3. Large-scale, controlled studies are warranted to confirm these findings.

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