

Evaluation of Topical Cyclosporine for the Treatment of Dry Eye Disease

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Objective: To evaluate the use of topical cyclosporine, 0.05% (Restasis; Allergan Inc, Irvine, California), for the treatment of mild, moderate, and severe dry eye disease unresponsive to artificial tears therapy.

Methods: This was a prospective clinical study. One hundred fifty-eight consecutive patients with dry eye disease unresponsive to artificial tears therapy were divided into 3 groups of disease severity: mild, moderate, and severe. Patients were evaluated using the Ocular Surface Disease Index for symptomatic improvement, tear breakup time, fluorescein staining, lissamine green staining, and Schirmer testing. Patients were observed

for 3 to 16 months. The main outcome measure was improvement in disease.

Results: Forty-six of 62 patients with mild dry eye disease (74.1%), 50 of 69 with moderate disease (72.4%), and 18 of 27 with severe disease (66.7%) showed improvement, with 72.1% improving overall.

Conclusions: Topical cyclosporine shows beneficial effects in all categories of dry eye disease. Symptomatic improvement was greatest in the mild group and the best results in improvement of disease signs were in patients with severe dry eye disease.

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A TOPICAL VERSION OF CYCLOSPORINE (Sandimmune; Sandoz Pharmaceuticals, East Hanover, New Jersey), a highly specific immunomodulator that primarily affects T lymphocytes, is used for treating dry eye disease caused by insufficient tear production. Topical cyclosporine does not inhibit wound healing or produce lens changes,^{1,2} which gives this drug a wide safety profile.³ In a multicentered randomized trial,⁴ topical cyclosporine, 0.05% (Restasis; Allergan Inc, Irvine, California), was reported to significantly improve the signs and symptoms of dry eye disease in patients with aqueous deficiency and keratoconjunctivitis sicca. Other studies further confirmed these findings by showing a statistically significant decrease in the levels of both inflammatory cells and markers in the conjunctival epithelium with a dramatic increase in the number of goblet cells.⁵⁻⁷ There were no systemic adverse effects from cyclosporine and no detectable serum levels in the trial.^{4,8} Long-term evaluation of cyclosporine has demonstrated that the drug may occasion-

ally halt progression of chronic dry eye disease in some patients and may be associated with a cure of signs and symptoms in another subset of patients with chronic dry eye disease.⁹

Prior studies with cyclosporine were only directed at patients with moderate to severe disease; we wished to include a cohort of patients with mild disease. The purpose of this study was to evaluate the effect of cyclosporine on treating mild, moderate, and severe dry eye disease that was unresponsive to artificial tears therapy.

METHODS

One hundred fifty-eight consecutive patients with dry eye disease unresponsive to artificial tears therapy were evaluated using the Ocular Surface Disease Index (OSDI) for symptomatic improvement and with fluorescein staining, lissamine green staining, tear breakup time (TBUT), and Schirmer testing for improvement of signs of the disease. All patients were followed up for 3 to 16 months and all tests were repeated at all visits.

Patients with chief complaints consistent with dry eye disease had a complete evaluation to determine if they met inclusion (**Table 1**)

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Table 1. Study Inclusion Criteria

Age ≥ 21 y
Best-corrected visual acuity $\geq 20/80$ OU
Ocular Surface Disease Index score ≥ 0.25 , unless patient had Sjögren syndrome or thyroid autoimmune disease
Participant understood and gave signed informed consent
Available for follow-up for ≥ 3 mo
Willing and able to cooperate with protocol requirements
Agreed to use a reliable form of contraception if female and of child-bearing potential
If the Schirmer test with anesthesia result was 0 mm of wetting, a Schirmer 1 test without anesthesia was performed; if this reading was 0 mm of wetting, then a Schirmer 2 was performed and a score of 3 mm or more of wetting was required; nasal stimulation was performed if the result of the Schirmer 2 test was 0 mm.

Table 2. Study Exclusion Criteria

Wore contact lenses (unless discontinued use ≥ 30 d before receiving study drug)
Ocular surgery within the past 3 mo
Active ocular allergies
Did not undergo a washout period of all excluded medications, including tetracycline antibiotics (including doxycycline and minocycline), during the 30 d before receiving study medication, or was expected to require the concomitant use of excluded medications during the course of the study
Use of corticosteroids, either systemically or topically, or other immunosuppressive agents 30 d before study enrollment
Current infections of the anterior segment or uveitis
Any disease of the eye leading to diffuse loss of conjunctiva, including ocular pemphigoid, chemical burns, Stevens-Johnson syndrome, and hypovitaminosis A
Any active ocular diseases, excluding glaucoma, other than blepharitis
Used or anticipated using another investigational drug or device during the 30 d before study entry or during the course of the study
History of hypersensitivity to cyclosporine
Pregnant, nursing, attempting to conceive, or not using a reliable form of contraception

and exclusion (**Table 2**) criteria. At study initiation, all patients underwent a comprehensive ocular examination, including ocular and systemic history, slitlamp evaluation, TBUT testing, fluorescein lissamine green staining, and the Schirmer test with anesthesia.

The OSDI consists of 12 questions measuring dry eye symptoms, each scored by the patient from 0 to 4, with a maximum of 48 points, which supplies the denominator. The numerator is the patient's score, with 0 being the minimum (OSDI score, 0) and 48 the maximum (OSDI score, 1). A score of 0.25 or greater is considered clinically significant and consistent with dry eye disease.

Corneal fluorescein staining was performed using a slitlamp cobalt blue filter 1 minute after fluorescein was added to the tear film. The intensity of corneal staining was recorded using the scale for each area (**Figure 1**). Scores from areas 1, 2, 3, and 4 of each eye were summed to obtain the fluorescein staining summary score. Scores from area 5 were used for safety evaluation only and were not considered in the summary score.

To measure TBUT, a fluorescein sodium strip (Fluorets; Smith and Nephew, Romford, England) moistened with a drop of nonpreserved saline solution (Unisol; Alcon, Ft Worth, Texas) was applied to the inferior palpebral conjunctiva. The precorneal tear film was examined with a biomicroscope with an $\times 10$ objective, and the elapsed time before the initial breakup, rup-

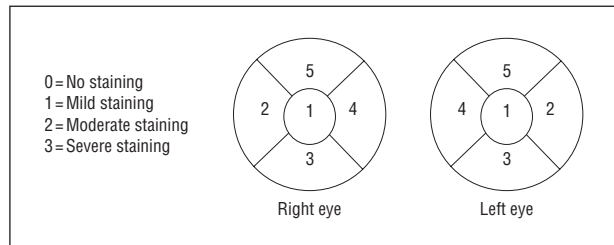


Figure 1. Diagram and scale used to measure intensity of corneal staining in patients with dry eye disease.

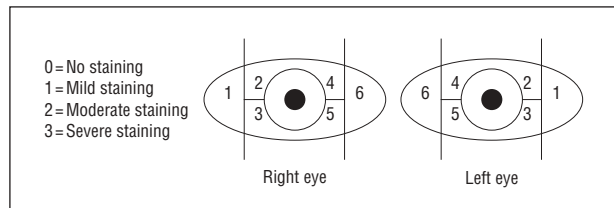


Figure 2. Diagram and scale used to measure intensity of lissamine green, 1%, staining in patients with dry eye disease.

Table 3. Demographic and Follow-up Data of Study Patients

| Characteristic | Dry Eye Disease Severity | | |
|---|--------------------------|-----------------|---------------|
| | Mild (n=62) | Moderate (n=69) | Severe (n=27) |
| Age, mean (range), y | 57 (23-78) | 66 (28-85) | 68 (55-88) |
| Sex, M/F, No. | 15/47 | 21/48 | 4/23 |
| Follow-up, mean (range), mo | 8 (3-16) | 8 (3-16) | 10 (3-16) |
| No. of patients lost to follow-up in first 2 wk | 5 | 4 | 2 |
| No. of patients lost to follow-up before 3-mo visit | 2 | 1 | 1 |
| Total No. of patients lost to follow-up | 7 | 5 | 3 |

ture of the tear film, or formation of dry spots was recorded. The test was performed 3 times for each eye and the results were averaged. An instantaneous TBUT was defined as 0 seconds.

To evaluate lissamine green staining, 1 drop of lissamine green solution, 1%, was applied to each eye. The degree of lissamine green staining was graded in each of 3 areas indicated in **Figure 2**. Scores from the areas were added for each eye and the totals were summed to give the lissamine green staining summary score.

To perform the Schirmer basic secretion tear test, eyes were anesthetized with 1 drop of proparacaine (Alcaine; Alcon) and a standard Schirmer test strip was placed in the temporal one-third of the lower eyelid before closing eyes for 5 minutes. The strips were removed and the length of the wet portion was measured in millimeters to determine the Schirmer test value.

The patients were grouped into 3 dry eye categories: mild, moderate, and severe (**Table 3**). The mild dry eye disease group exhibited minimal dry eye symptoms, including shortened TBUT; trace, or a score of 0 on, fluorescein corneal staining; and trace, or a score of 0 or 1 on, lissamine green conjunctival staining. Patients with moderate dry eye disease had nearly instantaneous TBUTs, fluorescein and lissamine green staining positive for the disease, and mildly decreased scores for Schirmer tests with anesthesia. In the severe dry eye disease group, patients had 0-second TBUTs, a score of at least 1 to 2 on fluorescein staining, positive lissamine green staining, decreased

tear meniscus, and a decreased Schirmer testing result of less than 4 mm in at least 1 eye, with or without anesthesia.

Meibomian gland disease was defined as inspissation of the meibomian gland orifices and neovascularization of the eyelid margins and was common in all groups, increasing with disease severity. All patients were counseled regarding their dry eye disease. During this session, the inflammatory nature of chronic dry eye disease was carefully explained to the patients. One drop of cyclosporine, 0.05%, twice daily was prescribed to each eye. The patients were encouraged to continue using preservative-free artificial tears. They were also instructed, when indicated, how to perform eyelid hygiene.¹⁰ The main focus was the use of cyclosporine in treating the inflammatory component of their dry eye disease. The mechanism of action of cyclosporine was discussed, and patients were given written material with illustrations documenting the effectiveness of the drug in its original therapeutic trials.^{4,8} The need for at least a 3-month trial period to fully gauge the effectiveness of this therapy was stressed to each patient. All patients were advised to contact us and return at any time should problems arise and in 3 months for a follow-up examination after their initial evaluations. Patients were also advised that burning on application of cyclosporine was common and usually disappeared after the first 2 weeks of therapy.

Statistical analysis of the data was performed using GraphPad Prism software (GraphPad Software Inc, La Jolla, California). All groups of data were first tested for normality, ie, gaussian distribution. If the data were normally distributed, the parametric test (*t* test for paired data) was used to compare differences in the data. If the data were not normally distributed, the nonparametric test (Wilcoxon matched-pairs test) was used.

RESULTS

There were 62 patients in the mild disease group, 69 in the moderate group, and 27 in the severe group (additional demographic data can be found in Table 3). Of the 158 patients evaluated, 15 patients (9.4%) failed to complete 3 months of treatment with cyclosporine and were counted as treatment failures (7 in the mild group, 5 in

the moderate group, and 3 in the severe group) (Table 3). None of these 15 patients had a follow-up OSDI evaluation. For the purpose of this study, they were removed from statistical analysis of the OSDI results. Most of the patients who dropped out (*n*=7) did so because of the burning on application of the medication during the first 2 weeks of therapy. A smaller number of patients in each group stopped therapy because of a variety of reasons, including blurred vision, itching, pain, lack of a positive effect, and expense of therapy. The number of punctal plugs in the patients varied with disease severity (mild, 6 plugs [11%]; moderate, 41 plugs [64%]; and severe, 26 plugs [96%]).

Of the various systemic diseases noted, only 2 were tabulated: Sjögren syndrome and thyroid autoimmune disease (Table 4). These 2 were used because of their association with keratoconjunctivitis sicca.

The mean OSDI scores at baseline were 0.40 for the mild group (range, 0.00-0.875); 0.42 for the moderate group (range, 0.00-0.932), and 0.39 for the severe group (range, 0.00-1.00) (Table 5 and Figure 3). The overall mean OSDI score at initiation was 0.41.

The OSDI scores were evaluated by within-group comparisons of change in OSDI score measured with paired-sample *t* tests, using a 2-tailed null hypothesis and an a priori α level of .05. Analysis of TBUT and Schirmer test results were also performed using a paired-sample *t* test. We used the nonparametric Wilcoxon matched-pairs test to analyze the fluorescein and lissamine staining results.

The OSDI scores show that most patients who completed the initial 3 months of therapy had their symp-

Table 4. Systemic Diseases of Study Patients

| Characteristic | Dry Eye Disease Severity | | |
|-------------------------------|--------------------------|-----------|----------|
| | Mild | Moderate | Severe |
| Patients with SS, No. (%) | 2 (3.5) | 6 (9.4) | 9 (37.5) |
| Patients with TAD, No. (%) | 10 (16.3) | 12 (17.4) | 9 (37.5) |
| Patients with SS and TAD, No. | 0 | 1 | 4 |
| Patients with SS or TAD, % | 19.8 | 24.4 | 62.5 |

Abbreviations: SS, Sjögren syndrome; TAD, thyroid autoimmune disease.

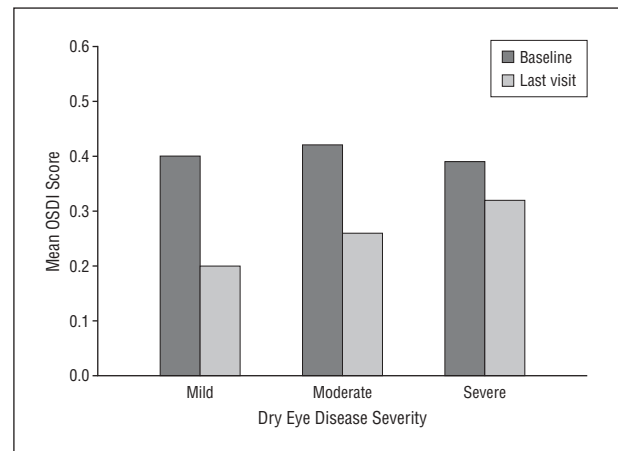


Figure 3. Mean Ocular Surface Disease Index (OSDI) scores at baseline and after treatment with cyclosporine, 0.05%, in patients with mild, moderate, and severe dry eye disease. The OSDI score=patient score divided by 48 (possible points).

Table 5. Dry Eye Disease Symptom Evaluation Using the Ocular Surface Disease Index (OSDI)

| OSDI Result | Dry Eye Disease Severity | | | Overall |
|--|--------------------------|-----------|-----------|------------|
| | Mild | Moderate | Severe | |
| Baseline score, mean | 0.40 | 0.42 | 0.39 | 0.41 |
| Score after treatment, mean | 0.20 | 0.26 | 0.26 | 0.24 |
| Percentage decrease in score | 50 | 38.2 | 33.3 | 40.1 |
| Patients with improved scores, No. (%) | 44 (80) | 45 (70.3) | 15 (62.5) | 104 (72.7) |

toms reduced. In the mild and moderate dry eye disease groups, 44 of 55 (80%) and 45 of 64 (70.3%) patients, respectively, showed an improvement in OSDI scores ($P < .001$, for both groups), while 15 of 24 patients in the severe group (62.5%) showed improvement ($P < .015$). Overall, 104 of 143 had improved scores (72.7%) ($P < .001$). Overall, there was a 40.1% decrease in mean OSDI scores ($P < .001$); 6.67% reported a worsening of their OSDI score. Twenty-two percent of patients reported that their symptoms did not change, as their scores did not vary by more than 0.02.

Mean Schirmer test results (length of wet portion of test strip) at baseline were 8.67 mm in the mild group, 6.33 mm in the moderate group, and 2.37 mm in the severe group. Mean Schirmer test results after treatment were 9.23 mm in the mild group ($P < .109$), 7.64 mm in the moderate group ($P < .015$), and 3.33 mm in the severe group ($P < .05$). Significance was obtained in the moderate ($P < .012$) and severe groups ($P < .047$) but not in the mild group ($P < .109$).

The TBUT decreased in each group as severity increased. At baseline, mean TBUT was 1.21 second (range, 0-5 seconds) in the mild group, 0.27 second (range, 0-5 seconds) in the moderate group, and 0.00 second in the severe group. After treatment, mean TBUT was 3.34 seconds (0-10 seconds) in the mild group (10 seconds was considered the upper limit; $P < .015$), 2.04 seconds (range, 0-10 seconds) in the moderate group ($P < .01$), and 1.45 seconds (range, 0-5 seconds) in the severe group ($P < .001$) (**Figure 4**).

The fluorescein staining scores at baseline were 0.40 in the mild group (range, 0-1), 1.22 in the moderate group (range, 1-3), and 2.67 in the severe group (range, 2-4). Scores after treatment were 0.30 in the mild group ($P < .001$), 0.69 in the moderate group ($P < .001$), and 1.85 in the severe group ($P < .001$).

Scores of lissamine green staining of the conjunctiva at baseline were 0.29 in the mild group (range, 0-2), 0.55 in the moderate group (range, 0-2), and 2.46 in the severe group (range, 1-4). Lissamine green staining after treatment was 0.18 in the mild group ($P < .001$), 0.48 in the moderate group ($P < .0078$), and 1.62 in the severe group ($P < .001$).

COMMENT

Our study demonstrates that in patients who have dry eye symptoms and are refractory to standard artificial tear therapy, cyclosporine may alleviate signs and symptoms of the disease. Surprisingly, the greatest symptomatic benefit occurred in the mild patient group. Previous studies have focused mainly on patients with moderate to severe dry eye disease.^{4,8,11} Patients with severe dry eye are the most difficult to treat and have the most problems tolerating any eye drop medication, including cyclosporine. We did not find any differences in outcomes with respect to the use of punctal plugs.¹²

The focus of this study was the efficacy of a Food and Drug Administration–approved drug in patients with mild, moderate, and severe dry eye disease. There were no articles in the peer review literature evaluating cyclosporine

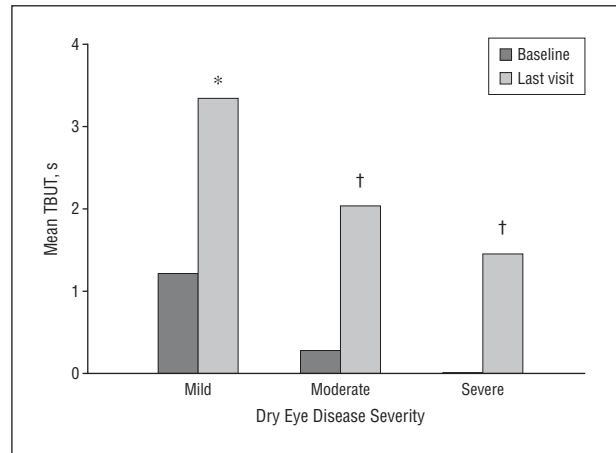


Figure 4. Tear breakup time (TBUT) in patients with mild, moderate, and severe dry eye disease treated with cyclosporine, 0.05%. *, $P < .05$; †, $P < .01$.

in patients with mild or moderate dry eye disease. There was no need for a control group in this study to determine if the drug was safe or effective, as safety and efficacy studies were performed in phase 1, 2, and 3 studies for the Food and Drug Administration. This was a post-market analysis of the efficacy of cyclosporine in a patient population with less severe disease than those previously studied. One of the limitations of the study is concluding that the active ingredient and not the vehicle was responsible for the improvement. However, enrollment criteria included only those patients who were unresponsive to artificial tears therapy. Therefore, it is less likely that our results are due to the effects of the vehicle.

The strengths of this study are that it was prospective, enrolled a large number of patients, had a relatively low patient dropout rate, had symptomatic OSDI testing at each visit, and had careful sequential evaluation of signs of dry eye disease at each visit. The minimum period of follow-up was the length of time that it typically takes cyclosporine to take effect, but it would have been better if the minimum follow-up had been 6 months for all patients.

Another limitation includes the important question of compliance with cyclosporine use. Compliance is a significant problem in medicine, ophthalmology in particular.^{13,14} There were no objective measures in this study to determine compliance. Winfield et al¹⁵ have pointed out that as few as 36% of patients take their glaucoma medications as directed. In prior studies, it was determined that asking patients to return medication vials or use dosing diaries could not accurately ascertain compliance.^{4,8,10} In 1 study in which patients were asked to return vials, some patients admitted to emptying them when they forgot to use the medication.¹⁰

In this study, the recommended supplemental use of artificial tears was not followed. However, there should be no benefit to observing this because all patients had used tears and had failed therapy with them (patients were not enrolled in the study if artificial tears had not already not worked for them). Also, decreased use of artificial tears with continued cyclosporine use has already been shown by Sall et al.⁴ Therefore, we conclude that the improvement seen in dry eye disease in our study was not due to the application of artificial tears.

Many of the patients in the mild disease group had a positive reaction to treatment that continued throughout their follow-up period. In this group, there was also a larger number of patients who did not complete therapy. This suggests that the patients who did not continue therapy because of adverse effects, lack of efficacy, or indifference might have experienced a positive effect if they had completed at least a 3-month treatment trial. This hypothesis is supported by the finding that the mild dry eye disease group was the most satisfied with their therapy as indicated by OSDI.

Most successful treatment responses correlated with an improvement in OSDI scores, though there was very little difference in the OSDI scores in the 3 groups. The little difference may be because even the patients with mild dry eye disease had to have an OSDI score of 0.25 or greater at baseline, which may reflect the well-documented nature of chronic disease states—patients develop tolerance to their diseases and learn to coexist with their symptoms.¹⁶

However, there were 2 patients in the mild group and 5 patients in the moderate group who noted no symptomatic improvement, though they were found to have longer TBUTs and less fluorescein and/or lissamine green staining. There were also 3 patients in the severe group who had definite signs of improvement though they were essentially unchanged symptomatically. Overall treatment success measured by OSDI was achieved in 104 of 143 patients (72.7%). For all patients who entered the study, the success rate dropped to 104 of 158 (65.8%). In those who completed at least 3 months of treatment, 114 of 143 patients (79.7%) had clinical improvement and/or improved OSDI scores. For all patients entering the study, 114 of 158 (72.1%) experienced clinical improvement and/or improved OSDI scores. The *P* values indicate that all comparisons (except the change in Schirmer values) are significant, ie, the final values are statistically significantly different from the initial ones and this change was most likely due to treatment with topical cyclosporine.

The increased benefits of treatment in the mild group suggest that early treatment of dry eye disease may yield the best results. This is not surprising because early treatment of most chronic diseases will similarly lead to the best therapeutic outcomes. Many of the patients in the mild disease group had associated systemic disorders that are frequently seen in patients with dry eye disease. The most frequently seen systemic condition in these patients was thyroid autoimmune disease. Several studies point out the association of this disease with keratoconjunctivitis sicca¹⁷⁻¹⁹ (which may be as high as 45%¹⁸). Perhaps early treatment of patients with thyroid autoimmune disease is warranted, given the high incidence of keratoconjunctivitis sicca and the safety of cyclosporine therapy.

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