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**Clinical Science**

**Comparison of Topical Cyclosporine, Punctal Occlusion, and a Combination for the Treatment of Dry Eye**

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**Purpose:** To compare the efficacy of topical cyclosporine, punctual occlusion, and a combination for the treatment of dry eye.

**Methods:** Patients with dry eye (N = 30) seen in a university-affiliated private practice were randomized to 1 of 3 treatments: cyclosporine 0.05% ophthalmic emulsion (RESTASIS) twice daily, lower-lid punctal plugs (PARASOL), or a plugs-cyclosporine combination. Tear volume, ocular surface staining, and artificial tear use were assessed at baseline and 1, 3, and 6 months.

**Results:** All treatments improved Schirmer scores by 6 months (P ≤ 0.005 vs. baseline), with plug-containing regimens favored at 1 and 3 months (P < 0.001 vs. cyclosporine alone). Cyclosporine-containing regimens, but not plugs alone, improved rose bengal staining at 3 and 6 months (P ≤ 0.010 vs. baseline). Artificial tear use decreased with plug-containing regimens at 1 month and with all treatments at 3 and 6 months (P ≤ 0.005 vs. baseline). Combination therapy produced the greatest overall improvements and was superior to plugs alone in decreasing artificial tear use at 6 months (P = 0.012).

**Conclusions:** All 3 regimens effectively treated dry eye. Plug-containing regimens increased wetness initially; cyclosporine appeared to promote long-term ocular surface health. The effects may be additive. Patients with punctal occlusion may benefit from adjunctive cyclosporine.

**Key Words:** cyclosporine, punctal occlusion, dry eye, keratoconjunctivitis sicca

Dry eye disease has been classically defined as a disorder of the tear film caused by aqueous insufficiency or excessive evaporation, with mainstay therapies such as artificial tears and punctual occlusion aimed at supplementing or conserving existing tears. A growing body of evidence has led to a new understanding of dry eye as a disorder of tear film composition in which an unstable and unrefreshed tear film inadequately supports the normal functioning of the ocular surface epithelium. Tear film alterations in dry eye include decreased tear volume, increased osmolarity, altered cytokine balance favoring an inflammatory state, and an increase in matrix metalloproteinases. Unhealthy tears promote pathologic ocular surface alterations such as increased expression of immune activation and adhesion molecules and increased apoptosis of the conjunctival and glandular epithelium. Ultimately, this cascade of events leads to ocular surface staining, further decreased tear volume, and symptoms of discomfort characteristic of dry eye.

This broader understanding of dry eye disease has led to the development of topical cyclosporine, the first FDA-approved therapy for dry eye that aims to normalize tear composition and production through modulation of the underlying immune pathology. In two 6-month phase III clinical trials involving 877 patients with dry eye comparing cyclosporine 0.05% ophthalmic emulsion with vehicle, cyclosporine significantly improved corneal fluorescein staining, categorized Schirmer scores (with anesthesia), blurred vision, photophobia, itching, dryness, and concomitant artificial tear use, with no significant safety findings except for transient burning (15% of cyclosporine-treated patients vs. 7% of vehicle-treated patients). Overall, 59% of patients had increased Schirmer scores, with 15% having an increase of 10 mm or more (vs. 5% of vehicle-treated patients; P < 0.01). These results were accompanied by significant increases in goblet cell density and decreases in expression of immune activation markers CD11a and human leukocyte antigen-DR and the inflammatory cytokine interleukin (IL)-6. These results suggest that, while cyclosporine can treat the underlying immune pathology of dry eye disease and produce clinically significant improvements in tear volume, the responses of individual patients can vary.

Dry eye treatment patterns are evolving as topical cyclosporine is integrated into clinical practice. One area of interest is the relationship of pharmacologic therapies with punctal occlusion, the most common nonpharmacologic therapy. Published practice patterns call for punctal occlusion in severe cases after traditional aqueous enhancement has failed. Punctal occlusion has been shown to improve objective and subjective measures of dry eye but may exacerbate ocular surface inflammation in subjects with overt clinical inflammation. The latter results show the importance of normal tear clearance for ocular surface health and suggest...
that punctal occlusion may trap unhealthy tears on the ocular surface. Because of this issue, an international panel of experts developing comprehensive treatment guidelines for ocular surface disorders recommended that the inflammatory condition be treated before punctal occlusion. However, no comparative studies have been published to date evaluating punctal occlusion and topical cyclosporine therapies for patients with dry eye disease. This study was designed to compare the efficacy of topical cyclosporine and punctal occlusion separately and in combination for the relief of signs and symptoms of dry eye in a patient population with moderate dry eye.

MATERIALS AND METHODS

This prospective, randomized, 6-month clinical trial was conducted at 1 study center between October 2003 and January 2005. The study setting was a university-affiliated private practice. Patients were enrolled consecutively if they had moderate dry eye disease, defined as meeting all 3 of the following criteria: (1) chronic symptoms of burning, sandy, or scratchiness in both eyes; (2) daily need for multiple applications of artificial tears; and (3) rose bengal staining of grade 2 or higher (scale described below). Patients were excluded if they had any prior ocular surgery other than cataract surgery, were concurrently using any other topical ocular medications, or had prior experience with either punctal plugs or topical cyclosporine. Informed consent was obtained from all patients in this institutional review board–approved study.

At the baseline visit, patients were screened, enrolled, and randomly assigned by using a computer-generated randomization schedule to 1 of 3 treatment groups: (1) cyclosporine ophthalmic emulsion 0.05% (RESTASIS; Allergan, Irvine, CA) eye drops to both eyes twice daily, (2) bilateral punctal occlusion of the lower lids only (PARASOL Punctal Occluder; Odyssey Medical, Memphis, TN), or (3) a combination regimen consisting of bilateral lower lid punctal occlusion and cyclosporine eye drops to both eyes twice daily. For convenience, these treatment groups are referred to as cyclosporine, combination, and plugs, respectively. For patients who received punctal plugs, each punctum was measured, and an appropriately sized plug was selected (small: 0.3–0.6 mm; medium: 0.6–0.8 mm; large: 0.9 mm). Medication was dispensed open-label. Patients were allowed to use concomitant artificial tears of the brand of their choice as needed throughout the study. Patients were evaluated at baseline and after 1, 3, and 6 months of treatment. Patients were instructed to adhere to their assigned treatment regimen and as-needed use of artificial tears for the duration of the study, including the days of follow-up visits. Patients who withdrew prematurely from the study were replaced.

The outcome measures were Schirmer scores without anesthesia, corneal and conjunctival rose bengal staining, and artificial tear use. Schirmer tests were performed by lightly dabbing the inferior fornix with a cotton tip applicator to remove excess tears, bending the Schirmer strip at the notch, and placing the strip beneath the temporal lid margin with the notch at the lid margin. After 3 minutes, during which the patient was instructed to keep the eyes open and blink normally, the strip was removed and measured to the point of maximum wetting. Rose bengal staining was performed immediately after the Schirmer test by using a sterile opthalmic strip impregnated with 1.3 mg of rose bengal (ROSEGLO; Rose Stone Enterprises, Alta Loma, CA). Staining was done by moistening the strip with saline solution and touching the conjunctival fornix with the strip. Rose bengal staining was graded on the following scale: 0 = no staining, 1 = staining of the nasal conjunctiva only, 2 = staining of both the nasal and temporal conjunctiva, 3 = peripheral corneal staining, 4 = central corneal staining. Investigators verbally queried the patient at baseline and at subsequent visits regarding the number of times per day artificial tears were applied over the previous 3 days.

The enrollment goal for this study was 30 patients, with 10 per each treatment group. Two patients withdrew from the study prematurely: additional patients were enrolled to replace them and maintain the size of the treatment groups at 10. For Schirmer testing and rose bengal staining, data were collected from both eyes and averaged before statistical analysis. Standard descriptive statistics were calculated for each treatment group. Paired t tests were used to compare outcome measures at each study visit with baseline; unpaired t tests were used for between-group comparisons at each study visit.

RESULTS

Study Population

Thirty patients completed the study, 10 in each treatment group. The mean age of the study population was 52.1 years (range, 38–63 years). Most patients were women; 5 (16.7%) of 30 were men. There were no statistically or clinically significant differences in demographics among treatment groups. Among patients who received punctal plugs, no losses of plugs occurred during the study.

Schirmer Testing

Mean Schirmer scores at baseline ranged from 2.5 to 2.7 mm/3 min among the 3 treatment groups (Table 1). At the 1- and 3-month study visits, both the combination and plug groups showed statistically significant improvement relative to baseline (P ≤ 0.005) and relative to cyclosporine alone (P < 0.001). Initial response was not seen in the cyclosporine group, but by study exit at 6 months, improvements in Schirmer scores were statistically significant (P ≤ 0.005 vs. baseline) and were indistinguishable from the other groups (Table 1; Fig. 1A). Over the course of the study, Schirmer scores improved an average of 3.0 mm for the cyclosporine group, 3.9 mm for the combination group, and 3.8 mm for the plug group.

Rose Bengal Staining

The mean staining grade at baseline ranged from 2.0 to 2.3 among the treatment groups, corresponding to staining of both the nasal and temporal conjunctiva (Table 1). Although no statistically significant changes from baseline were seen in any group at the 1-month visit (Table 1), both the cyclosporine and combination treatments provided significant improvements in staining by the 3-month visit (P = 0.010). At 6 months, mean staining for both the cyclosporine and
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**TABLE 1. Outcome Measures by Treatment Group**

<table>
<thead>
<tr>
<th>Treatment Group (n = 10 per Group)</th>
<th>Baseline Score (Mean ± SEM)</th>
<th>Change From Baseline (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Month 1</td>
</tr>
<tr>
<td>Schirmer scores (mm/3 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.7 ± 0.52</td>
<td>-1.5 ± 0.31*</td>
</tr>
<tr>
<td>Cyclosporine + plugs</td>
<td>2.6 ± 0.48</td>
<td>4.5 ± 0.64*†</td>
</tr>
<tr>
<td>Plugs</td>
<td>2.5 ± 0.40</td>
<td>4.5 ± 0.43*‡</td>
</tr>
<tr>
<td>Rose bengal staining (scale 0–4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2.3 ± 0.15</td>
<td>-0.3 ± 0.15</td>
</tr>
<tr>
<td>Cyclosporine + plugs</td>
<td>2.0 ± 0.00</td>
<td>-0.3 ± 0.15</td>
</tr>
<tr>
<td>Plugs</td>
<td>2.3 ± 0.15</td>
<td>-0.2 ± 0.15</td>
</tr>
<tr>
<td>Artificial tear use (uses per day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>5.7 ± 0.37</td>
<td>-0.6 ± 0.27</td>
</tr>
<tr>
<td>Cyclosporine + plugs</td>
<td>5.5 ± 0.50</td>
<td>-2.2 ± 0.49*</td>
</tr>
<tr>
<td>Plugs</td>
<td>6.0 ± 0.42</td>
<td>-2.3 ± 0.63*</td>
</tr>
</tbody>
</table>

*P < 0.005 vs. baseline.
†P < 0.05 vs. baseline.
‡P < 0.01 vs. cyclosporine.
§P < 0.012 vs. plugs.

Combination groups had decreased 0.9 and 1.0 grade, respectively; these differences were each significantly improved from baseline (P ≤ 0.005) but not significantly different from each other. Rose bengal staining was not significantly improved from baseline in the plug group at 6 months (Fig. 1B) nor at earlier time points (Table 1).

**Artificial Tear Use**

Baseline mean artificial tear use ranged from 5.5 to 6 applications/d (Table 1). Mean artificial tear use declined significantly in every group at the 1- and 3-month visits, except for cyclosporine at 1 month (Table 1). By the end of the study, mean use declined by 3.2 applications/d in the cyclosporine group and 3.9 applications/d in the combination group, changes that were significantly improved from baseline (P ≤ 0.005) and statistically indistinguishable from each other. Artificial tear use also declined significantly in the plug group to 2.1 applications/d (P ≤ 0.005); however, this level of improvement was significantly less than that seen in the combination group (P = 0.012 for combination vs. plugs; Fig. 1C).

**Safety and Tolerability**

Two patients withdrew from the study prematurely: 1 in the plug group because of discomfort of the plugs and 1 in the cyclosporine group because of burning due to the study drug. No other adverse effects of the treatments were noted during the study.

**DISCUSSION**

Because punctal occlusion and topical cyclosporine treat chronic dry eye by different mechanisms, this study was designed to examine their efficacy singly and in combination. We evaluated 3 treatment regimens consisting of topical cyclosporine twice daily, punctal plugs, and a combination of cyclosporine and plugs over 6 months. Outcome measures were chosen to evaluate different aspects of chronic dry eye disease: Schirmer tests for tear volume, rose bengal staining for ocular surface integrity, and frequency of artificial tear use to monitor patients' need to self-medicate. In general, all 3 treatment regimens were efficacious. The results confirm the benefits of punctal occlusion for immediate conservation of existing tears and are consistent with a role for cyclosporine in restoring ocular surface health over time.

All of the treatment regimens increased tear volume to a similar extent over the course of the study. Mean Schirmer scores more than doubled for all treatment regimens by 6 months, representing clinically and statistically significant increases in tear volume from pretreatment levels, with no statistically significant differences among the groups. However, at 1 and 3 months, regimens that included punctal plugs were superior to cyclosporine alone in improving Schirmer scores. These results are consistent with the known function of punctal occlusion in physical conservation of existing tears.

Cyclosporine-containing regimens significantly reduced rose bengal staining at 3 and 6 months relative to pretreatment scores, suggesting improved ocular surface health for these patients. Rose bengal staining indicates damage to ocular surface epithelia by highlighting dead cells and areas deficient in mucin coverage and correlates well with reduced goblet cell density.16,17 Staining was not significantly altered in patients treated solely with punctal occlusion for 6 months, indicating minimal improvement of the ocular surface. These results, taken together with the Schirmer test results, are consistent with the idea that punctal occlusion may benefit tear conservation in the short run but may also exacerbate ocular surface staining over time if the tears being conserved are toxic. Tears may potentially become toxic through pathologic alterations of tear composition. It is also theoretically possible that use of artificial tears containing a toxic preservative (eg, benzalkonium chloride) may increase the potential for ocular surface irritation in a patient with punctal occlusion. Furthermore, these results agree with those of previous studies.
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FIGURE 1. Results after 6 months of treatment with topical cyclosporine (RESTASIS) twice a day, punctal plugs (PARASOL), or both together. A, Tear volume. B, Rose bengal staining. C, Artificial tear use. Values presented are mean change from baseline ± SEM.

For each panel, N = 30 patients (n = 10 per treatment group).

*P < .005 vs. baseline; †P = .012 vs. punctal plugs alone.

showing topical cyclosporine-mediated improvements in several measures of ocular surface health including corneal staining, goblet cell density, and markers of inflammation.5,8,9

Artificial tears, when used as an adjunct to other therapies for chronic dry eye, are a means for patients to obtain temporary relief from ocular symptoms such as dryness and burning. Before treatment, patients in this study used artificial tears an average of 5.5 to 6.0 times/d. At the final study visit, patients in all 3 treatment groups had reduced their use of artificial tears significantly to 2.5 (cyclosporine), 1.6 (combination), and 3.9 times/d (plugs only), suggesting that all the therapies were efficacious in relieving dryness. The combination therapy was superior to plugs alone in reducing artificial tear use (P = 0.012) and produced the greatest overall improvement in all measures at 6 months, suggesting a possible additive effect of punctal occlusion and topical cyclosporine.

Patterns of artificial tear use varied among the groups over time. Patients treated solely with punctal occlusion showed an initial reduction in artificial tear use after 1 month that was essentially unchanged during the rest of the study, a pattern consistent with preservation of existing tears. In contrast, patients treated with cyclosporine (with or without punctal occlusion) showed continued reduction of artificial tear use throughout the study, although for the cyclosporine-only group, the initial reduction in artificial tear usage at 1 month was not statistically significant. The pattern shown by cyclosporine-treated patients is consistent with continual improvement of the underlying cause of chronic dry eye over time.

The apparent additive effect of cyclosporine and punctal occlusion is clinically relevant. There could be a synergy between these modalities that combines the advantages of tear conservation with pharmacologic treatment of the underlying immune pathology associated with chronic dry eye. Punctal occlusion increases the contact time of tears with the ocular surface, which in the presence of concomitant topical cyclosporine would also increase the residency time of medication. This could potentiate greater absorption of medication and increase the probability of a greater therapeutic response.

An important limitation of this study is the length of treatment; a longer treatment period may have resulted in more definitive comparisons among treatment groups. This is because patients receiving cyclosporine improved throughout the study and may have continued to improve their Schirmer scores, rose bengal staining, and frequency of artificial tear use with ongoing cyclosporine treatment. Thus, the effect of cyclosporine therapy relative to punctal occlusion may have been underestimated. Another study limitation is the inherent inability to mask which patients received punctal plugs, which necessitated an open-label study design.

In summary, although all the treatments in this study effectively treated chronic dry eye, some trends regarding specific modalities are evident. In the near term, punctal occlusion (alone or in combination with cyclosporine) produced the most rapid improvements in wetness, as assessed by Schirmer testing and patient self-medication with artificial tears, consistent with the tear-conserving function of punctal plugs. Over the longer term, cyclosporine-containing regimens produced improvements in these same measures that were...
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statistically indistinguishable from, or were superior to, the plugs-only regimen. Furthermore, only the cyclosporine-containing regimens significantly improved ocular surface staining over time. These observations are consistent with the known roles of topical cyclosporine in addressing the underlying immune pathology of chronic dry eye disease. There may be an additive effect of topical cyclosporine and punctal occlusion that would merit their concomitant use in certain situations; for example, patients with chronic dry eye being treated with punctal occlusion over a long period may benefit from the addition of topical cyclosporine.

**REFERENCES**