Efficacy of Topical Cyclosporine for the Treatment of Ocular Rosacea

Barry A. Schechter

ABSTRACT

Introduction: This study was designed to compare the efficacy of cyclosporine ophthalmic emulsion 0.05% with an artificial tear solution for the treatment of rosacea-associated eyelid and corneal pathology. Methods: Double-masked, randomized, 3-month clinical trial of 37 patients with rosacea-associated eyelid and corneal changes (defined as lid margin telangiectasia, meibomian gland inspissation, and/or fullness of the lid margin). All findings were standardized and compared to photographs for grading. Results: There was a statistically significant increase in Schirmer (with anesthesia) scores of 2.7±2.2 mm after 3 months of treatment in the topical cyclosporine group (P<0.001), compared with a mean decrease of –1.4±4.6 mm (P=0.271) in the artificial tears group. The mean tear break-up time score significantly improved in the topical cyclosporine group (mean increase of 3.56±1.5 seconds, P=0.271) in the artificial tears group. The mean tear break-up time score significantly improved in the topical cyclosporine group (mean increase of 3.56±1.5 seconds, P=0.022). Limitations of the study included an older, predominantly Caucasian patient population and short trial length. Conclusions: Topical cyclosporine 0.05% is more effective than artificial tears for the treatment of rosacea-associated lid and corneal changes.

Keywords: artificial tears; cyclosporine; meibomian gland; ocular rosacea; telangiectasia

INTRODUCTION

Rosacea is a common ocular cutaneous disorder, primarily affecting the sebaceous glands of the face and the meibomian glands of the eyelids. Recent studies estimate that ocular pathology in this potentially blinding condition affects between 6% and 18% of patients with acne rosacea.1 Despite the substantial impact on quality of life and significant
break-up time (TBUT), leads to decreased tear film instability, characterized by rapid tear in blurred vision, tearing, and burning. Tear bilateral presentation is common, but unilateral involvement has also been noted.3 The pathology compared with healthy subjects.5 with ocular rosacea often exhibit significant neal and conjunctival epithelia of patients 2 Adv Ther (2009) 26(6):. the disease are treated by an ophthalmologist. 1 morbidity of ocular rosacea, few patients with 2 weeks prior to study entry, and patients with eyelid defects or lagophthalmos were excluded. The study was a double-masked clinical trial. Patients (n=37) were randomized to either study medication were enrolled. Patients had a diagnosis of ocular rosacea-associated eyelid and corneal changes. For the purposes of this study, “rosacea-associated eyelid and corneal changes” were defined as lid margin telangiectasia, meibomian gland inspissation, and/or fullness of the lid margin. All the findings were standardized and compared to photographs for grading.

MATERIALS AND METHODS

This study was a multiple-site, randomized, double-masked clinical trial. Patients (n=37) with rosacea-associated eyelid and corneal changes were enrolled. Patients had a diagnosis of ocular-associated rosacea confirmed by a dermatologist. Any patients with active infections were treated with lid scrubs and antibiotics prior to enrollment. All patients were withdrawn from oral doxycycline for at least 2 weeks prior to study entry, and patients with eyelid defects or lagophthalmos were excluded. Any patients who demonstrated sensitivity to either study medication were excluded. Pregnant women or nursing mothers were not enrolled. After infections were clinically controlled, patients were randomized by computer to cyclosporine twice daily or artificial tears twice daily for 3 months. It should be noted that the vials for each product are identical when the labels are removed, ensuring patient and clinician masking.

At each visit, patients were assessed by the Ocular Surface Disease Index (OSDI) questionnaire. The OSDI is a standardized, validated patient questionnaire designed to determine the impact of ocular surface disease (normal, mild to moderate, and severe) on patient quality of life. The index is assessed on a scale of 0 to 100, with higher scores representing greater disability. It demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease.17 In addition to the OSDI, patients also underwent Schirmer testing with local anesthesia (bilateral, simultaneous for 3 minutes), measurement of corneal staining, and TBUT at each study visit. After completing the TBUT evaluation (fluorescein solution was instilled and covered the ocular surface; after several blinks, the amount of time until a bare area on the cornea appeared was noted), the entire cornea was examined for staining using the yellow barrier filter and the slit lamp's cobalt blue illumination with a 3 mm slit width and 16× magnification. (The yellow barrier filter is the researchers’ standard filter used when fluorescein dye is used or present on the ocular surface.) Corneal fluorescein staining was evaluated only after 30 seconds but before 2 minutes had elapsed following the instillation of the fluorescein. Staining was scored using an Oxford staining scale evaluating the five regions of the cornea and two in the conjunctiva. Bron et al.18 described the Oxford Scheme for grading ocular surface staining in dry eye, and staining in this study followed those parameters. The total score was the sum of each of these sections.
RESULTS

Patient Demographics

The mean age of the patients enrolled in the topical cyclosporine arm was 75.6 years (n=21), compared with a mean age of 69.6 years in the artificial tears arm (n=16). As the primary recruitment site was in Florida, we expected an older patient population. All but one of the patients was Caucasian.

All patients were symptomatic and demonstrated classic ocular changes of rosacea (such as lid margin telangiectasia and meibomian gland involution) as determined by the dermatologist and confirmed by an ophthalmologist. Patients were enrolled sequentially as they were diagnosed in clinic with rosacea.

There were no significant between-group differences in any patient demographic variable (Table 1). There was no significant between-group difference in mean Schirmer scores at the initial visit (9.7±5.1 mm in the cyclosporine group, compared with 10.2±5.8 mm in the artificial tears group; P=0.765). After 3 months there was a statistically significant increase in Schirmer scores of 2.7±2.2 mm (P<0.001) in the patients dosed with topical cyclosporine.

Conversely, Schirmer scores worsened in the artificial tears group, with a mean decrease of –1.4±0.6 mm (P=0.271). The improvement in mean Schirmer score was statistically significantly greater in the cyclosporine group than in the artificial tears group (P=0.002) (Figure 1).

Although there were no significant between-group differences in mean TBUT scores at the initial study visit in the topical cyclosporine-treated group and the artificial tear-treated group (5.83±3.6 seconds compared with 5.46±3.6 seconds, respectively; P=0.776), 3 months of cyclosporine improved mean TBUT scores more than artificial tears (P<0.001). Mean TBUT scores improved in the cyclosporine-treated patients (mean increase of 3.56±1.5 seconds, P<0.001; Figure 2). However, mean TBUT scores slightly worsened in the tears group, although the difference was not statistically significant (mean decrease of –0.04±1.6 seconds, P=0.929).

There was no significant difference between groups in mean OSDI scores at the initial study visit in the topical cyclosporine-treated group and the artificial tear-treated group (19.1±13.9, compared with 16.9±15.8, respectively; P=0.671). Three months of cyclosporine improved mean OSDI scores significantly more than 3 months of artificial tears (P=0.022). Cyclosporine-treated patients had a mean reduction (improvement) in OSDI scores of –11.5±8.8, while patients who used artificial tears had a mean decrease of –2.9±11.6 (P=0.348, Figure 3).

Mean corneal staining scores at the initial study visit were similar in the topical cyclosporine-treated group and the artificial tear-treated group (1.4±0.8, compared with 0.9±0.7, respectively; P=0.064). Three months of cyclosporine usage reduced corneal staining significantly more than 3 months of artificial tears (P<0.001). The mean reduction in corneal staining was –1.3±0.53 in the cyclosporine-treated patients (P=0.001) compared with a mean reduction of –0.2±0.83 in the artificial tear-treated patients (P=0.328, Figure 4).

Table 1. Patient demographics.

<table>
<thead>
<tr>
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<th>Cyclosporine</th>
<th>Artificial tears</th>
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<td>Mean age, years</td>
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Figure 4. Change in mean corneal staining from initial visit after 3 months of treatment. *P<0.001.

Figure 5. Evaluation of rosacea-associated ocular signs and symptoms in patients nonresponsive to artificial tear therapy who then switched to cyclosporine for 1 month.

None of the patients treated with artificial tears experienced satisfactory resolution of their signs or symptoms. Seven of the 15 patients who were randomized to artificial tears and completed the month-3 study visit agreed to switch to cyclosporine therapy and return in 1 month for the month-3 study visit. In the cyclosporine group, one patient was lost to follow-up and one patient discontinued, complaining of “stinging” upon instillation. In the tears group, one patient was lost to follow-up.

Other Outcome Measures

After 3 months of treatment, the mean number of unoccluded, expressible meibomian glands increased from 3.95±2.22 at baseline to 6.67±2.16 in the cyclosporine group but was unchanged in the artificial tears group (mean reduction of 0.03±0.61). The difference between the groups was statistically significant (P<0.001).

Although not a primary outcome measure, both treatments were well tolerated, and there was a high rate of completion in each study group (90.5% in the topical cyclosporine group and 93.8% in the artificial tear group). Only three patients exited the study prior to the month-3 visit. In the cyclosporine group, one patient was lost to follow-up and one patient discontinued, complaining of “stinging” upon instillation. In the tears group, one patient was lost to follow-up.

DISCUSSION

In the present study, topical cyclosporine 0.05% provided statistically significantly greater improvements in Schirmer scores, OSDI, TBUT, and corneal staining scores than artificial tears on rosacea-associated eyelid and corneal changes. The improvements seen with topical cyclosporine are most likely due to the effects of topical cyclosporine 0.05% has on increasing tear production and decreasing inflammation.9,14 Furthermore, the ability of topical cyclosporine 0.05% to significantly improve Schirmer scores, OSDI, TBUT, and corneal staining scores may be due to a cyclosporine-mediated reduction in the number of activated lymphocytes within the conjunctiva.15 By reducing activated lymphocytes and increasing tear production, topical cyclosporine 0.05% decreases inflammation within the eye and improves patient signs and symptoms.

Ocular rosacea is an inflammatory disease as well, sometimes associated with MGD. Traditional treatments for both diseases include lid hygiene, oral tetracyclines, steroids, and antibiotics. Ocular rosacea, however, is more involved than MGD; the latter can be (mis)diagnosed as dry eye,16 while the former is a manifestation of a dermatologic disorder. Both, however, are strongly associated with age.17 It is not surprising that subjects in this study presented with both ocular rosacea and MGD, as the geographic location of this study yields an older population. Zengin et al.18 also found a strong correlation between rosacea and MGD. In that study, patients with poor meibum secretion and inspissation exhibited tear film instability and experienced premature tear evaporation.

Barton et al.19 noted reduced tear turnover, its inverse correlation with interleukin-1alpha, and the absence of tumor necrosis factor-alpha in the tears of patients with ocular rosacea, suggested that the increased concentration of interleukin-1alpha observed may be largely because of clearance failure of cytokines normally produced at the ocular surface. A separate study suggested that after 6 months of use, topical cyclosporine was shown to decrease inflammatory cytokines in the conjunctival epithelium of dry eye patients.21

Despite the relatively common incidence of ocular rosacea, the diagnosis is routinely missed by ophthalmologists or, when it is made, often undertreated. Akpek et al.3 describes the non-specific nature of these signs and symptoms is likely to contribute to the possibility of misdiagnosis. However, this same report underscores the potential consequences of undertreating ocular rosacea. Although the majority of patients (86.3%, 113/131) studied received oral tetracycline (a common treatment for rosacea), 13 patients had decreased visual acuity at the time of presentation due to corneal complications. Six of these patients required penetrating keratoplasty during the course of their disease. Seven patients had severe cicatrising conjunctivitis at the time of referral and seven patients were left with visual acuity less than 20/400. One patient underwent enucleation for corneal involvement as a result of rosacea.3,7,16,22

The finding that cyclosporine is an effective treatment for the signs and symptoms of ocular rosacea is consistent with another study. Perry et al.23 reported that topical cyclosporine was effective in treating ocular rosacea patients who were unresponsive to standard therapy. Moreover, most patients in that cohort (71%) were able to discontinue all other medications. These authors also found that topical cyclosporine was safe and well tolerated in...
patients with ocular rosacea. Perry et al. also found several objective examination findings between the placebo and topical cyclosporine groups to be statistically significant at the 3-month visit, including lid margin vascular injection, tarsal telangiectasia, and fluorescein staining (all P<0.05). The most significant of changes (P<0.001) was the greater decrease in tarsal telangiectasia, and fluorescein staining (all

ACKNOWLEDGMENTS

The author wishes to acknowledge IMEDS for assistance in the statistical analysis and in the preparation of the paper.

This paper was presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology; May 1-5, 2005, Fort Lauderdale, Florida, USA.

Declaration of interest: This study was funded by an unrestricted educational grant from Allergan, Inc.

REFERENCES


CONCLUSION

Topical cyclosporine 0.05% is more effective than artificial tears for the treatment of rosacea-associated lid and corneal changes.

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