

More than Dry Eye: Other Uses for Cyclosporine

This article discusses two studies which used cyclosporine for treating blepharitis and rosacea.

BY SANJAY N.
RAO, MD
CHICAGO, IL



AND BARRY
SCHECHTER, MD
POMPANO
BEACH, FL



Comparison of Cyclosporine Vs. Tobradex for the Treatment of Posterior Blepharitis

BY SANJAY N. RAO, MD

Described as generalized inflammation of the posterior lid margin, posterior blepharitis is a very common chronic eyelid condition that often presents with inspissated meibomian glands and oily tear film as well as inflammation and vascularization of the meibomian gland orifices. Individuals with posterior blepharitis often complain of significant discomfort including burning, itching, irritation and photophobia. They may also have other associated symptoms of dry eye and may be plagued by blurred vision and gradual contact lens intolerance, as well as an increased risk of ocular surface damage and ocular infection.¹⁻⁴

Current Treatments Are Limited

Posterior blepharitis has traditionally been managed with eyelid hygiene, topical antibiotics, systemic antibiotics (specifically tetracycline) and corticosteroids.^{5,6} While corticosteroids are effective for suppressing acute inflammation associated with this condition, their use in a chronic process can lead to serious side effects including elevated IOP, development of cataracts and potential reactivation of viral keratitis.⁷⁻¹⁰

Current treatments for posterior blepharitis

are limited, in part, by their inability to target the underlying pathophysiologic processes. Although the exact mechanism is still not completely understood, there is ample evidence that posterior blepharitis is the result of an underlying inflammatory-mediated process affecting both the meibomian glands and the ocular surface.^{3,6}

Cyclosporine targets the underlying pathology (immune-mediated activation) in posterior blepharitis by targeting T-cells.^{11,12} Given the abundance of evidence in the literature to support the T-cell-mediated component of posterior blepharitis and its associated conjunctivitis, cyclosporine appears to be a viable therapeutic candidate that helps to alleviate patients' symptoms.

We conducted a study to evaluate the efficacy of topical cyclosporine 0.05% ophthalmic emulsion (Restasis, Allergan) vs. a commonly prescribed topical steroid-antibiotic combination, tobramycin 0.3%/dexamethasone 0.1% (Tobradex, Alcon) in reducing the signs and symptoms of posterior blepharitis.

Methods

We conducted a prospective, randomized study of 30 patients with posterior blepharitis. Patients were randomized to twice a day treatment with either cyclosporine or Tobradex. Visual acuity, slit-lamp appearance and intraocular pressure were evaluated every two

weeks for three months. In addition, Schirmer's tests, non-invasive fluorescein break-up time and tear lysozyme were also performed.

Measures of eyelid health, including lid erythema, meibomian gland metaplasia, meibomian gland expression and meibomian gland secretion quality, were also evaluated. Patients were queried regarding symptoms of itching, burning, tearing and blurred vision.

Results

Posterior blepharitis improved significantly with both treatments, though cyclosporine provided greater improvements in Schirmer scores ($P < 0.001$) and tear break-up time ($P = 0.018$) than tobramycin/dexamethasone after 12 weeks of treatment.

Eyelid health also improved in both groups, but the mean improvement in gland secretion quality was significantly greater with cyclosporine than with tobramycin/dexamethasone ($P = 0.015$). Moreover, a higher percentage of patients in the cyclosporine treatment group had improvements in blurred vision, burning and itching, and more cyclosporine-treated patients experienced resolution of lid margin metaplasia and lid telangiectasia.

Conclusions

The results of this study suggest that topical cyclosporine 0.05% is an effective treatment for signs and symptoms of posterior blepharitis. Three months of cyclosporine therapy provided

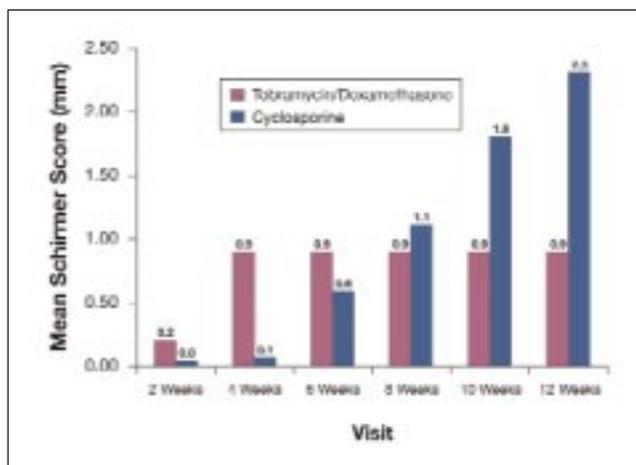


Figure 1. Mean change in Schirmer scores at each study visit.

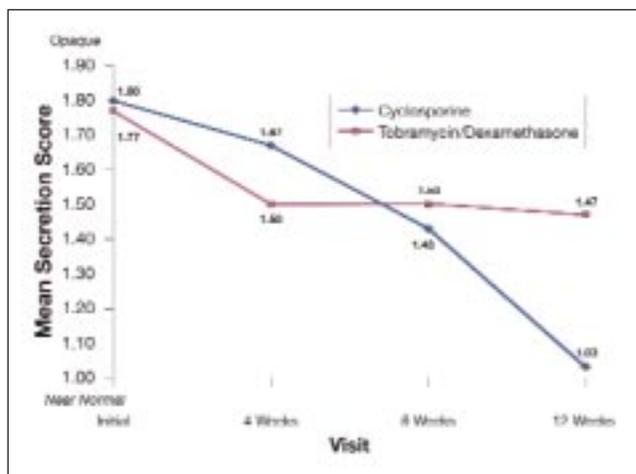


Figure 2. Mean secretion quality at each study visit.

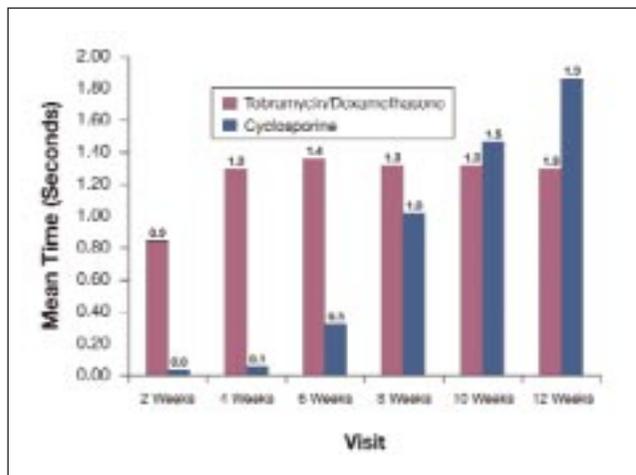


Figure 3. Mean TBUT scores at each study visit.

statistically significantly greater improvements in Schirmer scores, TBUT and mean secretion quality than three months of tobramycin/dexamethasone.

Further, a greater percentage of cyclosporine-treated patients than tobramycin/dexamethasone-treated patients reported improvement in blurred vision, itching and burning. Cyclosporine-treated patients also showed greater improvements in lid erythema, telangiectasia and meibomian gland metaplasia than tobramycin/dexamethasone-treated patients.

The findings in this prospective study, therefore, suggest that cyclosporine is safe and effective for the signs and symptoms of posterior blepharitis. Further studies, such as a larger double-blind prospective study using the Restasis vehicle as a control would further advance our knowledge of cyclosporine as an agent to treat posterior blepharitis.

Dr. Rao is the Director of the Cornea and Refractive Surgery Service at the University of Chicago. He specializes in corneal transplantation, small incision cataract surgery, surgery for keratoconus, management of corneal infectious diseases and treatment of ocular surface disorders.

REFERENCES

1. Mathers WD, Choi D. Cluster analysis of patients with ocular surface disease, blepharitis, and dry eye. *Arch Ophthalmol.* 2004;122:1700-1704.
2. Kaercher T, Brewitt H.

- Blepharitis. *Ophthalmology*. 2004;101:1135-1147.
3. Kocak-Altintas AG, Kocak-Midillioglu I, Gul U, Bilezikci B, Isiksacan O, Duman S. Impression cytology and ocular characteristics in ocular rosacea. *Eur J Ophthalmol*. 2003;13:351-359.
 4. Farpour B, McClellan KA. Diagnosis and management of chronic blepharokeratoconjunctivitis in children. *J Pediatr Ophthalmol Strabismus*. 2001;38:207-212.
 5. Cheung J, Sharma S. Ophthalmic problem. Blepharitis. *Can Fam Physician*. 2000;46:2393, 2400.
 6. McCulley JP, Shine WE. Changing concepts in the diagnosis and management of blepharitis. *Cornea*. 2000;19:650-658.
 7. Bertelmann E, Pleyer U. Immunomodulatory therapy in ophthalmology - is there a place for topical application? *Ophthalmologica*. 2004;218:359-367.
 8. Ishida Y, Kato T, Minamoto A, Yokoyama T, Jian K, Mishima HK. Retinal pigment epithelial tear in a patient with central serous chorioretinopathy treated with corticosteroids. *Retina*. 2004;24:633-636.
 9. Yeung CK, Chan KP, Chan CK, Pang CP, Lam DS. Cytotoxicity of triamcinolone on cultured human retinal pigment epithelial cells: comparison with dexamethasone and hydrocortisone. *Jpn J Ophthalmol*. 2004;48:236-242.
 10. Garrott HM, Walland MJ. Glaucoma from topical corticosteroids to the eyelids. *Clin Experiment Ophthalmol*. 2004;32:224-226.
 11. Kunert KS, Tisdale AS, Stern ME, Smith JA, Gipson IK. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. *Arch Ophthalmol*. 2000;118:1489-1496.
 12. Turner K, Pflugfelder SC, Ji Z, Feuer WJ, Stern M, Reis BL. Interleukin-6 levels in the conjunctival epithelium of patients with dry eye disease treated. *Cornea*. 2000 Jul;19(4):492-6.

Efficacy of Topical Cyclosporine for the Treatment of Ocular Rosacea

BY BARRY A SCHECHTER, MD

A common oculodermal disorder, ocular rosacea primarily affects the sebaceous glands of the face and meibomian glands of the eyelids. Recent studies estimate the prevalence of potentially blinding ocular pathology to be between 6 percent and 18 percent of patients with acne rosacea. Despite the potentially serious nature of this disorder, few of these patients are treated by an ophthalmologist.¹ Ocular manifestations of this inflammatory-based disease routinely produce tear film abnormali-

ties, resulting in complaints of blurred vision, tearing and/or burning.

Tear film instability, characterized by a rapid tear breakup time, leads to corneal epithelial drying and punctate keratopathy. Chronic inflammation leads to decreased tear production and function.² As a result, the corneal and conjunctival epithelium of these patients often exhibits significant pathology compared to normal subjects.³ While artificial tears have been used to treat acute dry eye symptoms, they provide insufficient long-term symptomatic relief in most patients and fail to address the underlying pathology.

I often use topical Cyclosporine A for my dry eye patients because it has been shown to increase tear production and improve the quality of naturally produced tears. Topical cyclosporine works by reducing the number of activated T-cells and other inflammatory markers within the conjunctiva⁴ and lacrimal gland leading to an increase in tear production.

Current Treatment

For mild cases of ocular rosacea, traditional treatments often include warm soaks and lid hygiene, as well as the use of artificial tears. Oral tetracyclines and topical antibiotics are the mainstays of treatment since tetracyclines decrease the viscosity of naturally secreted oils, thereby reducing meibomian gland "plugging" or inspissation which often occurs with ocular rosacea. A short course of topical corticosteroids can be used to bring severe cases under control.

Unfortunately, not all patients respond to the above traditional therapies or they may be unable to tolerate oral tetracyclines and may require a different approach. I con-

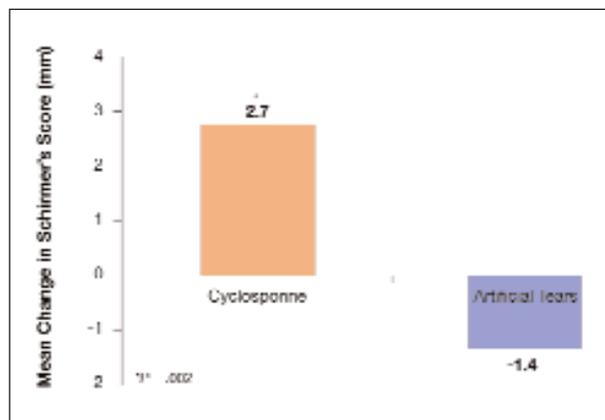


Figure 1. Mean change in Schirmer's score (with anesthesia) from initial visit after three months of treatment.

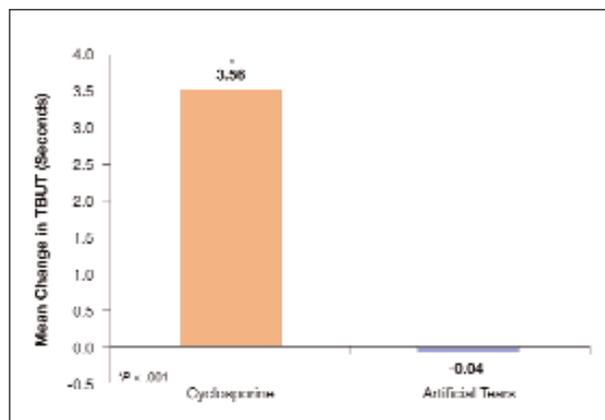


Figure 2. Mean change in TBUT score from initial visit after three months of treatment.

ducted a study comparing the efficacy of cyclosporine A (Restasis, Allergan) to an artificial tear solution (Refresh Plus, Allergan) used as a control, for the treatment of rosacea-associated eyelid and corneal pathology. Restasis has been shown to have almost no systemic absorption and limited local side effects.

Methods

In a randomized, double-masked clinical trial, patients (n=37) with rosacea-associated eyelid and corneal changes were enrolled after any active infections were treated with lid scrubs and antibiotics. Once the infection was clinically controlled, patients were randomized to cyclosporine BID or artificial tears BID for three months. All patients were withdrawn from oral doxycycline for at least two weeks prior to the study's onset. Patients with eyelid defects or lagophthalmos were excluded.

At each visit, patients were assessed by the FDA approved ocular surface disease index (OSDI) questionnaire, which assesses patients' symptoms and assigns a numerical determination of severity, Schirmer's testing with anesthesia, measurement of corneal staining and tear break-up time (TBUT). The number of meibomian glands expressed (due to inspissation) and the quality of the excreta were evaluated at each study visit. Changes from baseline were described, and final patient success was evaluated at the month three visit. Patients who were still symptomatic after their initial regimen (at the Month 3 evaluation) were offered a switch to the alternate regimen

and returned for a follow-up assessment one month later.

Results

Topical cyclosporine provided statistically significantly greater improvements in Schirmer's scores, TBUT, corneal staining and OSDI scores compared with artificial tears after three months of treatment. Cyclosporine produced a statistically significant increase in Schirmer's (with anesthesia) scores of 2.7 ± 2.2 mm after three months ($P < 0.001$). Conversely, Schirmer's scores worsened in the artificial tears group, with a mean decrease of 1.4 ± 4.6 mm ($P = 0.271$).

Similarly, the mean TBUT score sig-

nificantly improved in the cyclosporine-treated patients (a mean increase of 3.56 ± 1.5 seconds, $P < 0.001$) but worsened in the control group (a mean decrease of 0.04 ± 1.6 seconds, $P = 0.929$). Cyclosporine-treated patients exhibited a significantly greater mean reduction in corneal staining (-1.3 ± 0.53) compared with artificial tears (-0.2 ± 0.83) after three months of treatment ($P < 0.001$). Moreover, cyclosporine provided significantly greater improvement in OSDI scores of patient symptoms than did artificial tears (mean reduction of 11.5 ± 8.8 with cyclosporine versus a mean decrease of 2.9 ± 11.6 with artificial tears, $P = 0.022$).

In the present study, cyclosporine A provided statistically significantly greater improvements in Schirmer's scores, OSDI, TBUT and corneal staining scores compared to artificial tears. This is likely due to cyclosporine's associated increase in tear production and decrease in localized inflammation.⁵

The findings reported here are consistent with another recent evaluation of the efficacy of topical cyclosporine for the treatment of ocular rosacea. Perry et al also found topical cyclosporine to be effective in treating patients with this disorder who were unresponsive to standard therapy. Moreover, most patients in that cohort (71 percent) were able to discontinue all other medications.⁶ The authors of this study also concluded that topical cyclosporine was safe and well tolerated in patients with ocular rosacea.

Conclusion

The results of this study conclude that topical cyclosporine A is superior to artificial tears for the treatment of clinical signs and patients' symptoms

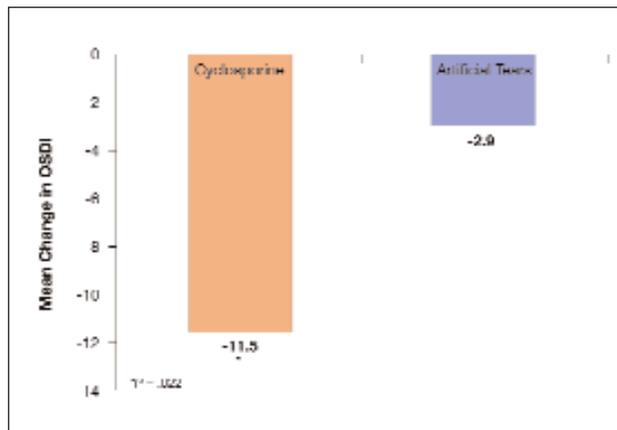


Figure 3. Change in OSDI (ocular surface disease index) score from initial visit.

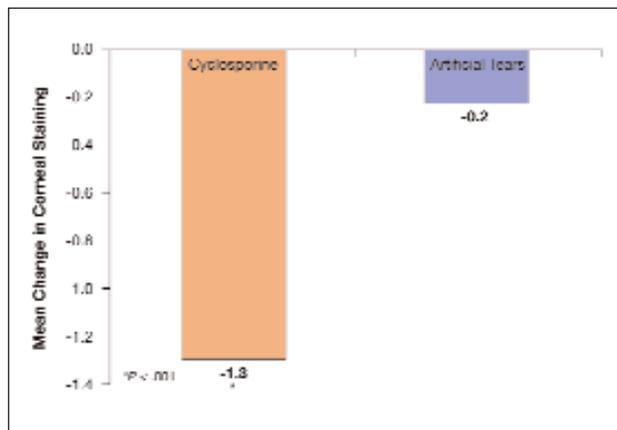


Figure 4. Change in mean corneal staining from initial visit after three months.

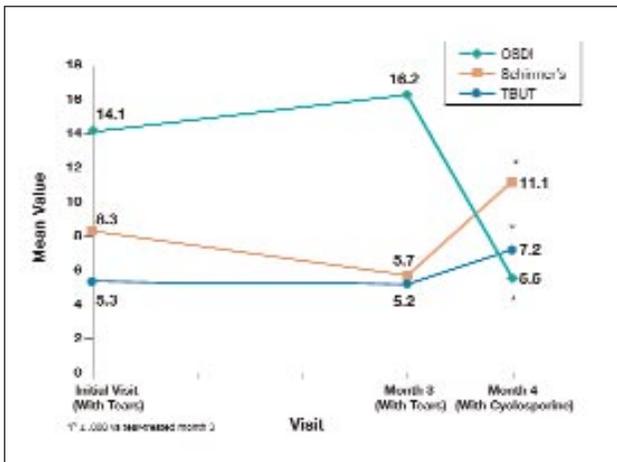


Figure 5. Evaluation of rosacea-associated ocular signs and symptoms in patients nonresponsive to artificial tear therapy who then switched to cyclosporine for one month.

of rosacea-associated lid and corneal changes. Most patients with ocular rosacea present with meibomian gland dysfunction and varying degrees of ocular surface involvement. Treatment should consist of lid hygiene, lubricants and anti-inflammatory medications. Since many patients have an associated dry eye, topical cyclosporine may be the therapy of choice for the treatment of ocular rosacea. [RCCL](#)

Dr. Schechter is Director, Department of Cornea and External Diseases at the Rand Eye Institute in Pompano Beach, FL.

REFERENCES

1. Stone DU, Chodosh J. Ocular rosacea. An update on pathogenesis and therapy. *Curr Opin Ophthalmol.* 2004; 15:499-502.
2. Bowman RW, McCulley JP, Jester JV. Meibomian gland dysfunction and rosacea. In: Pepose J, Holland G, Wilhelmus K, eds. *Ocular Infection and Immunity.* St. Louis, MO: Mosby-Year Book; 1996:334-343.
3. Kocak-Altintas AG, Kocak-Midillioglu I, Gul U, Bilezikci B, Isiksacan O, Duman S. Impression cytology and ocular characteristics in ocular rosacea. *Eur J Ophthalmol.* 2003;13:351-359.
4. Kunert KS, Tisdale AS, Stern ME, Smith JA, Gipson IK. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. *Arch Ophthalmol.* 2000;118:1489-1496.
5. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology.* 2000;107:631-639. Erratum in: *Ophthalmology.* 2000;107:1220.
6. Perry HD, Wittpenn JR, D'Aversa G, Donnenfeld ED. Topical cyclosporine 0.05% for the treatment of chronic, active ocular rosacea. Presented at: The Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); May 1-5, 2005; Fort Lauderdale, FL.