Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

PERSIST: Physician's Evaluation of Restasis® Satisfaction in Second Trial of topical cyclosporine ophthalmic emulsion 0.05% for dry eye: a retrospective review

This article was published in the following Dove Press journal:
Clinical Ophthalmology
27 November 2012
Number of times this article has been viewed

Francis Mah[1]
Mark Milner[2]
Samuel Yiu[3]
Eric Donnenfeld[4]
Taryn M Conway[5]
David A Hollander[5]

[1]University of Pittsburgh, Pittsburgh, PA, [2]The Eye Center, Hamden, CT, [3]University of Southern California, Los Angeles, CA, [4]Ophthalmic Consultants of Long Island and Connecticut, Rockville Centre, New York, NY, [5]Allergan Inc, Irvine, CA, USA

Background: Chronic dry eye disease often requires long-term therapy. Tear film alterations in the setting of dry eye may include reduced tear volume as well as an increase in inflammatory cytokines and osmolarity. Topical cyclosporine ophthalmic emulsion 0.05% (Restasis®; Allergan Inc, Irvine, CA) is indicated to increase tear production in patients with dry eye and reduced tear production presumed to be due to ocular inflammation. This study was designed to evaluate the efficacy of a second trial of topical cyclosporine in patients with dry eye who were previously considered treatment failures.

Materials and methods: This multicenter (three cornea practices) retrospective chart review evaluated clinical outcomes in patients with dry eye who received a second trial of cyclosporine after a prior treatment failure, defined as prior discontinuation of topical cyclosporine after less than 12 weeks.

Results: Thirty-five patients, most of whom were female (71.4%) and Caucasian (62.9%), were identified. Prior discontinuation was most commonly due to burning/stinging (60%). The median duration of second treatment was 10 months (range 1 week to 45 months). Physician education was provided in the second trial in 97.1% of cases. At initiation of the second trial of cyclosporine, 10 (28.6%) patients received courses of topical corticosteroids. Physicians reported on a questionnaire that 80% of patients achieved clinical benefit with a second trial of cyclosporine.

Conclusion: A repeat trial with topical cyclosporine can achieve clinical success. Direct patient education via the physician and staff may be key to success. Proper patient education may overcome adherence issues, particularly with respect to the need for long-term treatment of chronic dry eye. This study has the usual limitations associated with a retrospective chart review, and future prospective studies are warranted.

Keywords: cyclosporine, Restasis®, dry eye, tear cytokines, tear hyperosmolarity, corneal staining, keratoconjunctivitis sicca

Introduction

Dry eye has traditionally been classified as a condition of tear insufficiency secondary to either decreased tear production, increased tear evaporation, or a combination of both. It is now recognized that the tear-secreting glands and ocular surface, via sensory and autonomic nerve connections, form an integrated functional lacrimal unit that maintains ocular surface health.[1] Dysfunction in any component of the functional lacrimal unit leads to an unstable tear film and ocular surface inflammation, which ultimately manifests clinically as dry eye.[1,2] The dysfunction may stem from or be exacerbated

Correspondence: Francis Mah
University of Pittsburgh Medical Center, Department of Ophthalmology, 203 Lothrop Street, Pittsburgh, PA 15213, USA
Tel +1 412 647 2214
Fax +1 412 647 5119
Email mahfs@upmc.edu

by hormonal changes, age, systemic autoimmune diseases, environmental conditions, surgical interventions, and systemic medications.[3,4]

Dry eye is currently diagnosed by the presence of symptoms of ocular irritation and/or objective clinical signs, such as ocular surface staining. An International Task Force of 17 dry eye specialists, using a Delphi consensus technique, categorized dry eye into four levels of severity and established treatment guidelines based on severity of disease.[5] The International Task Force panelists agreed that inflammation triggers or sustains most cases of dry eye disease, even in those cases in which inflammation is not clinically apparent. Therefore, topical anti-inflammatory therapies (corticosteroids, topical cyclosporine) were recommended beginning at disease level 2 (moderate-severe symptoms, mild corneal punctate staining, conjunctival staining).[5]

Dry eye is a chronic disease, which may have a substantial impact on a patient's quality of life.[6] While short 2–4-week courses of topical corticosteroids can often lead to symptomatic improvement,[7] long-term use of topical corticosteroids may be associated with glaucoma, cataracts, and other steroid-related side effects.[8,9] In contrast, topical cyclosporine, which specifically blocks T-cell activation, may be a more appropriate long-term therapy because it is not associated with either significant systemic adverse events or the common steroid-related ocular side effects. Topical cyclosporine ophthalmic emulsion 0.05% (Restasis®; Allergan Inc, Irvine, CA), approved in 2002 by the US Food and Drug Administration, is indicated to increase tear production in patients with reduced tear production presumed due to ocular inflammation. In two multicenter, randomized, prospective, Phase III clinical trials, topical cyclosporine 0.05% was shown to improve categorized Schirmer values, reduce corneal staining, and improve subjective measures, including blurred vision and dependence on artificial tears relative to vehicle.[10] Burning and stinging upon instillation were the most common treatment-related side effects.[10]

Multiple, prospective randomized studies have demonstrated progressively greater clinical impact over time with the use of topical cyclosporine in dry eye patients.[10,11] Nevertheless, as with many therapies for chronic diseases, many patients may discontinue topical cyclosporine treatment early in the treatment course. The purpose of this study was to evaluate treatment strategies and outcomes in dry eye patients who received a second trial of topical cyclosporine after previously discontinuing therapy after less than 12 weeks.

Materials and methods

A retrospective chart review was conducted at three tertiary care, cornea-specialist sites (two academic, one private practice). Inclusion criteria specified that all patients were older than 16 years in age, were previously diagnosed with chronic dry eye, had discontinued an initial course of topical cyclosporine after less than 12 weeks of treatment and were subsequently treated at a later date with a second course of topical cyclosporine. For inclusion, at least 2 weeks separated the initial and second trial of topical cyclosporine. All patients included in this review were prescribed topical cyclosporine as a second trial prior to June 1, 2008 to allow at least one year of follow-up. Patients treated with topical cyclosporine for conditions other than dry eye, such as contact lens intolerance[12] and ocular rosacea[13] were excluded.

The study protocol was approved and a waiver for collection of informed consent and authorization for use and release of health research study information from patients was obtained from all institutional review boards. The study is registered on ClinicalTrials.gov (NCT00827255). Clinical charts were reviewed and assessed at the following established times: baseline visit (initiation of second trial of topical cyclosporine), visit 1 (6 ± 1 weeks), visit 2 (3 ± 1 months), visit 3 (6 ± 2 months), and visit 4 (12 ± 3 months). Response measures collected (if recorded) included Schirmer scores, tear break-up time, corneal staining, use of artificial tears, and use of other concomitant topical and systemic medications.

Data collected included medical and ophthalmic history, initial reasons for discontinuation of cyclosporine treatment, whether patient education was performed with second trial of topical cyclosporine, the use of any additional dry eye therapies, and a physician evaluation of whether clinical benefits were achieved during the second treatment of topical cyclosporine.

Results

A total of 35 patients satisfied the inclusion criteria and were included in this study. Eight (22.9%) of 35 patients were referred from other ophthalmologists. The demographics and baseline characteristics of the patients included in the study are listed in Table 1. Most patients were female (71.4%) and Caucasian (62.9%). Approximately half of the patients (48.6%) were younger than 60 years of age. Systemic immunologic conditions associated with chronic dry eye were reported in 20% (seven of 35) of the patients, including two (5.7%) Sjögren's syndrome, two (5.7%) rheumatoid arthritis, two (5.7%) scleroderma, and one (2.9%) sarcoidosis. Fifteen (42.9%) patients had previously undergone refractive surgery

Table 1 Patient demographics and baseline characteristics

	All patients n = 35
Sex, n (%)	
Male	10 (28.6)
Female	25 (71.4)
Age group, years, n (%)	
<40	7 (20.0)
40–49	2 (5.7)
50–59	8 (22.9)
60–69	5 (14.3)
70–79	11 (31.4)
≥80	2 (5.7)
Race, n (%)	
White	22 (62.9)
Asian	4 (11.4)
Unknown	9 (25.7)
Duration of dry eye symptoms, years, n (%)	
<1	3 (8.6)
1–2	2 (5.7)
3–5	12 (34.3)
6–10	8 (22.9)
>10	4 (11.0)
Unknown	6 (17.1)
History of refractive surgery: yes, n (%)	15 (42.9)

in at least one eye and one (2.9%) patient had had a prior penetrating keratoplasty. Seventeen (48.6%) of the patients had reported dry eye symptoms for 5 years or less.

The reasons underlying discontinuation by patients from an initial treatment course of topical cyclosporine for dry eye after less than 12 weeks are listed in Table 2. The most common reason for discontinuing initial therapy was burning/stinging (60%). During the initial trial with topical cyclosporine, artificial tears were used by 26 (74.3%) patients. In addition to artificial tears, at least one additional concomitant therapy was utilized in 14 (40%) patients to address ocular surface symptoms. Concomitant therapies included punctal plugs (11 patients; 31%), topical corticosteroids (three patients; 9%), oral nutritional supplements (two patients; 6%), and a topical antihistamine (one patient; 3%).

At the baseline visit in which patients were restarted on topical cyclosporine, 25 (71.4%) patients were using artificial tears (2–15 drops daily), 14 (40%) patients had punctal plugs already in place, and two (5.7%) patients were on topical corticosteroids. In addition, one (2.9%) patient was on serum eye drops and oral nutritional supplements at baseline. At baseline, education about dry eye and topical cyclosporine was provided to patients in the vast majority of cases (97.1%) as shown in Table 3. Patient education was provided through multiple avenues, including via direct physician instruction

Table 2 Reasons for discontinuing first trial of cyclosporine ophthalmic emulsion 0.05%

Reason, n (%)[a]	Patients n = 35
Burning/stinging	21 (60.0)
Physician instruction	8 (22.9)
Lack of efficacy	5 (14.3)
Lack of understanding need for chronic treatment	3 (8.6)
Cost	0 (0.0)
Other/unknown	5 (14.3)

Note: [a]More than one reason may be given for discontinuation of initial trial.

(94.3%), dialog with office staff (22.9%), or a handout or pamphlet (20.0%). Patient education on topical cyclosporine most commonly addressed tolerability (77.1%) and/or duration of treatment (48.6%).

At the baseline visit, 23 (65.7%) patients had best-corrected visual acuity of 20/40 or better in both eyes while three (8.6%) patients had best-corrected visual acuity worse than 20/100 in one or both eyes. At baseline, Schirmer's testing was recorded in 14 of the 35 patients. Schirmer values < 10 mm were recorded in at least one eye in 13 of these 14 patients (range 0–12 mm in lowest of two eyes). An assessment of staining was performed and recorded in 25 of 35 patients at baseline. Documented corneal staining was present in 19 (76%) of these 25 patients. Eight (32%) of these 25 patients had central staining present in at least one eye.

A total of 10 (28.6%) patients were treated with topical corticosteroids (once or twice daily) at the time of the initiation of the second trial of topical cyclosporine. Eight of these 10 patients initiated treatment with topical corticosteroids concurrent with initiation of topical cyclosporine and two began treatment with topical corticosteroids prior to cyclosporine. In addition to a topical corticosteroid, one patient was also started on oral doxycycline and one patient was started on N-acetylcysteine at the baseline visit when the second trial with topical cyclosporine was initiated. Eight of the 10 patients treated with topical corticosteroids

Table 3 Format of patient education in second trial of topical cyclosporine

Type of education provided, n (%)[a]	Patients n = 35
Direct physician discussion	33 (94.3)
Discussion with office staff	8 (22.9)
Handout/pamphlet	7 (20.0)
Other	2 (5.7)
No documented patient education	1 (2.9)

Note: [a]More than one reason may be given for discontinuation of initial trial.

concomitant with topical cyclosporine had discontinued their first course of topical cyclosporine at least partially due to stinging and burning. Five of the 10 patients were tapered off topical corticosteroids between 2 and 6 weeks and three patients were tapered off between 6 and 12 weeks after initiating the second trial of topical cyclosporine. There was one additional patient with a history of penetrating keratoplasty who remained on treatment with topical steroids twice per week throughout follow-up.

The median time that patients remained on topical cyclosporine during the second trial was 10 months (mean [SD] 12 ± 11 months) and the range was one week to 45 months. Three (8.6%) patients discontinued the second trial of topical cyclosporine after less than 4 weeks, two due to burning and stinging and one due to noncompliance. Fifteen (42.9%) patients remained on topical cyclosporine for 12 months or more, and seven of these 15 patients were still on topical cyclosporine at the end of the study. From the baseline visit, 18 (51.4%) patients did not receive any additional treatments or procedures for dry eye, with the exception of artificial tears. During follow-up, punctal plugs were placed in four additional patients between 6 weeks and 12 months. Short courses of topical corticosteroids were prescribed in two additional patients after the baseline visit. At the time of the last recorded visit, topical corticosteroids had been tapered off in all but three patients. Additional dry eye treatments or procedures performed following baseline included addition of oral doxycycline (three patients), oral N-acetylcysteine (two patients), serum tears (two patients), polyvinylpyrrolidone (FreshKote®; Focus Laboratories Inc, North Little Rock, AR; one patient), and eyelid surgery (one patient) for exposure.

On a questionnaire at the end of the study, physicians reported that clinical benefit was achieved in 80% of patients on initiation of the second trial of topical cyclosporine. The most common reasons cited for determining clinical success included improvement in patient symptoms (57.1%) and reduction in corneal staining/improved corneal surface appearance (22.9%). Complete clearing of corneal staining was observed in six (33.3%) of 18 patients for whom records were available at both baseline and the final visit during treatment with topical cyclosporine. Absence of any corneal staining was noted at the final visit in 14 (48.3%) of 29 patients with records available at the final visit. Qualitative improvements in tear break-up time were noted in four of seven patients in whom tear film break-up time was recorded at both baseline and final visits, though specific values for tear break-up time were not recorded. Increases in Schirmer values were noted in three of four patients in which Schirmer scores were measured at both baseline and the final visit.

Discussion

It is presently estimated that 4–5 million people in the United States aged 50 years or older suffer from dry eye disease.[14,15] The tear film alterations that occur in dry eye disease include a decrease in aqueous tear production, an increase in inflammatory cytokines and matrix metalloproteinases, and an increase in tear osmolarity. While artificial tears are the most common initial therapy employed to relieve dry eye symptoms, artificial tears alone do not directly address the underlying ocular surface inflammation.[16] Developing successful algorithms and strategies for treating the underlying inflammation in patients with dry eye is critical in order to address the chronic nature of dry eye, minimize potential ocular side effects, and potentially limit the progression of disease.

The present study population consisted entirely of patients who had previously discontinued therapy with topical cyclosporine, most commonly due to tolerability. While data are not available on whether education was provided to patients on their initial course of therapy, patient education was an essential component in the initiation of the repeat course of topical cyclosporine treatment in 97% of patients. This education often included direct instruction by the treating physician as well as an additional discussion with office staff or a patient handout and focused most commonly on duration of therapy and tolerability. It is critical for patients to understand that dry eye is a chronic disease potentially requiring long-term therapy.[4,17–19] Patients should be educated that the effects of topical cyclosporine often continue to improve with use, as evidenced in the Phase III clinical trials.[10] Patients should be educated that burning and stinging may be experienced with initiation of treatment because these are the most common treatment-related adverse events.[10] In addition, symptoms of burning and stinging, which are related to the severity of dry eye disease and the degree of ocular surface inflammation and epithelial breakdown,[20] often mitigate over time.[10]

In the present study, topical corticosteroids were prescribed in conjunction with topical cyclosporine in 28.6% of patients in the repeat trial cyclosporine. The use of topical corticosteroids was prohibited in the original Phase III trials with topical cyclosporine. However, more recent studies have demonstrated that topical corticosteroids may reduce stinging associated with topical cyclosporine,[21] and may be particularly useful as adjuncts to topical cyclosporine in patients who experience significant burning or stinging upon

cyclosporine instillation. Of note, 80% of the patients treated with concurrent topical corticosteroids at the initiation of the second trial had reported that burning and stinging with topical cyclosporine was at least one of the reasons why they discontinued treatment at an earlier time period. Potentially as a result of patient education as well as use of adjunctive medications in a subset of patients, only two patients in the present study discontinued in the first month during the repeat trial of topical cyclosporine due to burning and stinging. Furthermore, the median time that patients remained on topical cyclosporine in the second trial was 10 months, allowing for better results than in patients who received initial treatment for less than 12 weeks. Recently, Rao has demonstrated progressive improvements in such signs as Schirmer score and staining with sustained treatment with topical cyclosporine over 24 months.[19]

In this retrospective chart review, physicians were asked whether patients achieved clinical success during the second trial of topical cyclosporine despite having discontinued a prior course of topical cyclosporine after less than 12 weeks. Overall, physicians reported that 80% of patients clinically improved, though success may have been based on objective signs and/or patient symptoms. Each patient received an individualized treatment course based on physician preference. The addition of medications or treatments to topical cyclosporine was not considered a failure of topical cyclosporine in the present study. In addition to courses of topical corticosteroids, some patients may have also received doxycycline to address underlying meibomian gland disease, lid surgery for exposure keratopathy, as well as serum tears or other additional medications in some of the more severe cases of dry eye. It is recognized that patients with more severe dry eye disease and other concomitant ocular surface conditions may require multidrug therapy.[5,20]

The authors recognize that this study suffers from the usual limitations associated with a retrospective chart review. Data for such measures as staining, Schirmer score or tear break-up time may not have been recorded at the given time periods selected for review. There may have been a selection bias towards more severe disease based on the inclusion of tertiary care corneal practices and the requirement that all patients had been previously prescribed topical cyclosporine. Both the criteria for diagnosing dry eye and selection of a particular medication adjunctive to topical cyclosporine during the treatment course were based on individual practice patterns of the treating physician. In addition, the decision as to whether clinical success was achieved was based on the physician's assessment of the patient's course following the second trial of topical cyclosporine. The success reported in this study is somewhat higher than the physicians' subjective assessment of global response of 68.5% of patients exhibiting an improvement at month 6 in the Phase III trials.[10] This higher success rate, in potentially more severe patients, may have been influenced by the use of adjunctive therapies such as topical corticosteroids at initiation of topical cyclosporine, particularly in patients who discontinued the initial course of topical cyclosporine due to burning and stinging. Nevertheless, this study does reveal that some patients, who may have been previously considered treatment failures due to discontinuing cyclosporine after less than 12 weeks, may receive clinical benefit upon retrial of topical cyclosporine. Ultimately, larger prospective studies are warranted to validate the findings of the present study.

Treatment patterns for dry eye disease continue to evolve with increased understanding of the pathophysiology of dry eye. Anti-inflammatory therapies are currently recommended even in the absence of hyperemia or other clinically apparent inflammation for patients with level 2 or greater disease severity.[5,22] When needed for chronic disease, long-term therapy with topical cyclosporine has been shown to reduce disease progression[11] and has not been associated with ocular complications such as intraocular pressure elevation, which remains a risk factor with sustained topical corticosteroid use.[9] The results of the present study demonstrate that a repeat trial with topical cyclosporine ophthalmic emulsion 0.05% can achieve clinical success in patients with chronic dry eye. Proper patient education may overcome adherence issues, particularly with respect to the need for long-term treatment for dry eye disease, and long-term prospective studies are warranted.

Disclosure

Julia R Gage provided writing support and SCI Scientific Communications and Information provided editorial support for this research; both were funded by Allergan Inc. The authors report no other conflicts of interest in this work.

References

1. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea*. 1998;17(6):584–589.
2. Perry HD. Dry eye disease: pathophysiology, classification, and diagnosis. *Am J Manag Care*. 2008;14(3 Suppl):S79–S87.
3. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five-year review. *Cornea*. 2000;19(5):644–649.
4. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):75–92.

5. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. *Cornea*. 2006;25(8):900–907.
6. Miljanovic B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol*. 2007;143(3):409–415.
7. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome. *Ophthalmology*. 1999;106(4):811–816.
8. Pflugfelder SC. Antiinflammatory therapy for dry eye. *Am J Ophthalmol*. 2004;137(2):337–342.
9. Rajpal RK, Digby D, D'Aversa G, Mah F, Hollander DA, Conway T. Intraocular pressure elevations with loteprednol etabonate: a retrospective chart review. *J Ocul Pharmacol Ther*. 2011;27(3):305–308.
10. 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. CsA Phase 3 Study Group. *Ophthalmology*. 2000;107(4):631–639.
11. Rao SN. Topical cyclosporine 0.05% for the prevention of dry eye disease progression. *J Ocul Pharmacol Ther*. 2010;26(2):157–164.
12. Hom MM. Use of cyclosporine 0.05% ophthalmic emulsion for contact lens-intolerant patients. *Eye Contact Lens*. 2006;32(2):109–111.
13. Schechter BA, Katz RS, Friedman LS. Efficacy of topical cyclosporine for the treatment of ocular rosacea. *Adv Ther*. 2009;26(6):651–659.
14. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol*. 2003;136(2):318–326.
15. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. *Arch Ophthalmol*. 2009;127(6):763–768.
16. Lemp MA. Management of dry eye disease. *Am J Manag Care*. 2008;14(3 Suppl):S88–S101.
17. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. *Ophthalmology*. 2007;114(1):76–79.
18. Su MY, Perry HD, Barsam A, et al. The effect of decreasing the dosage of cyclosporine A 0.05% on dry eye disease after 1 year of twice-daily therapy. *Cornea*. 2011;30(10):1098–1104.
19. Rao SN. Reversibility of dry eye deceleration after topical cyclosporine 0.05% withdrawal. *J Ocul Pharmacol Ther*. 2011;27(6):603–609.
20. Wilson SE, Stulting RD. Agreement of physician treatment practices with the international task force guidelines for diagnosis and treatment of dry eye disease. *Cornea*. 2007;26(3):284–289.
21. Sheppard JD, Scoper SV, Samudre S. Topical loteprednol pretreatment reduces cyclosporine stinging in chronic dry eye disease. *J Ocul Pharmacol Ther*. 2011;27(1):23–27.
22. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):163–178.