Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease

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Objective: To compare the efficacy and safety of cyclosporin A ([CsA] 0.05% and 0.1% ophthalmic emulsions) to vehicle in patients with moderate to severe dry eye disease.

Design: Multicenter, randomized, double-masked, parallel-group, 6-month, vehicle-controlled.

Participants: A total of 877 patients with defined moderate to severe dry eye disease (292 to 293 in each treatment group).

Methods: Two identical clinical trials; patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle. The results of these two trials were combined for analysis.

Main Outcome Measures: Efficacy: corneal and interpalpebral dye staining, Schirmer tear test (with and without anesthesia), tear break-up time, Ocular Surface Disease Index (OSDI), facial expression, patient subjective rating scale, symptoms of dry eye, investigator's evaluation of global response to treatment, treatment success, and daily use of artificial tears. Safety: occurrence of adverse events, best-corrected visual acuity, intraocular pressure, biomicroscopy, and blood trough CsA concentrations.

Results: Treatment with CsA, 0.05% or 0.1%, gave significantly ($P \leq 0.05$) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). There was no dose-response effect. Both CsA treatments exhibited an excellent safety profile, and there were no significant topical or systemic adverse safety findings.

Conclusions: The novel ophthalmic formulations CsA 0.05% and 0.1% were safe and effective in the treatment of moderate to severe dry eye disease yielding improvements in both objective and subjective measures. Topical CsA represents a new pharmacologically based treatment for dry eye disease that may provide significant patient benefits. *Ophthalmology 2000;107:631–639 © 2000 by the American Academy of Ophthalmology.*

Despite the millions of individuals who have dry eye disease,[1–4] there is currently no therapeutic treatment for this condition. Individuals plagued by the discomfort, burning, irritation, photophobia, and other symptoms of dry eye disease may also have blurred vision, gradual contact lens intolerance, and the inability to produce emotional tears, as well as an increased risk of ocular surface damage and ocular infection.[5–9] Yet, at this time, the only treatments available are palliative in nature, consisting of lubricating eyedrops or punctal occlusion procedures that attempt to supplement the patient's natural tears or improve the residence time of the limited quantity of tears that the patient can produce.

Until recently, attempts to develop therapeutic treatments for dry eye disease were hampered by a limited understanding of the underlying pathophysiologic processes. Although the exact mechanism is still not completely understood, there is now sufficient evidence to suggest that dry eye disease is the result of an underlying cytokine and receptor-mediated inflammatory process affecting both the lacrimal gland and the ocular surface.[2,10–14] This hypothesis is further supported by results from animal[15–18] and human [20–21] (Foulks et al, Invest Ophthalmol Vis Sci 1996;37:S646; Helms et al, Invest Ophthalmol Vis Sci 1996;37; S646; Kunert et al, Invest Ophthalmol Vis Sci 1999;40(4):S771;

Originally received June 16, 1999.
Accepted: December 8, 1999. Manuscript no. 99316.

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Supported by a grant from Allergan Inc.

Dr. Reis is an employee of Allergan, Inc. None of the other authors has a financial interest in any of the products mentioned in this paper.

ISSN 0161-6420/00/$–see front matter

Turner et al, Invest Ophthalmol Vis Sci 1999;40[4]:S558) studies that demonstrate that topical treatment with the immunomodulatory agent cyclosporin A (CsA) can have beneficial effects on the underlying inflammatory pathologic condition of dry eye disease, as well as improve the signs and symptoms of this condition.

Evidence of the inflammatory nature of dry eye disease and the success of preliminary investigations into the effects of topical CsA treatment led to a large-scale multicenter, vehicle-controlled, dose-ranging (phase 2) clinical trial of the efficacy and safety of CsA treatment in moderate to severe dry eye disease. This study demonstrated that such treatment was safe and resulted in significant improvements in the signs and symptoms of the disease.[21]

The objective of the studies described here was to compare the efficacy and safety of twice daily CsA, 0.05% and 0.1%, ophthalmic emulsions to vehicle in the treatment of moderate to severe dry eye disease in patients with or without Sjögren's syndrome. In addition, specialized assays were performed on conjunctival biopsy specimens from a subset of patients to investigate the levels of several inflammatory markers and the density of conjunctival goblet cells before and after treatment. The results of these specialized studies will be reported separately; preliminary reports have been presented (Kunert et al, Invest Ophthalmol Vis Sci 1999;40[4]:S771; Turner et al, Invest Ophthalmol Vis Sci 1999;40[4]:S558).

Materials and Methods

Study Design

Two identical multicenter, randomized, double-masked, parallel-group clinical trials were conducted to compare two concentrations of CsA ophthalmic emulsion to its vehicle. The 6-month treatment phase was preceded by a 2-week run-in phase to standardize all patients to a common regimen of artificial tear use. The results of these two trials were combined for analysis.

Both trials were conducted in compliance with Good Clinical Practices, investigational site Institutional Review Board Regulations, Sponsor and Investigator Obligations, Informed Consent Regulations, and the Declaration of Helsinki. Potential patients signed a prescreening informed consent. A second written informed consent was obtained from all patients before actual enrollment, and a separate informed consent was obtained for the subset of patients who participated in the pharmacokinetic evaluations.

Patients. Adult patients of either sex were eligible for participation if they had a diagnosis of moderate to severe dry eye disease as defined by the following criteria (detailed descriptions of each parameter are given under "Outcome Measures"): (1) Schirmer test without anesthesia of $\leq$ 5 mm/5 min in at least one eye (if Schirmer test without anesthesia of = 0 mm/5 min, then Schirmer with nasal stimulation had to be $>$ 3 mm/5 min in the same eye); (2) sum of corneal and interpalpebral conjunctival staining of $\geq +5$ in the same eye where corneal staining was $\geq +2$; (3) a baseline Ocular Surface Disease Index ([OSDI]; see later) score of 0.1 with no more than three responses of "not applicable"; and (4) a score of $\geq$ 3 on the Subjective Facial Expression Scale (see later). Signs and symptoms must have been present despite conventional management, which may have included artificial tear drops, gels and ointments, sympathomimetic agents, parasympathomimetic agents, and punctal occlusion. Eligible patients were enrolled if they were deemed capable of following the study protocol and considered likely to complete the treatment period and return for all scheduled visits; if they had normal lid position and closure, and a best-corrected ETDRS visual acuity score of +0.7 LogMar or better in each eye.

Patients were excluded from the study if they had participated in an earlier clinical trial with CsA ophthalmic emulsion or had used systemic or topical ophthalmic cyclosporine within 90 days before the study. Other exclusion criteria included the presence or history of any systemic or ocular disorder or condition (including ocular surgery, trauma, and disease) that could possibly interfere with the interpretation of the study results; current or recent use of topical ophthalmic or systemic medications that could affect a dry eye condition; known hypersensitivity to any component of the study or procedural medications; required contact lens wear during the study; recent (within 1 month) or anticipated use of temporary punctal plugs during the study; permanent occlusion of lacrimal puncta within 3 months of the study; or if they were pregnant, lactating, or planning a pregnancy. Patients were also excluded if they appeared to have end-stage lacrimal gland disease (Schirmer reading with nasal stimulation of $<$ 3 mm/5 min) or if their dry eye disease was the result of destruction of conjunctival goblet cells or scarring. Any patient who no longer met the criteria for moderate to severe dry eye (as defined previously) after completing the 2-week run-in phase was excluded from enrollment in the treatment phase of the study.

Patients could be discontinued before the completion of the study because of adverse events, pregnancy, protocol violations, lack of efficacy, or administrative or personal reasons.

Study Medications. CsA, 0.05% and 0.1%, ophthalmic emulsions and the vehicle of CsA ophthalmic emulsion were the study medications, with individually packaged preservative-free artificial tears (REFRESH Lubricant Eye Drops, Allergan, Inc.) provided as an adjunctive treatment to be used as frequently as needed. The doses of CsA used were based on the results of an earlier dose-ranging study.[21] Both the CsA emulsions and vehicle were sterile, nonpreserved castor oil in water emulsions whose precise formulation is proprietary. All the study medications were supplied in unit dose vials.

Concomitant Medications. Any therapy considered necessary for the maintenance of patient welfare was given at the discretion of the investigator and noted on the case report form. If the medication would not interfere with the response to study medication, the patient was kept in the study. During the study, all concomitant medication treatment regimens were kept as constant as permitted by accepted medical practice. Systemic and topical ophthalmic medications that could interfere with the response to study medications or the interpretation of the study results were prohibited during the study. This included cyclosporine, other immunomodulatory agents, general anesthetics, antihistamines, cholinergic agents, antimuscarinics, β-blocking agents, tricyclic antidepressants, phenothiazines, topical ophthalmic steroids, estrogen-progesterone (or other estrogen derivatives), or any topical ocular medications other than the assigned study medication and assigned artificial tears.

Study Protocol. During the 2-week run-in phase, all patients were instructed to use the assigned artificial tears only (as needed). During the treatment phase, patients were instructed to instill 1 drop of study medication twice daily in each eye for 6 months; once on waking in the morning and once at bedtime. Patients were allowed to use the assigned artificial tears as needed up to month 4. To avoid dilution of the study medication, patients were instructed not to use artificial tears within 30 minutes before or after use of the study medication. To minimize the habitual concomitant use of artificial tears, patients were asked to stop using artificial

tears 1 week before their month 4 study visit. At this visit, patients were encouraged to use artificial tears less than eight times a day for the rest of the study period.

During the treatment phase, patients returned for evaluation after 1, 3, 4, and 6 months of treatment.

Outcome Measures

Efficacy. The objective signs monitored were corneal and interpalpebral conjunctival staining, Schirmer tear test (with and without anesthesia), and tear break-up time. The subjective endpoints used were the OSDI, the facial expression subjective rating scale, symptoms of dry eye, investigator's evaluation of global response to treatment, treatment success, and artificial tears use. All these variables were evaluated at baseline and at each study visit, except for tear break-up time, which was not evaluated at the 1-month visit; the investigator's evaluation of global response to treatment, which could not be meaningfully assessed at baseline; and the Schirmer tear test with anesthesia, which was only evaluated at baseline, month 3, and month 6.

For corneal fluorescein staining, the entire cornea was examined using slit-lamp evaluation with a yellow barrier filter and cobalt blue illumination. Staining was graded using the Oxford Scheme 6-point scale (from 0 to 5), with each investigator using the same set of photographs (provided by the study sponsor) as a guide. Lissamine green was then instilled, and interpalpebral conjunctival staining was evaluated more than 30 seconds, but less than 2 minutes, later. Using white light of moderate intensity, the interpalpebral regions of the temporal and nasal conjunctiva were graded using the same Oxford Scheme. The sum of corneal and interpalpebral staining was therefore on a 0 to 15 point scale. On all scales, a negative change from baseline indicated an improvement.

The Schirmer tear test was performed both with and without anesthesia and graded on a 5-point scale as follows: 1 (< 3 mm/5 min), 2 (3–6 mm/5 min), 3 (7–10 mm/5 min), 4 (11–14 mm/5 min), and 5 (>14 mm/5 min) using the worse eye. A positive change from baseline indicated improvement. Categorized values were used to reduce overall within-patient variability known to occur for Schirmer wetting scores. The categories were chosen a priori on the basis of cutoff points suggested by a review of the medical literature and consultation with clinical investigators.

Time until random location tear break-up between blinks was measured only up to 10 seconds and recorded only if the value was less than 10 seconds.

The OSDI questionnaire was used to evaluate the impact of a patient's dry eye disease on vision-related functioning.[22] It consisted of 12 questions that were each rated from 0 = none of the time to 4 = all of the time. An overall score was calculated by dividing the sum of the responses for all questions answered by the total possible score. Thus, overall scores ranged from 0 = no disability to 1 = complete disability. A negative change from baseline indicated an improvement in vision-related functioning.

The Subjective Facial Expression Rating Scale[23] consisted of nine facial schematics ranging from 1 (the happiest face) to 9 (the unhappiest face) analyzed in five grades from 1 (pictures 1 and 2) to 5 (pictures 8 and 9). A negative change from baseline indicated an improvement.

Symptoms of ocular discomfort, such as stinging/burning, itching, sandiness/grittiness, blurred vision, dryness, light sensitivity, pain or soreness, were graded using a 5-point scale ranging from 0 = do not have this symptom to +4 = always notice this symptom). A negative change from baseline indicated an improvement.

The investigator completed a global evaluation of the overall effect of the study medication relative to the qualification visit using a 7-point scale in which 0 = completely cleared, 1 = ≈90% improvement, 2 = ≈75% improvement, 3 = ≈50% improvement, 4 = ≈25% improvement, 5 = condition unchanged, and 6 = condition worsened. Treatment success was defined as a global evaluation of ≈90% improvement or better.

Patient use of concomitant artificial tears was also monitored. At each study visit, patients were queried about the average number of times they used artificial tears each day during the past week and the number of days during the past week when they did not use any artificial tears.

Safety. The primary safety variable monitored was the occurrence of adverse events. The severity of each adverse event observed was rated from mild (awareness of sign or symptom, but easily tolerated) to severe (incapacitating with inability to work or do usual activity). The relationship of the event to the study medication was assessed by the investigator as none, unlikely, possible, probable, or definite.

Other safety variables monitored included best-corrected visual acuity (using the ETDRS chart), intraocular pressure (using Goldman applanation tonometry), and biomicroscopy (using slit-lamp examination without pupil dilation). Pharmacokinetic testing was also done on a subset of patients to determine blood trough CsA concentrations during treatment.

Safety variables were evaluated at baseline and at all study visits, except for intraocular pressure, which was only evaluated at baseline and month 6, and CsA blood levels, which were evaluated at baseline and months 1 and 6.

Other Measures

Blood was collected from all patients for autoantibody testing to aid in the prospective identification of individuals with Sjögren's syndrome. Frozen samples were sent to a central laboratory (Covance Central Laboratories Inc, Indianapolis, IN) for log in and inventory before shipment to the Scripps Reference Laboratory (San Diego, CA) for the actual tests. Blood samples were evaluated for the presence of antinuclear antibodies, rheumatoid factor, and class SS-A and class SS-B Sjögren's antibodies.

Blood was also collected from a subset of patients for determination of mean blood CsA trough concentration. Frozen samples were sent to the sponsor (Allergan, Inc.) for analysis, under Good Laboratory Practices regulations, using liquid chromatography-mass spectrometry mass/mass spectrometry (LC-MS/MS) with a quantitation limit of 0.1 ng/ml.

Statistical Methods

All analyses presented in this report were conducted on the intent-to-treat patient population (all patients randomized). A last-observation carried-forward method was used to input missing data, although baseline data (before study treatment) were not carried forward. For efficacy variables collected on both eyes, only the data from the "worse" eye were included in the analyses. The "worse" eye was defined as the eye with the worse Schirmer tear test value (without anesthesia) and the worse sum of corneal and interpalpebral conjunctival staining. If both eyes were comparable, then the right eye was used. The "worse" eye was defined on the basis of the baseline measurements, and data from this eye were used for all subsequent analyses. However, it should be noted that data were collected on both eyes throughout the study. All safety analyses included data from both eyes.

Descriptive statistics were used to summarize all continuous variables (such as all staining variables and the OSDI score) and categorical variables (such as the Subjective Facial Expression Rating Scale, symptoms of dry eye disease, and categorized Schirmer values). A two-way analysis of variance (ANOVA), with

Table 1. Patient Disposition

	CsA 0.05%	CsA 0.1%	Vehicle
Enrolled	293	292	292
Completed	235 (80.2%)	218 (74.7%)	218 (74.7%)
Discontinued			
Lack of efficacy	1 (0.3%)	3 (1.0%)	3 (1.0%)
Adverse events	19 (6.5%)	29 (9.9%)	13 (4.5%)
Lost to follow-up	4 (1.4%)	3 (1.0%)	11 (3.8%)
Personal reasons	9 (3.1%)	14 (4.8%)	9 (3.1%)
Protocol or enrollment violations*	19 (6.5%)	21 (7.2%)	30 (10.3%)
Other†	6 (2.0%)	4 (1.4%)	8 (2.7%)

CsA = cyclosporin A.

* Protocol or enrollment violations included improper entry, non-compliance, and use of prohibited medications.

† Other included pregnancy, relocation, and removal from the study by the sponsor.

group and investigator effects and interaction, was used to test for among-group differences in continuous variables. The Cochran-Mantel-Haenszel[24] procedure with modified ridits, stratified by site, was used to test for differences in change from baseline among treatment groups in categorical variables and for among-group differences in global response distributions. The paired *t* test method was used to analyze within-group changes from baseline in continuous variables, whereas the Wilcoxon signed rank test was used to analyze within-group changes from baseline in categorical variables.

Statistical adjustment of *P* values for multiple comparisons have been addressed by use of the Fisher's least significant difference protected tests to ensure that the experimental-wise error rate was 0.05. Specifically, a pair wise comparison between either cyclosporine group and vehicle groups is considered statistically significant if and only if (1) the overall comparison among the three groups is significant at the 0.05 level, and (2) the pair wise comparison between cyclosporine and vehicle is significant at the 0.05 level. In addition, although patients were evaluated at multiple time points throughout the study, the primary endpoint is on the last observation while on treatment during the 6-month study period, and no further adjustments need to be made.

Each trial was powered separately, whereby given an expected sample size of 100 per group, the power to detect a three-grade difference between treatment groups in the change from baseline for the sum of corneal and interpalpebral conjunctival staining was greater than 0.86, using a two-sided Wilcoxon rank sum test with an estimated standard deviation of 6.49.

A two-sided test with a *P* value ≤ 0.05 was considered statistically significant.

Patient Treatment Assignment

Qualified patients were randomly assigned to receive one of the three study medications in a 1:1:1 ratio using a block size of 3. Only a single randomization was used per trial. There was no stratification by either site or baseline factors.

Study Masking

The study medication was packaged, labeled, and masked in a manner consistent with Good Manufacturing Practices for investigational supplies. Identical unit-dose vials were used to hold the study treatments, which were each of an identical milky color.

Results

Participant Flow and Follow-up

A total of 877 patients was enrolled in approximately equal numbers in the three treatment groups and more than 76% (671/877) completed the study (Table 1). The first patient was enrolled in July 1997 and the last patient completed the 6-month treatment period and evaluation in September 1998. Most of the patients who exited the study prematurely did so as a result of protocol or enrollment violations, personal reasons, lost to follow-up, or other nontreatment-related reasons. Only 0.8% of patients (7/877) were discontinued because of lack of efficacy; 1 of 293 (0.3%) in the CsA 0.05% group, 3 of 292 (1.0%) in the CsA 0.1% group, and 3 of 292 (1.0%) in the vehicle group. Only 7.0% (61/877) were discontinued because of adverse events; 19 of 293 (6.5%) in the CsA 0.05% group, 29 of 292 (9.9%) in the CsA 0.1% group, and 13 of 292 (4.5%) in the vehicle group.

Patient Demographics

The demographic characteristics of the study population are listed in Table 2. Overall, most of the patients were women (82%; 715/877) and Caucasian (84%; 740/847). There were no statistically significant differences between the treatment groups in any of the demographic variables measured. The use of prior therapy, or the types of concomitant medications used during the study for other medical conditions, were similar among the treatment groups.

Sjögren's syndrome was defined as the presence of ocular symptoms, oral symptoms, and a Schirmer test ≤ 5 mm, as well as the presence of at least one of the following autoantibodies: antinuclear antibodies, rheumatoid factor, and Sjögren's antibodies class SS-A and SS-B. Of the 877 enrolled patients, 270 (30.8%) were determined to have Sjögren's syndrome on the basis of these criteria. The number of patients with Sjögren's syndrome identified may underestimate the number in the study population because some patients left the studies without having autoantibody data collected and therefore could not meet the criteria for Sjögren's syndrome.

Efficacy Analysis

Corneal Staining. At baseline, the mean values for corneal staining in the different treatment groups ranged between 2.61 and 2.77 (using the Oxford scale from 0 to 5), with no statistically signif-

Table 2. Patient Demographics

	CsA 0.05% (n = 293)	CsA 0.1% (n = 292)	Vehicle (n = 292)
Age (mean ± SD)	58.7 ± 13.9	60.1 ± 13.3	59.9 ± 14.3
Sex			
Male	49 (16.7%)	54 (18.5%)	59 (20.2%)
Female	244 (83.3%)	238 (81.5%)	233 (79.8%)
Race			
Caucasian	253 (86.3%)	243 (83.2%)	244 (83.6%)
African-American	8 (2.7%)	16 (5.5%)	15 (5.1%)
Asian	8 (2.7%)	6 (2.1%)	6 (2.1%)
Hispanic	23 (7.8%)	26 (8.9%)	26 (8.9%)
Other	1 (0.3%)	1 (0.3%)	1 (0.3%)
Iris color			
Blue	97 (33.1%)	95 (32.5%)	109 (37.3%)
Brown	126 (43.0%)	127 (43.5%)	116 (39.7%)
Green	20 (6.8%)	26 (8.9%)	18 (6.2%)
Black	0 (0.0%)	2 (0.7%)	0 (0.0%)
Hazel	48 (16.4%)	38 (13.0%)	46 (15.8%)
Other	2 (0.7%)	4 (1.4%)	3 (1.0%)
Sjögren's syndrome patients	96 (32.8%)	83 (28.4%)	91 (31.2%)

CsA = cyclosporin A.

icant differences among the groups. There was a statistically significant improvement from baseline in corneal staining (decrease in mean score) within all treatment groups at all follow-up visits ($P < 0.001$). The improvement in corneal staining was significantly greater in both CsA groups than the vehicle group ($P \leq 0.044$) at month 4, and in the CsA 0.05% group at month 6 ($P = 0.008$). There was also a trend ($P = 0.062$) toward a significantly greater improvement in the CsA 0.1% group than the vehicle group at month 6 (Fig 1).

Conjunctival staining. At baseline, the mean values for temporal interpalpebral conjunctival staining ranged between 2.22 and 2.26 (using the Oxford scale from 0 to 5), with no statistically significant differences among the groups. Similarly, the mean baseline values for nasal interpalpebral conjunctival staining ranged between 2.42 and 2.45, with no statistically significant differences among the groups. Statistically significant improvements from baseline were seen in both temporal and nasal conjunctival staining within all study groups at all follow-up visits ($P < 0.001$), but there were no statistically significant among-group differences.

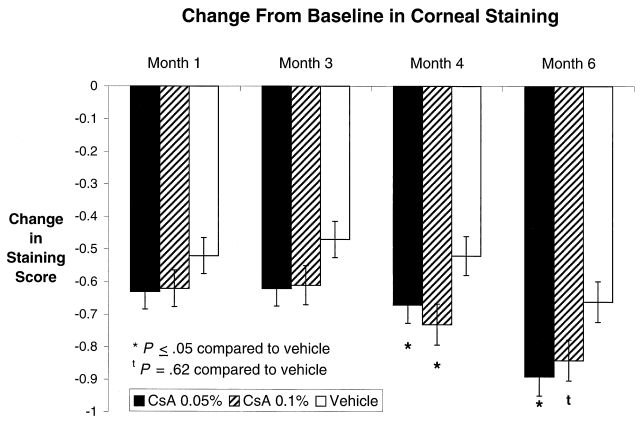

Figure 1. Change from baseline in corneal staining. Mean value ± standard error. Graded on a scale from 0 to 5.

Schirmer Tear Test. At baseline, the mean categorized Schirmer values (obtained with anesthesia) in the different treatment groups ranged between 1.94 and 2.11 (on a scale from 0 to 5 with 1 < 3 mm/5 min, 2 = 3–6 mm/5 min, 3 = 7–10 mm/5 min, 4 = 11–14 mm/5 min, and 5 >14 mm/5 min), with no statistically significant differences among the groups. At month 3, there was a significant worsening with the vehicle group ($P = 0.014$) and a significant difference among the treatment groups, with the CsA 0.05% group significantly greater than the vehicle group ($P = 0.009$). At month 6, there was a statistically significant improvement from baseline within both CsA groups. Moreover, the changes in Schirmer values in each of the CsA groups was significantly better than in the vehicle group (P < -0.007; Fig 2).

Schirmer tear tests were also conducted without anesthesia. At baseline, the mean categorized Schirmer values (obtained without anesthesia) in the different treatment groups ranged between 1.47 and 1.50 (on the same scale as was used for the Schirmer test with anesthesia), with no statistically significant differences among the

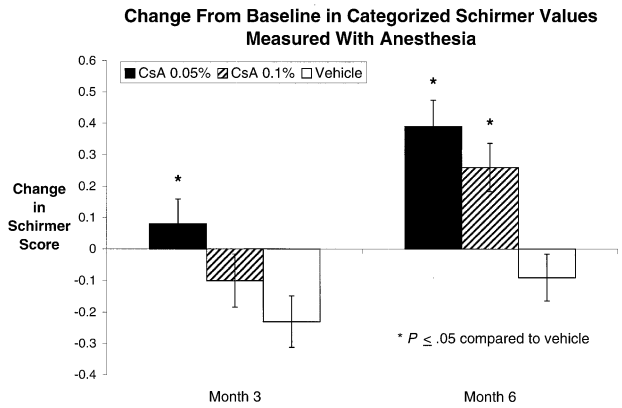

Figure 2. Change from baseline in categorized Schirmer values (measured with anesthesia). Mean value ± standard error. Categorized Schirmer values were graded on a 5-point scale as follows: 1 (< 3 mm/5 min), 2 (3–6 mm/5 min), 3 (7–10 mm/5 min), 4 (11–14 mm/5 min), and 5 (>14 mm/5 min) using the worse eye.

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