The Effect of Decreasing the Dosage of Cyclosporine A 0.05% on Dry Eye Disease After 1 Year of Twice-Daily Therapy

Michael Y. Su, MD, Henry D. Perry, MD, Allon Barsam, MA, MRCOphth, Alicia R. Perry, BS, Eric D. Donnenfeld, MD, John R. Wittpenn, MD, and Gerard D'Aversa, MD

Purpose: To evaluate the effect of decreasing topical cyclosporine 0.05% (tCSA) (Restasis; Allergan, Irvine, CA) from twice-daily dosing to once-daily dosing in patients who have already completed 12 months of twice-daily therapy for dry eye disease.

Design: Prospective, randomized, single-masked, parallel group comparison.

Participants: One hundred patients who had already been treated with tCSA twice daily for more than 1 year were randomized either to continue tCSA twice daily (n = 50) or to decrease tCSA once daily (n = 50).

Methods: Clinical measurement of dry eye variables was performed for all patients at baseline, 3 months, and 6 months. Mean data were used for within-group (longitudinal analysis) and between-group comparisons (once daily vs. twice daily).

Main Outcome Measures: Fluorescein tear break-up time, corneal fluorescein staining score, lissamine green staining score, Schirmer tear test, and ocular surface disease index.

Results: At the end of the study, patients whose treatment dose was decreased to once daily demonstrated statistically significant improvement in tear break-up time [4.13 seconds (n = 37) vs. 3.11 seconds at baseline (n = 50); $P = 0.0003$] and lissamine green staining score [4.42 (n = 37) vs. 6.51 at baseline (n = 50); $P = 0.024$]; fluorescein staining score, Schirmer test results, and ocular surface disease index did not change significantly ($P > 0.05$). Furthermore, the once-daily group demonstrated significantly superior ocular surface disease index compared with the twice daily group [15.91 (n = 37) vs. 22.62 (n = 48); $P = 0.0496$]. The remaining outcome measures between once daily and twice daily were not significantly different ($P > 0.05$). Seven of 50 patients (14%) in the once-daily group (vs. 0% in the twice-daily group) ended the study early because of worsening dry eye symptoms ($P < 0.05$) and went back to twice-daily dosing.

Conclusions: For patients with dry eye that has been controlled with tCSA twice daily for at least 1 year, decreasing to tCSA once daily may still allow suppression of the dry eye disease.

Key Words: dry eye, Restasis, cyclosporine

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Over the past decade, the importance of inflammation in the pathogenesis of dry eye has been elucidated.[1–5] Decreased tear production leads to chronic inflammation on the ocular surface.[6–13] This inflammatory response consists of inflammatory cell infiltration of the ocular surface, activation of the ocular surface epithelium with increased expression of adhesion molecules and inflammatory cytokines, increased concentration of inflammatory cytokines in the tear fluid, and increased activity of matrix-degrading enzymes such as matrix metalloproteinases in the tear fluid.[12] These inflammatory mediators reduce ocular surface sensitivity and secondarily decrease sensory-stimulated reflex tearing. This creates a self-perpetuating cycle of chronic inflammation and continual decrease in tear production.[7]

Until the recent introduction of topical cyclosporine A 0.05% (tCSA) ophthalmic emulsion (Restasis; Allergan, Irvine, CA), treatment of dry eye was limited largely to artificial tear solutions and punctal plugs—modalities that have proven unsatisfactory for many patients.[14–17] Unlike artificial tear solutions that only treat the symptoms of dry eye, cyclosporine A 0.05% acts as an immunomodulator with antiinflammatory effects and specifically targets the underlying pathology of dry eye disease—immune-mediated inflammation.[1] Although topical corticosteroids have had positive effects, long-term therapy has been associated with deleterious effects.[18,19] Other agents such as secretogogues, other immune mediators, and androgens are currently being evaluated.[20–26]

Topical cyclosporine blocks T-cell activation, reducing the production of inflammatory cytokines that recruit additional T cells and incite inflammatory T-cell inhibition of lacrimal tear production.[27,28] This leads to an increase in the quality and quantity of tears and decreases the damage to lacrimal gland tissue and the ocular surface.[29] At the same time, cyclosporine does not inhibit the phagocytic system as much as corticosteroids, allowing the antimicrobial arm of the immune system to fight infection.[30,31] Furthermore, cyclosporine A 0.05% does not inhibit wound healing or produce

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Reprints: Henry D. Perry, 2000 North Village Avenue, Suite 402, Rockville Centre, NY 11570.

lens changes. This creates a wide safety profile for this drug, allowing for safe long-term usage by the patient.

The efficacy of tCSA in relieving the signs and symptoms of dry eye has been demonstrated by Sall et al,[32] who reported that cyclosporine ophthalmic emulsion significantly improved Schirmer scores and patients' quality of life. Other investigators have confirmed its efficacy in dry eye disease and in treating patients with meibomian gland dysfunction.[33,34] Currently, topical cyclosporine is the only Food and Drug Administration–approved medication for increasing tear production in patients with chronic dry eye who produce insufficient tears because of ocular inflammation.

In contemporary medicine, pharmacotherapeutic trends favor once-daily dosing schedules to enhance compliance and adherence to prescribed therapy.[35] Numerous glaucoma studies have pointed out increasing compliance associated with decreasing daily dose regimens.[36,37] Furthermore, decreased dosing frequency lends itself to enhancing economic efficiency.[38] Although tCSA is currently approved and prescribed for use twice daily, the need for long-term twice-daily suppressive therapy remains in question. Thus, the purpose of this study was to evaluate the efficacy of twice-daily versus once-daily therapy with cyclosporine A 0.05% in patients who have already completed 12 months of twice-daily therapy.

METHODS

The study was a randomized, observer-masked, parallel group comparison of 100 adult patients who had already been treated with tCSA and had at least 1 year of remission in follow-up. This group consisted of both outside referrals and primary presentations to our general clinic. The characteristics of the study group, including baseline severity of dry eye disease, are fully described in the results section. Fifty patients were randomized to each group, either to continue receiving tCSA twice daily or to decrease to tCSA once daily in both eyes. Institutional Review Board approval was obtained from Mercy Medical Center (Rockville Centre, NY).

The initial screening visit was used to explain the purpose of the study and to obtain informed consent. Patients were was considered eligible if they met the following criteria:

- was 21 years of age or older;
- had clinical dry eye disease;
- had the ability to understand and give signed informed consent;
- was willing to and capable of cooperating with protocol requirements;
- agreed to use a reliable form of contraception if female and of child-bearing potential.

However, patients were considered ineligible if they:

- had been using contact lenses (unless discontinued ≥30 days before randomization);
- had active ocular diseases, excluding glaucoma, or infections other than blepharitis;
- had ocular surgery within the past 3 months;
- had active ocular allergies;
- had used another investigational drug or device during the 30 days before study entry or during the course of the study;
- had a history of hypersensitivity to cyclosporine A;
- were pregnant, nursing, attempting to conceive, or not using a reliable form of contraception.

The remainder of the initial visit was used to evaluate baseline values for the principal outcome measures: ocular surface disease index (OSDI), fluorescein tear break-up time (TBUT), corneal fluorescein staining, ocular surface lissamine green staining, and Schirmer tear test. Each patient completed a standardized OSDI survey. This questionnaire listed 12 common symptoms of dry eye disease, and patients scored each symptom, from 1 to 4, in terms of increasing severity. This survey permitted subjective quantification of symptoms.[39]

A fluorescein sodium strip (FUL-GLO; Akorn, Buffalo Grove, IL) moistened with a drop of sterile isotonic-buffered solution (OCuSOFT; Richmond, TX) was applied to the inferior palpebral conjunctiva without touching the superior bulbar conjunctiva. Patients were then asked to open and close their eyes and roll them around to distribute the dye in the tear film. Patients were then asked to blink and then open their eyes and refrain from blinking. The precorneal tear film was examined with a biomicroscope with a ×10 objective, and the elapsed time before the initial break-up or rupture of the tear film or formation of dry spots was recorded. The test was performed 3 times for each eye, and the results were averaged.

Using a biomicroscope fitted with a Wratten 12 barrier filter and a ×10 objective, the ocular surface was examined with light passed through a cobalt blue filter 5 minutes after instillation of fluorescein into the tear film. The intensity of corneal staining was recorded using a graded scale for each area indicated in Figure 1. Scores from areas 1, 2, 3, and 4 of each eye were summed for the fluorescein staining summary score. Scores from area 5 were used for safety evaluation only and were not considered in the fluorescein staining summary score. The results from both eyes were then averaged.

One drop of 1% lissamine green solution was applied to each eye. The bulbar conjunctiva was examined by slit light, and the degree of lissamine green staining was graded in each area indicated, illustrated by Figure 2. Scores from each area were added for each eye, and the totals for each eye were averaged to give the lissamine green staining score.

With the eyes anesthetized with 1 drop of proparacaine hydrochloride 0.5% ophthalmic solution (Akorn) and the excess of tear fluid wiped with a tissue paper, a standard Schirmer test strip was placed in the temporal one-third area of the lower eyelid of each eye. The patient was asked to close the eye. After 5 minutes, the strips were removed and the length of the wet portion was measured in millimeters to determine the Schirmer test value. The Schirmer test with anesthetic was used to try to minimize false-negative testing results from the strips, which cause irritation and reactive hyperlacrimation.

Based on retrospective evaluation of the patient's original presentation, the patient was grouped into 1 of the 3 dry eye categories: mild, moderate, or severe. The mild group was defined by minimal objective criteria: shortened TBUT, no worse than trace fluorescein staining, and no worse than 1+ lissamine green staining. The moderate group was

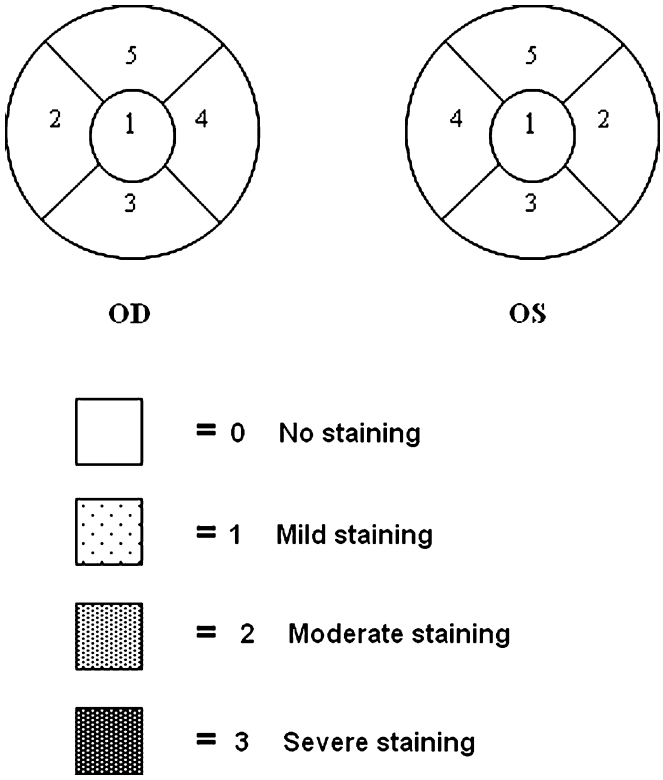

FIGURE 1. Map of corneal fluorescein staining.

defined as patients having the following characteristics: nearly instantaneous TBUT, positive fluorescein staining, positive lissamine green staining, and mildly decreased scores for Schirmer tests with anesthesia. The severe group was defined as patients with the following: TBUT of zero, greater than 1+ fluorescein staining, positive lissamine green staining, decreased tear meniscus, and decreased Schirmer testing of less than 4 mm in at least 1 eye.

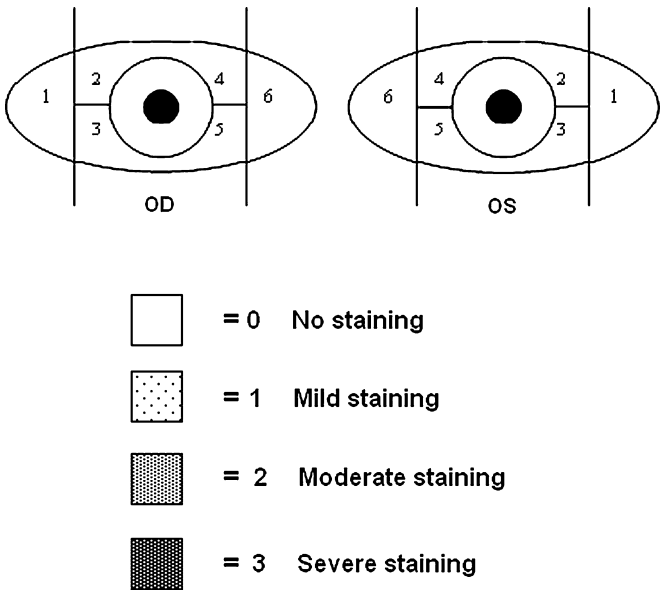

FIGURE 2. Map of ocular surface lissamine green staining.

Patients were reevaluated at 3 months and 6 months after initiation to remeasure all the aforementioned study parameters. Outcome measures were averaged. Longitudinal "within-group" analysis was performed, comparing interval data with baseline values. "Head-to-head" data analysis was then performed, directly comparing the mean data from the once-daily group to the average data from the twice-daily group at identical time points. Finally, the mean data were rederived after severity-based stratification (ie, mild, moderate, or severe) to determine the effect of tCSA dosage on different degrees of dry eye severity.

Patients were counseled to monitor themselves for any persistent increase in disease severity. Those demonstrating deterioration, either subjectively or clinically, were removed from the study and returned to twice-daily maintenance therapy. Of note, patients who were withdrawn from the study, in addition to patients who were lost to follow-up, still contributed baseline and interval data up to their last follow-up visit or up to the point at which they were withdrawn from the study.

Continuous data were evaluated using paired sample *t* tests for within-group and between-group comparisons. Nominal data were evaluated using χ^2 or Fisher exact tests, as appropriate. All tests were of a 2-tailed null hypothesis (no difference between twice-daily and once-daily dosing) and the a priori alpha level was set at 0.05.

RESULTS

Enrollment included a total of 16 men and 84 women ranging from 25 to 91 years of age. In the once-daily group, there were 8 men and 42 women ranging from 29 to 91 years of age. The mean age in the once-daily group was 67.3 years with an SD of 13.3 years. The twice-daily group included 8 men and 42 women ranging from 25 to 89 years of age. The mean age in the twice-daily group was 66.4 years with an SD of 15.2 years.

Eighty-eight of 100 patients were white. There were 5 black, 4 Hispanic, and 3 Asian patients. After randomization, the once-daily group had 3 black patients, 2 Hispanic patients, and no Asian patients; in the twice-daily group, 2 patients were black, 2 were Hispanic, and 3 were Asian.

Forty-five patients had mild dry eye disease. Thirty-eight patients had moderate disease. Seventeen patients had severe disease. After randomization, the once-daily group had 25 patients with mild disease, 15 patients with moderate disease, and 10 patients with severe disease; in the twice-daily group, there were 20 patients with mild disease, 23 patients with moderate disease, and 7 patients with severe disease.

Twenty-five patients had thyroid disease or collagen vascular disease. Eleven of these patients were grouped into once-daily dosing; the remaining 14 were grouped into twice-daily dosing. Of the 11 once-daily patients who had autoimmune disease, 4 had mild dry eye, 4 had moderate dry eye, and 3 had severe dry eye. In the group of 14 twice-daily patients with autoimmune disease, 4 had mild dry eye, 7 had moderate dry eye,

TABLE 1. Once-Daily Dosing at Months 0, 3, and 6

Month	TBUT	*P*	FSS	*P*	LISS	*P*	Schirmer Scores	*P*	OSDI	*P*
0	3.11 (n = 50)	—	2.53 (n = 50)	—	6.51 (n = 50)	—	9.81 (n = 49)	—	24.64 (n = 49)	—
3	4.24 (n = 44)	0.0042	1.22 (n = 44)	0.013	4.85 (n = 44)	0.041	11.52 (n = 44)	0.098	15.87 (n = 44)	0.0033
6	4.13 (n = 37)	0.0003	1.78 (n = 37)	0.06	4.42 (n = 37)	0.024	11.51 (n = 36)	0.25	15.91 (n = 37)	0.09

FSS, fluorescein staining score; LISS, lissamine staining score.

TABLE 2. Twice-Daily Dosing at Months 0, 3, and 6

Month	TBUT	*P*	FSS	*P*	LISS	*P*	Schirmer Scores	*P*	OSDI	*P*
0	3.14 (n = 49)	—	3.15 (n = 50)	—	7.43 (n = 50)	—	13.71 (n = 48)	—	27.66 (n = 48)	—
3	3.44 (n = 48)	0.34	2.63 (n = 48)	0.47	6.76 (n = 48)	0.58	12.21 (n = 48)	0.3	24.26 (n = 47)	0.33
6	4.17 (n = 48)	0.0057	2.19 (n = 48)	0.034	6.36 (n = 48)	0.12	11.71 (n = 48)	0.1	22.62 (n = 48)	0.11

FSS, fluorescein staining score; LISS, lissamine staining score.

and the remaining 3 had severe dry eye. Eleven of the 50 patients in the once-daily group had bilateral lower eyelid punctal plugs, whereas 15 of the 50 patients in the twice-daily group had bilateral lower eyelid punctal plugs.

Fifteen patients did not reach completion of the study for a variety of reasons:

1. Seven once-daily patients did not tolerate the decrease in drop frequency: 3 ended their participation before the first 3-month follow-up visit and 4 were stable through the first 3-month interval but still ended before completing the study. Three of the 7 patients had a history of autoimmune inflammatory disease. Three were originally classified as having mild dry eye disease; 3 had moderate dry eye disease; and 1 had severe dry eye disease. These patients resumed twice-daily tCSA dosing.
2. One patient in the once-daily group was removed from the study because of noncompliance.
3. Five patients (3 once-daily and 2 twice-daily) were lost to follow-up. Three of these patients were lost after the initial screening visit; only their baseline data were recorded. The other 2 patients maintained follow-up up to the 3-month visit before being lost to follow-up.
4. Two patients from the once-daily group died before the completion of the study. Only 1 of these patients completed the first follow-up visit.

In all cases, the baseline data and interval data recorded before termination were used in the overall analysis. Within-group analysis focused on the effect of once-daily dosing over time (Table 1). For the once-daily group, there was no statistically significant detriment to any outcome measure compared with baseline. Some of the dry eye disease variables showed statistically significant improvement. For example, at 6 months, patients using tCSA once daily demonstrated statistically significant improvement in TBUT [4.13 seconds (n = 37) vs. 3.11 seconds at baseline (n = 50); $P = 0.0003$] and lissamine green staining score [4.42 (n = 37) vs. 6.51 at baseline (n = 50); $P = 0.024$].

Similar within-group analysis of the twice-daily group did not reveal any worsening of any outcome measure compared with day zero (Table 2). The twice-daily patients revealed statistically significant improvement in TBUT [4.17 seconds (n = 48) vs. 3.14 seconds at baseline (n = 49); $P = 0.006$] and fluorescein staining score [2.19 (n = 48) vs. 3.15 at baseline (n = 50); $P = 0.034$].

TABLE 3. Once Dosing Versus Twice-Daily Dosing at Months 0, 3, and 6

Month	Dosing	TBUT	FSS	LISS	Schirmer Scores	OSDI
0	QD	3.11 (n = 50)	2.53 (n = 50)	6.51 (n = 50)	9.81 (n = 49)	24.64 (n = 49)
	BID	3.14 (n = 49)	3.15 (n = 50)	7.43 (n = 50)	13.71 (n = 48)	27.66 (n = 48)
	P	0.91	0.32	0.38	0.11	0.44
3	QD	4.24 (n = 44)	1.22 (n = 44)	4.85 (n = 44)	11.52 (n = 44)	15.87 (n = 44)
	BID	3.44 (n = 48)	2.63 (n = 48)	6.76 (n = 48)	12.21 (n = 48)	24.26 (n = 47)
	P	0.037	0.004	0.082	0.69	0.0078
6	QD	4.13 (n = 37)	1.78 (n = 37)	4.42 (n = 37)	11.51 (n = 36)	15.91 (n = 37)
	BID	4.17 (n = 48)	2.19 (n = 48)	6.36 (n = 48)	11.71 (n = 48)	22.62 (n = 48)
	P	0.93	0.41	0.073	0.91	0.0496

FSS, fluorescein staining score; LISS, lissamine staining score.

TABLE 4. Once Daily Versus Twice Daily: Patients With Mild Disease at Months 0, 3, and 6

Month	Dosing	TBUT	FSS	LISS	Schirmer Scores	OSDI
0	QD	2.96 (n = 25)	2.24 (n = 25)	4.62 (n = 25)	11.02 (n = 24)	25.95 (n = 24)
	BID	3.29 (n = 19)	2.40 (n = 20)	6.18 (n = 20)	16.25 (n = 18)	29.26 (n = 20)
	P	0.52	0.85	0.3	0.036	0.55
3	QD	4.86 (n = 22)	0.82 (n = 22)	2.43 (n = 22)	12.02 (n = 22)	14.55 (n = 22)
	BID	3.63 (n = 18)	2.03 (n = 18)	4.72 (n = 18)	14.64 (n = 18)	22.58 (n = 17)
	P	0.066	0.044	0.084	0.37	0.041
6	QD	4.32 (n = 20)	1.5 (n = 20)	2.53 (n = 20)	11.87 (n = 19)	15.18 (n = 20)
	BID	5.1 (n = 18)	1.28 (n = 18)	3.94 (n = 18)	14.53 (n = 18)	20.17 (n = 18)
	P	0.23	0.68	0.22	0.33	0.29

BID, twice daily; FSS, fluorescein staining score; LISS, lissamine staining score; QD, once daily.

In head-to-head comparison (Table 3), once-daily and twice-daily patients revealed similar baseline values for all dry eye measures ($P > 0.05$) except for Schirmer testing, for which twice-daily patients started with superior scores [13.71 mm (n = 48) vs. 9.81 mm for once daily (n = 49); $P = 0.011$]. However, at the 3-month interval, the once-daily patients achieved superiority over twice-daily patients in terms of TBUT [4.24 seconds (n = 44) vs. 3.44 seconds (n = 48); $P = 0.037$], fluorescein staining score [1.22 (n = 44) vs. 2.63 (n = 48); $P = 0.004$], and OSDI [15.87 (n = 44) vs. 24.26 (n = 47); $P = 0.0078$]. Lissamine staining and Schirmer scores at 3 months were not statistically different. By the end of the study, there was no statistically significant difference between groups with respect to any of the dry eye measures ($P > 0.05$), with the exception of the OSDI, which favored the once-daily group [15.91 (n = 37) vs. 22.62 for the twice-daily group (n = 48); $P < 0.05$].

In the mild dry eye disease group (Table 4), the Schirmer scores were initially higher in the twice-daily patients at baseline [16.25 mm (n = 18) vs. 11.02 mm for once daily (n = 24); $P = 0.011$]. At conclusion, there was no statistically significant difference in any of the study measures between once-daily dosing and twice-daily dosing ($P > 0.05$).

In the moderate group (Table 5), patients who were using twice-daily dosing also had initially higher Schirmer scores at baseline [12.13 mm (n = 23) vs. 8.13 mm for once daily (n = 15); $P = 0.035$]. At the 6-month visit, there was no statistically significant difference in any of the outcome measures between once-daily and twice-daily dosing ($P > 0.05$).

Of the patients who had severe dry eye disease (Table 6), the twice-daily patients had significantly worse OSDI compared with the once-daily patients [36.43 (n = 7) vs. 14.14 (n = 7); $P = 0.0037$]. Otherwise, there was no statistically significant difference in any of the outcome measures between once-daily and twice-daily dosing ($P > 0.05$).

DISCUSSION

Decreasing tCSA from twice-daily dosing to once-daily dosing was well-tolerated by the majority of patients, with only 14% reverting to twice-daily dosing. Head-to-head comparison revealed that, irrespective of disease severity, twice-daily dosing was not statistically better than once-daily dosing. This suggests that once-daily tCSA may be as effective as twice-daily tCSA for patients who have already responded well with 1 year of twice-daily treatment.

Interestingly, patients taking tCSA actually improved during the course of the study and performed better than the twice-daily group on the subjective OSDI. Unless a decrease in toxicity is to be credited, it seems improbable that a decrease in drug delivery should allow for improvement. Therefore, we speculate that the study triggered an interval enhancement of the patient's disease consciousness and improved self-direction.

The psychological effect of participation in scientific studies, as it relates to self-conscientiousness, has been

TABLE 5. QD Versus BID: Patients With Moderate Disease at Months 0, 3, and 6

Month	Dosing	TBUT	FSS	LISS	Schirmer Scores	OSDI
0	QD	3.33 (n = 15)	2.3 (n = 15)	6.13 (n = 15)	8.13 (n = 15)	27.97 (n = 15)
	BID	3.12 (n = 23)	2.76 (n = 23)	6.74 (n = 23)	12.13 (n = 23)	21.04 (n = 23)
	P	0.58	0.6	0.66	0.035	0.29
3	QD	3.76 (n = 13)	1.31 (n = 13)	5.58 (n = 13)	11.73 (n = 13)	18.49 (n = 13)
	BID	3.53 (n = 23)	2.39 (n = 23)	7.33 (n = 23)	10.11 (n = 23)	22.11 (n = 23)
	P	0.66	0.13	0.28	0.48	0.56
6	QD	4.27 (n = 10)	1.7 (n = 10)	4.25 (n = 10)	12.55 (n = 10)	18.6 (n = 10)
	BID	3.9 (n = 23)	1.87 (n = 23)	6.17 (n = 23)	9.87 (n = 23)	20.34 (n = 23)
	P	0.62	0.81	0.17	0.18	0.79

BID, twice daily; FSS, fluorescein staining score; LISS, lissamine staining score; QD, once daily.

TABLE 6. QD Versus BID: Patients With Severe Disease at Months 0, 3, and 6

Month	Dosing	TBUT	FSS	LISS	Schirmer Scores	OSDI
0	QD	3.15 (n = 10)	3.6 (n = 10)	11.8 (n = 10)	9.4 (n = 10)	16.5 (n = 10)
	BID	2.84 (n = 7)	6.57 (n = 7)	13.29 (n = 7)	12.36 (n = 7)	46.67 (n = 6)
	P	0.71	0.16	0.58	0.56	0.0073
3	QD	3.44 (n = 9)	2.06 (n = 9)	9.72 (n = 9)	10.0 (n = 9)	15.33 (n = 9)
	BID	2.66 (n = 7)	4.93 (n = 7)	10.14 (n = 7)	12.86 (n = 7)	35.43 (n = 7)
	P	0.37	0.11	0.9	0.54	0.006
6	QD	3.41 (n = 7)	2.71 (n = 7)	10.07 (n = 7)	9.07 (n = 7)	14.14 (n = 7)
	BID	2.64 (n = 7)	5.57 (n = 7)	13.21 (n = 7)	10.5 (n = 7)	36.43 (n = 7)
	P	0.16	0.076	0.34	0.78	0.0037

BID, twice daily; FSS, fluorescein staining score; LISS, lissamine staining score; QD, once daily.

described.[40] Scrutiny by an observer and/or a change in treatment would enhance patient resolve by altering a chronically mundane treatment regimen. In this particular study, once-daily dosing patients may have found the study motivating enough to enhance compliance and attention to adjunctive dry eye therapy (artificial tears, oral supplements, or eyelid hygiene). If this is the case, then quantitative measures of compliance and the use of dry eye therapies (in excess of tCSA alone) are needed to specifically elucidate the dose-dependent response to tCSA.

To our knowledge, this is the first comparison of once-daily and twice-daily tCSA as maintenance therapy for dry eye disease. tCSA is labeled for twice-daily dosing and should certainly be initially prescribed in that manner to achieve control of dry eye signs and symptoms. However, our findings demonstrate that the majority of patients with dry eye already controlled with tCSA twice daily for at least 1 year can maintain suppression of disease and even show continued improvement after decreasing to tCSA once daily.

A great advantage of once-daily dosing is the increased convenience to the patient, which translates into enhanced compliance and better outcomes.[37] Furthermore, the supply side can theoretically be extended, thereby diminishing the cost to the consumer. However, there may be patients who cannot tolerate the decreased dose, and this study did not identify factors that would increase this likelihood. Until such risk factors are elucidated, patients who are tapered to once-daily dosing require continued follow-up to monitor for exacerbation of the disease. Additional studies will also be needed to address how long patients can be maintained on once-daily tCSA and when (or if) tCSA can be discontinued completely.[41]

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