



Published in final edited form as:

*Cornea*. 2009 December ; 28(10): 1091–1096. doi:10.1097/ICO.0b013e3181a16472.

## High-frequency Topical Cyclosporine 0.05% in the Treatment of Severe Dry Eye Refractory to Twice-daily Regimen

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### Abstract

**Purpose**—The purpose of this study was to report the efficacy of topical cyclosporine 0.05% at a frequency of 3 to 4 times daily in severe dry eye disease.

**Methods**—We retrospectively identified a cohort of patients with severe dry eye disease who had shown inadequate response to at least a 4-month course of treatment with twice-daily use of topical cyclosporine 0.05% but who showed significant improvement to more frequent dosing.

**Results**—Twenty-two patients, including 13 patients with ocular graft versus host disease and 9 patients with primary or secondary Sjögren's syndrome, were included. After a minimum of a 2-month course of treatment with more frequent dosing of cyclosporine 0.05% (3 times a day in 7 patients and 4 times a day in 15 patients), overall dry eye symptoms were improved in 15 (68.2%) patients (9 patients with ocular graft versus host disease and 6 patients with Sjögren's syndrome). Mean corneal fluorescein staining scores (National Eye Institute scale of 0–15) improved (decreased) from the baseline (precyclosporine use) by  $-3.5$  (range, 0 to  $-7$ ) in patients with ocular graft versus host disease ( $P \leq 0.0008$ ) and  $-2.8$  (range, 0 to  $-5$ ) in patients with Sjögren's syndrome ( $P \leq 0.001$ ). After treatment with high-frequency use of cyclosporine 0.05%, the global physician assessment of dry eye status was favorable (improved) in 16 (72.7%) patients. Three (13.6%) patients reported new-onset symptoms of burning or irritation with the use of high-frequency dosing of topical cyclosporine. No other associated adverse effect was reported.

**Conclusion**—These data suggest that patients with severe dry eye may require more frequent dosing of topical cyclosporine 0.05% than twice daily.

### Keywords

topical cyclosporine; severe dry eye disease; ocular graft versus host disease; Sjögren's syndrome

## INTRODUCTION

Topical cyclosporine 0.05% (Restasis; Allergan, Irvine, CA) has been shown to be an effective therapeutic agent for the treatment of moderate to severe dry eye disease in phases II and III clinical trials, leading to US Food and Drug Administration approval of the drug in 2002.<sup>1,2</sup> Although most treatments for dry eye disease are palliative rather than disease-modifying, topical cyclosporine addresses the underlying inflammatory process in dry eye

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Presented in part at the Cornea Society/EBAA Fall Educational Symposium and at the American Academy of Ophthalmology Annual Meeting, November 2007, New Orleans, LA.

disease. Patients with dry eye exhibit chronic inflammation at the ocular surface and in the lacrimal gland.<sup>3–6</sup> Cyclosporine inhibits T-cell activation and downregulates inflammatory cytokines in the conjunctiva and lacrimal gland, processes thought to be involved in the pathogenesis of dry eye.<sup>7–9</sup> By suppressing inflammation, cyclosporine is considered to result in enhanced tear production.<sup>1,2,10,11</sup> Topical cyclosporine also increases conjunctival goblet cell density and decreases epithelial cell apoptosis.<sup>2,12,13</sup>

Both phase II and III clinical trials of topical cyclosporine did not demonstrate an unequivocal dose–response relationship among the different drug concentrations.<sup>1,2</sup> In clinical experience, however, a group of patients with severe dry eye disease do not appear to adequately respond to twice-a-day application of the cyclosporine 0.05% emulsion even after months of treatment, although they appear to partially respond, characterized by some improvement in symptoms and/or signs of disease. Several hypotheses may explain this lack of adequate clinical response in this group: incomplete drug effect as a result of insufficient dosing, end-stage lacrimal gland disease as a consequence of complete destruction or conjunctival scarring, or individual risk factors and ocular surface-specific immunologic mechanisms that are yet unknown. Because there is a close relationship between systemic cyclosporine dose and its immunosuppressive potency,<sup>14</sup> together with the relatively very low cyclosporine concentration (0.05%) in the commercially available topical formulation, one may question the adequacy of the dosing regimen of twice-daily use of topical cyclosporine 0.05% in the treatment of severe dry eye disease, particularly in patients with significant inflammatory ocular surface diseases.

To report the efficacy of topical cyclosporine 0.05% 3 to 4 times daily in severe dry eye disease, we retrospectively identified a cohort of patients with severe dry eye disease who had inadequate responses to twice-daily use of cyclosporine 0.05% but who showed significant improvement to more frequent dosing.

## MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board at the Massachusetts Eye and Ear Infirmary. Since October 2006, one of the authors (R.D.) has prescribed more frequent dosing (off-label use of 3 to 4 times a day) of the commercially available preparation of 0.05% cyclosporine (Restasis; Allergan, Irvine, CA) to patients diagnosed with severe dry eye but who had responded inadequately to at least a 4-month course of twice-daily use of topical cyclosporine 0.05% in addition to aggressive conventional therapy (eg, punctal plugs, preservative-free artificial tears, moisture goggles, and so on). All patients had a baseline Schirmer test  $\leq 5$  mm/5 minutes of wetting before initiation of a twice-daily cyclosporine 0.05% regimen with symptoms of dry eye (burning, irritation, grittiness, foreign body sensation, or fluctuating vision) and punctate epithelial keratopathy ( $\geq +3$  on a scale of 0–15; National Eye Institute scale)<sup>15</sup> detected with fluorescein. Inadequate response to twice-daily dose of cyclosporine 0.05% was considered if the patient showed some improvement in symptoms and/or signs of dry eye disease but still the subjective assessment of overall dry eye symptoms was not favorable (no change), and the patient showed significant residual corneal fluorescein staining score ( $\geq +3$  on a scale of 0–15) after at least 4-month course of treatment.

Patients were excluded if they appeared to have end-stage lacrimal gland disease (baseline Schirmer test with anesthesia of = 0 mm/5 min) or if their dry eye disease was the result of destruction of conjunctival goblet cells or scarring (cicatricial pemphigoid, limbal stem cell deficiency, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation). Patients who had previous ocular surgery, including laser refractive surgery or who had a history of herpetic eye disease were excluded. Patients were also excluded if they had initiated or made

any changes to the dosing of other topical ophthalmic medications less than 4 weeks previously or during the high-frequency course of cyclosporine treatment. Use of artificial tears and ocular lubricants, however, was permitted. Moreover, patients who had uncertain compliance with the use of topical cyclosporine typically because of burning on drug instillation were not included in this study.

After a minimum 2-month course with more frequent dosing of topical cyclosporine 0.05% (3–4 times a day), subjective assessment of overall dry eye symptoms, corneal fluorescein staining score (on a scale of 0–15; National Eye Institute scale), basal tear secretion values (Schirmer test with anesthesia at 5 minutes), and global physician assessment of dry eye status were recorded. For subjective assessment of overall dry eye symptoms, patients were asked to mark improved, no change, or worse for the symptoms of dryness or ocular discomfort. For the global physician assessment of dry eye status, the treating ophthalmologist evaluated the overall effect of the treatment relative to the baseline visit (initiation of high frequency cyclosporine 0.05%) as 1) condition improvement; 2) condition unchanged; or 3) condition worsened.<sup>16</sup> In addition, any potential associated adverse effects or patient reports of adverse symptoms with treatment were noted.

Differences in mean corneal fluorescein staining scores and Schirmer test readings were compared among the baseline (precyclosporine treatment) visit, after 4 months of twice-daily use, and after the subsequent 2 months of more frequent use of topical cyclosporine 0.05% by using paired-sample *t* tests. The means for both eyes were used for each of these analyses. A 2-sided test with a *P* value  $\leq 0.05$  was considered statistically significant.

## RESULTS

The demographic characteristics of the study population, including age, gender, type of dry eye disease, punctal occlusion status, daily use of artificial tears, duration of twice-daily use of cyclosporine 0.05%, and frequency/duration of subsequent course of treatment with cyclosporine 0.05%, are listed in Table 1. Patients comprised of 8 men and 14 women with a mean age ( $\pm$  standard deviation) of  $51.2 \pm 14.9$  years. Thirteen patients with ocular graft versus host disease (GVHD) and 9 patients with either primary or secondary Sjögren's syndrome (SS) were included (22 patients in total). Ocular GVHD was diagnosed in patients who had hematopoietic stem cell (bone marrow) transplantation and a known diagnosis of systemic GVHD<sup>17</sup> presented with new-onset symptoms and signs of dry eye disease. SS was defined as the presence of ocular symptoms, oral symptoms, Schirmer test  $\leq 5$  mm, and one of the following antibodies: antinuclear antibodies, rheumatoid factor, and Sjögren's antibodies class SS-A, or SS-B.

At the time of initiation of high-frequency use of topical cyclosporine 0.05%, mean duration of twice-daily use of the medicine was 5.2 months, ranging from 4 to 14 months. With the exception of one case, all patients had at least 2 occluded puncta, and the frequency of use of artificial tears for the majority (63%) of patients was 6 to 8 times a day or more (range, up to 12 times a day). In the subsequent course of treatment, the frequency of topical cyclosporine 0.05% was 3 times a day in 7 patients and 4 times a day in 15 patients.

After a minimum of a 2-month course of high-frequency use of topical cyclosporine, subjective assessment of overall dry eye symptoms was favorable (improved) in 15 (68.2%) patients (9 patients with ocular GVHD and 6 patients with SS), whereas 4 (18.2%) patients (2 patients with ocular GVHD and 2 with SS) reported no change in the severity of their symptoms, and 3 (13.6%) patients (2 patient with ocular GVHD and one with SS) reported an overall worsening of the dry eye symptoms (Fig. 1).

At baseline, before the treatment using twice-daily topical cyclosporine 0.05%, the mean values for corneal staining was 7.4 (range, 4–11) and 5.8 (range, 3–9) for ocular GVHD and SS groups, respectively (National Eye Institute scale 0–15). After initial treatment with twice-daily use of cyclosporine 0.05%, the mean change from baseline in corneal staining (decrease in mean score) was  $-1.4$  (range, 0 and  $-2$ ) in the ocular GVHD group and  $-1.1$  (range, 0 and  $-2$ ) in the SS group. With high-frequency use of topical cyclosporine 0.05%, however, the mean change from baseline in corneal staining was  $-3.5$  (range, 0 and  $-7$ ) in the ocular GVHD group and  $-2.8$  (range, 0 and  $-5$ ) in the SS group (Fig. 2). The improvement in corneal staining was statistically significant in both groups compared with the initial response to twice-daily dosing ( $P \leq 0.0008$  in ocular GVHD and  $P \leq 0.001$  in SS).

Pre- and posttreatment basal tear secretion testing was available in 10 patients (6 with GVHD and 4 with SS) and showed a mean pretreatment (before initiation of twice-daily topical cyclosporine 0.05% regimen) value of 2.5 mm (range, 1–5 mm), a mean posttreatment (twice-daily dose of cyclosporine 0.05%) value of 2.8 mm (range, 1–7 mm), and a mean posttreatment (high-frequency use of cyclosporine 0.05%) value of 3.2 mm (range, 0–8 mm). These figures, however, did not achieve statistical significance.

After treatment with high-frequency cyclosporine 0.05%, the global physician assessment of dry eye status was favorable (improved) in 16 (72.7%) patients (9 patients with ocular GVHD and 7 with SS) (Fig. 3). Five (22.7%) patients (3 patients with ocular GVHD and 2 with SS) were evaluated as condition unchanged, whereas one patient with ocular GVHD (4.5%) was evaluated as their condition worsened. Patients whose physician's subjective global assessment of dry eye status was not favorable (no change or worse) reported no change or an overall worsening in the severity of dry eye symptoms, and the change from baseline in corneal fluorescein staining score was zero or  $-1$ .

Three (13.6%) patients reported new-onset symptoms of burning or irritation with the use of high-frequency dosing of topical cyclosporine, which significantly eased on cold application of the medicine by keeping it refrigerated between uses. No other associated adverse effect was reported.

## DISCUSSION

Cyclosporine is a potent immunomodulator that has been in widespread use for nearly 3 decades. Systemic dosing of 2 to 10 mg/kg per day is administered orally or intravenously for immunosuppression after organ transplantations (kidney, heart, liver, and lung allografts) and treatment of various immunologic and autoimmune disorders such as rheumatoid arthritis, inflammatory bowel disease, and moderate to severe psoriasis.<sup>18–21</sup> Ocular diseases that have been treated with systemic cyclosporine include uveitis, Behçet's disease, and bird shot retinochoroiditis as well as prophylaxis and treatment for rejection of corneal and limbal stem cell allografts.<sup>22–25</sup>

Cyclosporine is a neutral, hydrophobic, cyclic undecapeptide with a molecular weight of 1.2 kDa. Given its physicochemical properties and hydrophobicity, cyclosporine has presented ocular formulation challenges that provide adequate concentration, stability, reliable drug delivery, and acceptable vehicle safety.<sup>26</sup> To improve delivery of cyclosporine to ocular tissues, a castor oil–water emulsion formulation was developed and used for topical cyclosporine 0.05% (Restasis; Allergan) that produces sustained cyclosporine concentrations sufficient for immunomodulation in external ocular tissues. On instillation directly into the eyes, cyclosporine partitions from the oil droplets into ocular surface tissues. The ocular retention time for this emulsion vehicle has been estimated as approximately 2 hours.<sup>27</sup>

Ocular absorption and tissue distribution of cyclosporine after topical administration have been studied extensively in rabbits and dogs.<sup>27–32</sup> Bioavailability of topical cyclosporine ophthalmic solutions can be improved either by raising the drug concentration or by higher-frequency administration. It has been shown that cyclosporine concentrations in the conjunctiva, cornea, and lacrimal gland increase as the cyclosporine strength in the castor oil–water emulsion increases from 0.05% to 0.2%.<sup>33</sup> Work by Acheampong et al<sup>27</sup> has also shown that after repeated administration of the castor oil–water emulsion formulation, cyclosporine accumulation increases in the conjunctiva, cornea, and lacrimal gland. In systemic immunosuppressive therapy for organ transplants, cyclosporine has shown clear dose–response effects.<sup>34,35</sup> Using a mouse heart transplant model, a close relationship has been shown between cyclosporine dose and its immunosuppressive potency.<sup>14</sup> These data are also consistent with observations in patients who have been treated with cyclosporine.<sup>34,36</sup> The dose–response nature of systemic cyclosporine allows clinicians to adjust and individualize the cyclosporine dosing in different phases of immunosuppression based on the clinical status of the patient.

Notwithstanding what we report here, both phase II and III clinical trials of topical cyclosporine failed to demonstrate clear dose–response relationships among the different cyclosporine concentrations.<sup>1,2</sup> Although the higher concentrations of cyclosporine were demonstrated to be safe, the lack of any additional therapeutic benefit with increasing the concentration led to approval of the cyclosporine 0.05% formulation for twice-daily dosing. In our series, however, the majority of patients with severe dry eye disease who had inadequate responses (limited improvement but still with significant residual symptoms and/or signs of dry eye disease) to twice-daily use of cyclosporine 0.05% showed significant improvement to more frequent (3–4 times a day) dosing. The apparent additive effect of more frequent use of topical cyclosporine 0.05% in an objective measure (corneal staining) (Fig. 2) strongly suggests that the subjective improvements are a result of an improvement in the underlying immunopathology of the disease and not just symptomatic changes. The significant decrease in corneal staining is of particular relevance because it represents an improvement in the health of the ocular surface caused by the additional suppression of inflammatory processes. There have been reported cases of severe dry eye disease that failed conventional therapy, including topical cyclosporine 0.05%, but that eventually responded to systemic immunosuppressive therapy, including systemic cyclosporine.<sup>37</sup> Taken together, these findings suggest that a group of patients with severe inflammatory dry eye disease may need further immunosuppression than that afforded by twice-daily application of topical cyclosporine 0.05%.

Because cyclosporine 0.05% is the only commercially available ophthalmic emulsion, and the custom-made higher concentrated topical preparations are not readily available, therefore, the most convenient solution for augmenting the bioavailability of topical cyclosporine is to increase the frequency of its application. Given that the ocular retention time for cyclosporine emulsion is approximately 2 hours, potential effectiveness of a higher-frequency regimen is certainly conceivable. Higher-frequency topical cyclosporine would increase the residency time of medication. This could potentiate greater absorption of medication and increase the probability of a greater therapeutic response.

In our study, none of our patients showed any drug-related adverse events not seen with the lower-frequency application of twice a day. This observation is consistent with previous extensive preclinical and clinical safety studies of topical cyclosporine.<sup>1,2,38,39</sup> In a preclinical safety study, Angelov et al<sup>39</sup> have shown no ocular or systemic toxicity with long-term ocular administration of cyclosporine at concentrations up to 0.4% given as many as 6 times daily for 6 months in rabbits and 1 year in dogs. Serum cyclosporine concentration after twice-daily ocular administration of cyclosporine 0.05% and 0.1% has

also been shown to be extremely low or undetectable in rabbits, dogs, and humans, obviating concerns about systemic toxicity.<sup>38,39</sup>

The present study has certain limitations. Small sample size, heterogeneity of the patient population/treatment regimen, and the absence of a comparison or control group are the major drawbacks of this study. The improvement observed in our study population may not only be the result of a direct effect of higher dose–response of cyclosporine itself, but also other properties of the formulation other than cyclosporine content (eg, the vehicle). In phase II and III clinical trials, the vehicle used in the cyclosporine ophthalmic emulsion provided substantial palliative benefits, producing significant improvements in several outcome measures, particularly in the early follow-up period.<sup>1,2</sup> This prominent vehicle effect prompted subsequent marketing of the vehicle as a tear-stabilizing lubricant with prolongation of tear breakup time.<sup>40</sup> The significant improvement in the objective sign (corneal staining) of disease in our study patients, however, suggests that the treatment effect is likely not purely palliative in nature and represents the added therapeutic effect of higher-frequency dosing of topical cyclosporine 0.05%. To further address this issue, well-controlled (including vehicle control) studies using different frequencies of topical cyclosporine are clearly required.

In summary, our findings suggest that patients with severe inflammatory forms of dry eye disease such as ocular GVHD or SS may benefit from more frequent dosing of topical cyclosporine 0.05% than twice daily.

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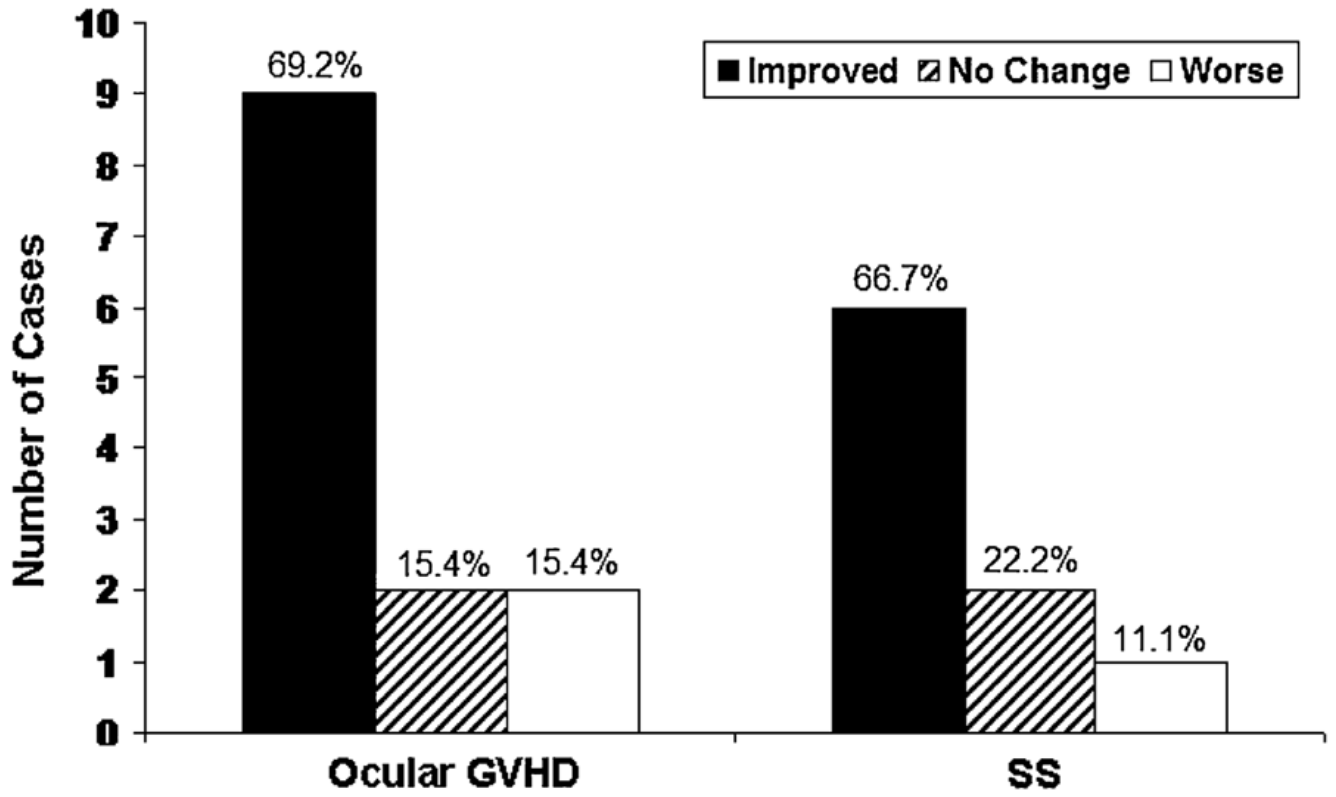


FIGURE 1.

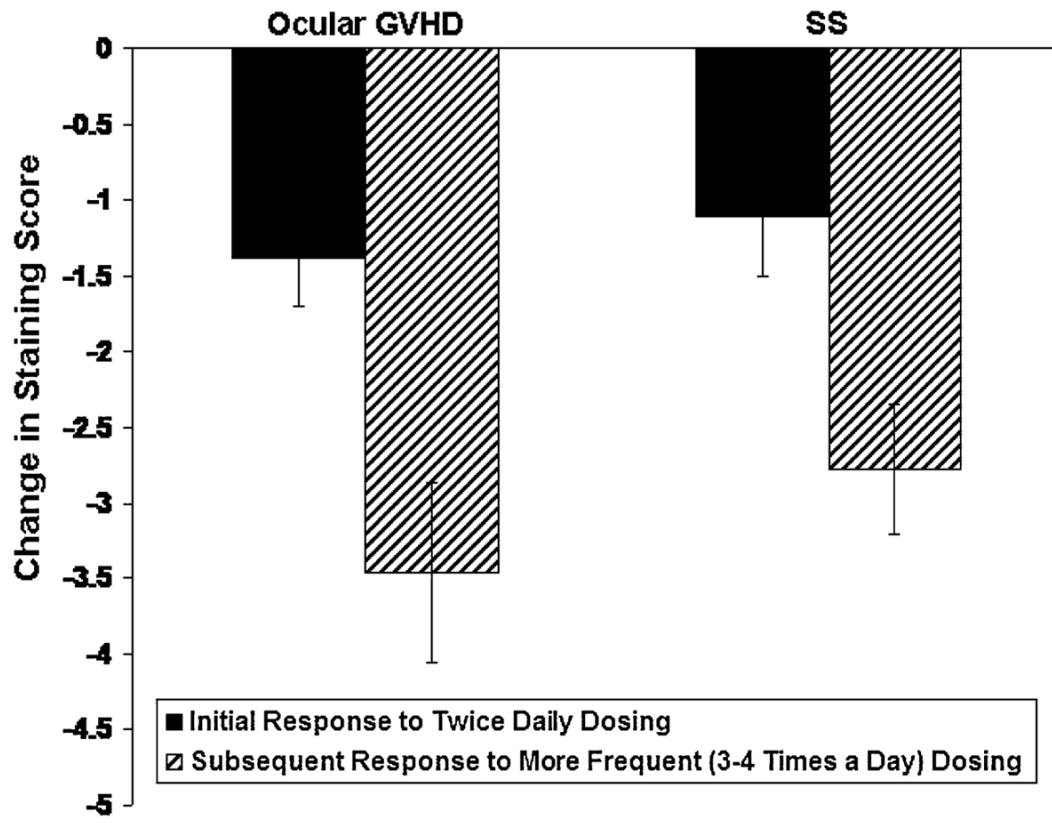


FIGURE 2.

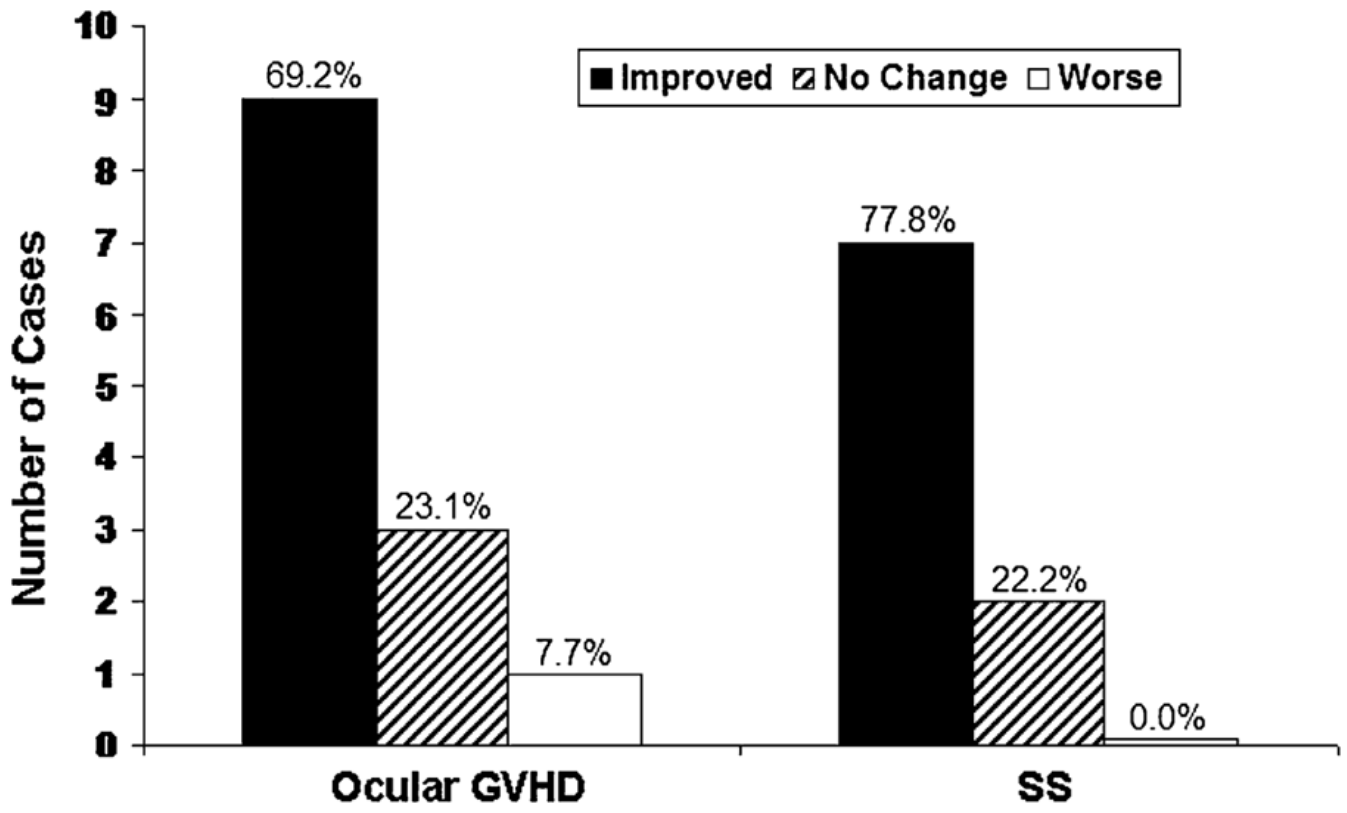


FIGURE 3.

TABLE 1

## Patient Demographic Data

Patient No.	Age (years)	Gender	Dry Eye Disease	No. of Punctal Occlusion	Use of Artificial Tears (times/day)	Duration of Twice-Daily Use of Cyclosporine A (months)	High-frequency Cyclosporine A Dosing (times/day)	Duration of High-frequency Use of Cyclosporine A (months)
1	47	F	GVHD	2	6-8	4	4	2
2	36	M	GVHD	2	4-6	4.5	3	3
3	63	F	SS	2	4-6	6	3	2
4	65	F	GVHD	4	10-12	4	4	3
5	54	F	SS	2	5-6	4	3	2.5
6	56	M	GVHD	3	6-8	4.5	4	3
7	28	F	GVHD	2	9-10	4	4	3
8	59	F	SS	2	6-8	5	4	2
9	61	M	GVHD	4	8-10	4	4	2
10	32	F	SS	2	7-8	4	4	3
11	66	M	GVHD	4	6-8	6	4	2
12	42	F	SS	0	4-6	8	3	3
13	56	F	SS	2	4	4	3	4
14	45	F	SS	2	6-8	6.5	4	3
15	72	M	GVHD	4	5-6	4	4	2.5
16	31	F	GVHD	3	6-8	4	4	3
17	67	M	GVHD	2	5-6	4	3	3
18	78	M	GVHD	4	6	4.5	4	2
19	54	M	GVHD	2	6-8	4	4	2
20	53	F	SS	2	6-8	7	3	2.5
21	38	F	SS	2	6-8	14	4	2
22	25	F	GVHD	2	5-6	5	4	3

GVHD, graft versus host disease; SS, Sjögren's syndrome.