Treatment of Refractory Dry Eye Associated with Graft Versus Host Disease with 0.03% Tacrolimus Eyedrops

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Abstract

Purpose: We investigate the efficacy of 0.03% topical tacrolimus eyedrops for the treatment of dry eye in graft versus host disease (GVHD) patients resistant/intolerant to 0.05% topical cyclosporine.

Methods: Forty-three patients were enrolled in this prospective study. After completing a 1-year run-in period of using artificial tears, 50% autologous serum eyedrops, and punctal plug occlusion, all the symptomatic patients ($n=29$) were treated with 0.05% topical cyclosporine (Restasis®; Allergan, Inc.). After 1 month, the patients who presented topical or systemic intolerance to cyclosporine were instructed to instill 0.03% topical tacrolimus once a day for 3 months ($n=14$). All the patients were allowed to continue with their basal dry eye treatment. Visual acuity, fluorescein staining, Schirmer test, fluorescein tear break-up time, and tear meniscus height measurement were evaluated fortnightly (minimum 3 months). Subjective assessments of symptoms were also reported at the beginning and at the end of the study.

Results: Dry eye symptoms and signs improved statistically ($P<0.05$) and significantly with tacrolimus and cyclosporine topical treatment. No significant differences were observed between both the groups. The mean follow-up time was 12.14 ± 2.69 months (range 10–18 months).

Conclusion: The findings of this prospective pilot study suggest that cyclosporine-intolerant patients with dry eye associated with GVHD can be effectively treated with topical tacrolimus.

Introduction

CHRONIC GRAFT VERSUS HOST DISEASE (GVHD) affects 40%–70% of allogeneic hematopoietic stem cell transplant patients and is responsible for 50% of nonrelapse-related deaths.¹ Dry eye is one of the major late complications affecting the quality of life, sometimes leading to blindness after hematopoietic stem cell transplantation. Ocular GVHD usually develops or worsens at the approximate time of discontinuation of systemic immunosuppressive therapy after bone marrow transplantation (BMT), which typically occurs after 6 months.²

The pathophysiology of GVHD has been associated with BMT donor antigen-presenting cells and donor T-helper type 2 cells derived from the graft, which increases interleukin production and transforms growth factor- β 1 resulting in fibrosis.³ A higher CD4/CD8 ratio in the corneal stroma and more CD14 cells (macrophages) in symptomatic sicca syn-

drome patients has been found to be implicated in the pathophysiology of ocular GVHD.⁴ Moreover, lowered goblet cell density and an increased expression of inflammatory markers (intracellular adhesion molecule-1) have also been demonstrated.⁵ In affected lacrimal glands, fibroblasts may function as antigen-presenting cells and the periductal region may be the primary site for CD4 and CD8 T-cell activation, consequently with excessive fibrosis in the extracellular matrix, lobules, ducts, and vessels.⁶

Treatments for deactivating or eliminating donor T cells are routinely used to prevent GVHD in accordance with the important role of T lymphocytes, such as cyclosporine^{7,8} or tacrolimus.^{9,10} Other systemic treatments include steroids, rituximab (targeting B cells), and photopheresis.⁷

Immunosuppressive agents, especially cyclosporine and tacrolimus, have proven successful for dry eye treatment in GVHD patients.^{9,10} Both act by blocking T-lymphocyte activity. Tacrolimus and cyclosporine inactivate the enzymatic

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activity of calcineurin and, thus, ultimately inhibit the transcription of cytokines, namely, interleukin (IL)-2, IL-3, IL-4, and IL-5, interferon- γ , tumor necrosis factor- α , and granulocyte and macrophage colony-stimulating factor.¹¹ The fact that calcineurin is important to T-lymphocyte activation accounts for the sensitivity of T lymphocytes to tacrolimus and cyclosporine.¹¹ Tacrolimus, a macrolide produced by *Streptomyces tsukubaensis*, was discovered in 1984 in Japan while searching for new immunosuppressive and cancer chemotherapeutic agents. It was first used clinically in 1989 to successfully replace cyclosporine in hepatic transplant recipients who were experiencing intractable rejection or as the baseline drug from the time of operation.¹² It also blocks T-lymphocyte activity, but its immunosuppressive potential is higher than cyclosporine.^{11,12} Tacrolimus is 50–100 times more potent than cyclosporine *in vitro* due to differences in partition coefficients and increased binding affinity of tacrolimus for FK506 binding protein (FKBP) compared with cyclosporine affinity for cyclophilin.^{11,12}

However, the systemic administration of immunosuppressive drugs implies a greater risk of infection and systemic toxicity. To avoid these side effects, topical eyedrops containing cyclosporine or tacrolimus would be a preferable therapy for dry eye in patients with GVHD.^{9,10} Topical 0.05% cyclosporine and 0.03% tacrolimus ointment have proven effective to treat dry eye in GVHD patients.^{10,8,13} Nevertheless, some patients present local or systemic intolerance to cyclosporine and cannot be treated with this drug, and the tacrolimus ointment has been designed for skin (Protopic®; Astellas Pharma Ltd), but not for ocular use. Although the beneficial effects of topical tacrolimus eyedrops remain to be shown in GVHD patients, it has proven effective in preventing corneal rejection¹⁴ and as a treatment for severe allergic conjunctivitis.¹⁵ Therefore, we initiated a pilot study to assess the efficacy and safety of 0.03% tacrolimus eyedrops in topical or systemic cyclosporine-intolerant GVHD patients with severe keratoconjunctivitis sicca.

Methods

This is an open-label, single-center prospective study with consecutive patients presenting dry eye associated with GVHD between October and December 2009 ($n=43$). All the patients provided a signed informed consent. The study protocol complied with the provisions of the Declaration of Helsinki and the Ethics Committee of the University La Fe Hospital of Valencia, where approval was obtained. The patients included in this study were selected by the Ophthalmology Department at the University La Fe Hospital of Valencia.

After completing a 1-year run-in period of using artificial tears (on-demand treatment, range 1–10 times per day, Hypromellose 3.2 mg/mL, Artific® Angelini Farmacéutica S.A.; Barcelona, Spain), 50% autologous serum eyedrops (4 times per day), and punctal plug occlusion (Mini Parasol punctal occluder®; Odyssey Medical, Inc., Bartlett, TN), all the symptomatic patients ($n=29$) were treated with 0.05% topical cyclosporine (Restasis®; Allergan, Inc., Irvine, CA). After 1 month, the patients who presented topical or systemic intolerance to cyclosporine were instructed to instill 0.03% topical tacrolimus once a day ($n=14$). All the patients were allowed to continue with their basal dry eye treatment. Thus, the patients who received 0.03% tacrolimus eyedrop treatment fulfilled the criteria listed in Table 1.

TABLE 1. INCLUSION CRITERIA

Older than 18 years
Present graft versus host disease
Moderate-to-severe dry eye confirmed by:
Schirmer test < 5 mm
Immediate FBUT
Presence of corneal keratitis
Dry eye symptoms
Have been treated with artificial tears, autologous serum, and punctal plug occlusion during 1 year without relief
Resistance or intolerance to cyclosporine, described as:
Intense stinging
Worsening of conjunctival hyperemia
Worsening of corneal keratitis
Patient's complaint

FBUT, fluorescein break-up time.

Tacrolimus eyedrops were produced by adding a balanced salt solution to the tacrolimus vial for injection (Prograf; Astellas Pharma, Inc., Dublin, Ireland) under sterile conditions to achieve a 0.03% concentration in the Department of Pharmacology at La Nueva Fe Hospital, Valencia.

The treatment duration with tacrolimus and cyclosporine eyedrops was 3 months. The mean follow-up time with tacrolimus treatment was 12.14 ± 2.69 months (range 10–18 months). All the patients were evaluated every 3 months, and the patients with topical immunosuppressive therapy were examined monthly. The following data were collected and analyzed: patients' demographic characteristics (age, gender, basal disease, year of bone marrow transplant, and systemic medication), visual acuity tests, slit-lamp examinations, fluorescein staining, Schirmer basal secretion tests, and fluorescein break-up time (FBUT).

The FBUT was the time measured in seconds between the full opening of eyelids after a complete blink and the first break in the tear film. The Schirmer basal secretion test was performed during each study visit. After 1 drop of tetracaine and oxibuprocaine instilled into each eye, the patients were asked to keep their eyes open (blinking gently if necessary). The lower conjunctival fornix was dried using a cotton-tip applicator, and a standard Schirmer strip was placed into the lower conjunctival sac. The results were reported as millimeters of wetting at 5 min.

The Van Bijsterveld scoring system, in which the ocular surface was divided into 3 zones—nasal conjunctival, corneal, and temporal conjunctival—was used. In each zone, a staining score in points was used, with the minimum being 0 and the maximum being 3.

The Ocular Surface Disease Index (OSDI) questionnaire was used at the beginning and during the last visit of the study (Supplementary Data are available online at www.liebertpub.com/jop). Patients were asked about the frequency of artificial tear instillation (not including tacrolimus eyedrop instillations) and tolerance to tacrolimus eyedrops. Tacrolimus tolerance was classified as good (3, no red eye without stinging), regular (2, red eye with or without mild stinging), or bad (1, intense stinging with red eye). Possible adverse effects were documented in each visit.

A paired *t*-test was used to compare the pretreatment and post-treatment quantitative results, and the *t*-test was used to compare the cyclosporine treatment group and the tacrolimus treatment group; the Wilcoxon test was used to

compare the artificial tear instillation frequency and dry eye symptoms. A Spearman rho correlation coefficient was used to evaluate the association of age and final outcome. The means of the left eye were used for all these analyses. The *a priori* level of significance for all the tests was $P=0.05$.

Results

The most frequent underlying hematological disease was chronic myeloid leukemia and the mean of the post-transplant period was 61.29 ± 28.75 months.

All the patients continued their immunosuppressive medication prescribed by the Hematology Department. Immunosuppressive medication remained stable throughout the follow-up; only dose systemic corticosteroids were modified according to systemic clinical status in each patient. Table 2 lists the epidemiological data (age, gender), type of BMT, and immunosuppressive medication of the 29 patients who required topical immunosuppressive medication.

The mean Schirmer basal secretion score before any treatment was 5.13 ± 1.89 mm, FBUT was 3.09 ± 2.10 s, fluorescein staining score was 8.46 ± 0.70 , OSDI score was 90.89 ± 3.43 , the mean frequency of artificial tears instillation was 7.95 ± 3.35 , and the visual acuity was 0.21 ± 0.25 log-MAR. After completing a 1-year run-in period of using ar-

tificial tears, 50% autologous serum eyedrops (4 times per day), and punctal plug occlusion, the mean Schirmer basal secretion score was 6.88 ± 2.42 mm, FBUT was 5.05 ± 3.42 s, fluorescein staining score was 5.37 ± 2.48 , OSDI score was 66.51 ± 23.5 , the mean frequency of artificial tears instillation was 5.37 ± 2.47 , and the visual acuity was 0.10 ± 0.11 log-MAR. All the values were statistically different ($P < 0.001$) except visual acuity ($P > 0.05$). About 32.56% (14/43) of the patients were asymptomatic after the 1-year run-in period with hydration treatment and punctal plug occlusion, and they did not require adjuvant topical immunosuppressive treatment.

About 67.44% of the patients (29/43) were instructed to apply 0.05% cyclosporine eyedrops three times a day. One month after, 48.27% (14/29) of the patients presented local or systemic intolerance to cyclosporine eyedrops, and these patients were finally treated with 0.03% tacrolimus eyedrops; 9 patients were men. The mean age of the patients was 44.07 ± 6.77 years (range 34–54 years) in the tacrolimus group and 43.3 ± 5.88 years (range 35–51 years) in the cyclosporine group. No statistical differences were observed for age between both the groups ($P < 0.05$).

Thirteen patients (92.8%) completed the 3-month treatment with 0.03% tacrolimus eyedrops, and one patient (7.14%) stopped the treatment at 5 weeks due to local

TABLE 2. THE DEMOGRAPHIC PROFILE, TYPE OF BONE MARROW TRANSPLANTATION, INCIDENCE OF ACUTE GRAFT VERSUS HOST DISEASE, AND SYSTEMIC IMMUNOSUPPRESSIVE TREATMENT DATA OF OUR STUDY

Patient	Gender	Age	BMT	Donor	Acute GVHD	Systemic immunosuppressive drug	Cyclosporine intolerance
1	Male	43	Allogeneic	Umbilical cord	Yes	Tacrolimus 20 mg and prednisone 30mg	Systemic
2	Male	45	Allogeneic	Umbilical cord	Yes	Tacrolimus 15 mg and prednisone 30mg	Systemic
3	Male	40	Allogeneic	Related	Yes	MFF 500 mg	Local
4	Female	46	Allogeneic	Related	Yes	MFF 250 mg	Local
5	Male	51	Allogeneic	Related	Yes	Cyclosporine 200 mg	Local
6	Male	51	Allogeneic	Related	Yes	Cyclosporine 150 mg	Local
7	Male	35	Allogeneic	Umbilical cord	Yes	Tacrolimus 20 mg	Systemic
8	Male	39	Allogeneic	Umbilical cord	Yes	Tacrolimus 20 mg	Systemic
9	Female	43	Allogeneic	Unrelated	Yes	Prednisone 15 mg	Local
10	Female	52	Allogeneic	Umbilical cord	Yes	Prednisone 15 mg	Local
11	Female	54	Allogeneic	Umbilical cord	No	No	Local
12	Female	49	Allogeneic	Umbilical cord	No	No	Local
13	Male	34	Allogeneic	Umbilical cord	No	No	Local
14	Male	35	Allogeneic	Unrelated	Yes	No	Local
15	Male	43	Allogeneic	Umbilical cord	Yes	Cyclosporine 100 mg	—
16	Male	44	Allogeneic	Umbilical cord	Yes	Cyclosporine 100 mg	—
17	Male	46	Allogeneic	Umbilical cord	Yes	Cyclosporine 150 mg	—
18	Male	47	Allogeneic	Umbilical cord	No	Prednisone 10 mg	—
19	Female	51	Allogeneic	Umbilical cord	Yes	MFF 250 mg	—
20	Female	50	Allogeneic	Unrelated	Yes	MFF 250 mg	—
21	Female	38	Allogeneic	Umbilical cord	Yes	MFF 250 mg	—
22	Female	37	Allogeneic	Related	Yes	Cyclosporine 200 mg	—
23	Male	40	Allogeneic	Related	Yes	Cyclosporine 200 mg	—
24	Male	36	Allogeneic	Unrelated	Yes	Cyclosporine 150 mg	—
25	Male	47	Allogeneic	Related	Yes	Cyclosporine 150 mg	—
26	Male	51	Allogeneic	Umbilical cord	Yes	MFF 250 mg	—
27	Male	36	Allogeneic	Related	No	No	—
28	Male	35	Allogeneic	Related	No	No	—
29	Male	49	Allogeneic	Related	No	Prednisone 15 mg	—

Immunosuppressive treatment was stable during the study, except for oral prednisone, which was modified according to the patient's systemic symptoms. The dose of prednisone in the table dates from the baseline visit. The first 14 patients in the table were treated with 0.03% topical tacrolimus eyedrops because of systemic or local intolerance to cyclosporine.

BMT, bone marrow transplantation; GVHD, graft versus host disease; MFF, mycophenolate mofetil.

FIG. 1. Survival curve. Fourteen patients were finally included in the tacrolimus treatment group. Treatment duration was 3 months. Thirteen patients (92.8%) completed the 3-month treatment, and one patient (7.14%) stopped treatment after 5 weeks due to local intolerance. No systemic adverse effects were observed.

intolerance. The results are shown on the survival curve (Fig. 1). Improvement started 2 weeks after the treatment with tacrolimus eyedrops. No significant adverse events were noted during the follow-up. No patients developed secondary ocular infections or an intense local inflammation reaction. No systemic intolerance was observed, and 71.43% (10/14) of the patients well tolerated eyedrops locally. Of all the patients, 21.43% (3/14) complained of some discomfort after instillation but did not discontinue the treatment. Moreover, 7.14% (1/14) of the patients complained of significant ocular stinging upon instillation and discontinued the treatment after 5 weeks. The mean follow-up was 12.14 ± 2.69 months, with a range of 10–18 months. Table 3 describes the tolerance to 0.03% tacrolimus eyedrops and other concomitant ophthalmological treatments and follow-up.

After 3 months of instilling 0.03% tacrolimus eyedrops, the mean Schirmer test score improved statistically up to 7.93 ± 2.7 mm ($P=0.001$), FBUT increased up to 7.50 ± 4.97 s ($P=0.007$), and fluorescein staining improved statistically up to 2.57 ± 1.55 (range 1–6; $P=0.001$; Table 4 and Figs. 2 and 3). On the other hand, after 3 months of instilling 0.05% cyclosporine eyedrops, the mean Schirmer test increased statistically up to 8.00 ± 2.33 mm ($P=0.003$), FBUT increased up to 7.2 ± 4.52 s ($P=0.007$), and fluorescein staining improved statistically up to 2.6 ± 1.55 (range 1–6; $P=0.001$; Table 4 and Figs. 2 and 3). In addition, comparing the tacrolimus and cyclosporine treatment groups, no significant differences were observed between both the groups for the Schirmer test ($P=0.766$), FBUT ($P=0.641$), and fluorescein staining ($P=0.930$; Table 4 and Figs. 3 and 4).

TABLE 3. TOLERANCE TO TACROLIMUS EYEDROPS, SURFACE LUBRICANT UNDERLYING TREATMENT, AND FOLLOW-UP

Patient	Other surface lubricant treatment	Follow-up (months)	Tolerance to tacrolimus eyedrops	Frequency of artificial tear instillation pretreatment	Frequency of artificial tear instillation post-treatment
1	AS ^a + punctal plug occlusion ^b + artificial tears ^c	11	1	5	5
2	AS + punctal plug occlusion + artificial tears	11	1	5	5
3	AS + punctal plug occlusion + artificial tears	12	1	5	3
4	AS + punctal plug occlusion + artificial tears	12	1	5	3
5	AS + punctal plug occlusion	11	3	10	5
6	AS + punctal plug occlusion + artificial tears	11	3	10	5
7	AS + artificial tears	10	2	5	3
8	AS + artificial tears	10	2	5	3
9	Artificial tears	10	3	3	0
10	Artificial tears	10	3	3	0
11	Artificial tears	13	3	7	3
12	Artificial tears	13	3	7	3
13	Artificial tears	18	3	8	5
14	Artificial tears	18	3	10	5

The mean follow-up time was 12.14 ± 2.69 months, with a range of 10–18 months. Patients were asked about intensity of dry eye symptoms and frequency of artificial tear instillation. The tolerance was classified as good (3, no red eye), regular (2, red eye with or without mild stinging), or bad (1, intense stinging with red eye) according to the subjective questionnaire filled in by each patient during the first and the last visits.

^aAS, Autologous serum eyedrops 50%.

^bMini Parasol punctal occluder.[®]

^cTreatment as needed with Hypromellose 3.2 mg/mL, Artific.[®]

TABLE 4. DRY EYE MEASUREMENTS BEFORE AND AFTER LUBRICANT TREATMENT AND TACROLIMUS TREATMENT

Patient	OSDI score pretreatment	OSDI score post-treatment	Schirmer treatment	Schirmer pretreatment	Schirmer post-treatment	Meniscometry pretreatment	Meniscometry post-treatment	FBUT pretreatment	FBUT post-treatment	Primary VA (logMAR)	VA pretreatment (logMAR)	VA post-treatment (logMAR)	Initial frequency of artificial tear instillation pretreatment	Frequency of artificial tear instillation pretreatment	Frequency of artificial tear instillation post-treatment
1	91.66	95.83	6	5	7	0	0	1	1	0.70	0.22	0.15	12	5	5
2	100.00	100.00	5	7	10	0	0	3	3	0.40	0.10	0.05	12	5	5
3	93.75	93.75	5	5	5	185	119	3	3	0	0	0	8	5	3
4	95.83	93.75	6	4	4	74	111	5	4	0.05	0.05	0.05	8	5	3
5	91.66	72.91	3	7	7	267	452	3	15	0.40	0.10	0.10	10	10	5
6	91.66	64.58	3	4	7	141	237	0	1	0.70	0.30	0.30	10	10	5
7	85.41	35.41	5	7	7	119	193	5	4	0.15	0.15	0.15	12	5	3
8	89.58	37.50	7	7	8	74	44	7	7	0.05	0.05	0.05	12	5	3
9	89.58	60.41	4	6	10	267	356	6	15	0.30	0.30	0.15	3	3	0
10	87.50	64.58	4	6	10	163	215	6	12	0.22	0.10	0.10	3	3	0
11	100.00	57.50	22	13	15	222	259	2	8	0	0	0	7	7	3
12	92.50	42.50	5	5	7	170	200	4	10	0	0	0	7	7	3
13	91.66	35.41	3	5	6	178	281	3	13	0	0	0	15	8	5
14	93.75	37.50	2	5	8	215	285	4	9	0	0	0	15	10	5

After 3 months of 0.03% tacrolimus eyedrop instillation, the Schirmer test, FBUT, OSDI questionnaire scores, and meniscometry were statistically different to both previous situations, unlike visual acuity, which was not. Patients 1 and 2 have no meniscometry measurements because of the poor-quality images obtained.

OSDI, Ocular Surface Disease Index; VA, visual acuity.

FIG. 2. Box plot of the Schirmer test, fluorescein break-up time (FBUT), and fluorescein staining before and after lubricant treatment, and before and after 0.03% tacrolimus or 0.05% cyclosporine eyedrops. A paired *t*-test was used to compare the pretreatment and post-treatment Schirmer basal secretion tests (plot 1), FBUT (plot 2), and fluorescein staining (plot 3). After the 0.03% tacrolimus eyedrop and 0.05% cyclosporine eyedrop treatment, the Schirmer test (plot 1), FBUT (plot 2), and fluorescein staining (plot 3) improved statistically. No significant differences were reported between both immunosuppressive topical treatments.

Improvement in the OSDI scores was also reported for both the groups. The OSDI score statistically improved ($P < 0.001$): 63.69 ± 24.3 (range 35.41–100), after tacrolimus treatment. Otherwise, the OSDI score statistically improved ($P = 0.003$): 62.61 ± 23.77 (range 35.41–100), in the cyclosporine treatment group. The number of artificial tear instillations per day lowered from the baseline 5.37 ± 2.45 (1 year of dry eye treatment) to 3.43 ± 1.74 times per day after 0.03% topical tacrolimus treatment, which is statistically different ($P < 0.0001$). Nonetheless, it also decreased significantly, up to 3.67 ± 1.59 times per day after the treatment with 0.05% topical cyclosporine. No significant differences were observed between both the groups for the OSDI score ($P = 0.946$) and the number of artificial tear instillations ($P = 0.968$; Table 4 and Figs. 3 and 4).

A poor correlation was found between age and treatment outcomes: FBUT ($r_s = -0.28$, $P = 0.34$), visual acuity ($r_s = -0.361$, $P = 0.205$), and the Schirmer test ($r_s = -0.45$, $P = 0.107$). The correlation was also poor between duration of the post-transplantation period and the results: FBUT ($r_s = -0.114$, $P = 0.698$), visual acuity outcome ($r_s = 0.036$, $P = 0.902$), and the Schirmer test ($r_s = -0.274$, $P = 0.343$). No differences were observed between men and women in both groups, being only artificial tear instillations significantly higher in men with 0.03% topical tacrolimus treatment compared with women with 0.03% topical tacrolimus treatment (*t*-Student test, $P = 0.009$) (Supplementary Table 1; Supplementary materials are available online at <http://www.liebertpub.com/jop>). Finally, dry eye measurements were assessed according to the age of patients. The patients were classified in 5 groups (40–45-year-old, 45–50-year-old, 50–55-year-old, 55–60-year-old), no differences were observed between the groups, except for OSDI score, which was significantly higher in the 40–45-year-old group (ANOVA test, $P = 0.001$) (Supplementary Table 2).

Discussion

The results of this study suggest that 0.03% topical tacrolimus is effective to treat cyclosporine-intolerant patients with dry eye associated with GVHD. After 3 months of 0.03% topical tacrolimus therapy, tacrolimus provided statistically significant improvements in the evaluated outcome measures in direct relation to dry eye (Schirmer basal secretion test, FBUT, fluorescein staining, OSDI results, and artificial tear instillations), and no statistical differences were reported between the 0.05% cyclosporine group and the 0.03% tacrolimus treatment group.

The proven efficacy of tacrolimus in this group of patients is presumably based on its ability to effectively target T cells. There is considerable evidence that dry eye associated with GVHD is a T2-cell-mediated disease,⁴ as mentioned above. Therefore, tacrolimus may interfere with the induction of cytokines and genes required for the immune response blocking T cells. Our study shows the effectiveness of tacrolimus in severe dry eyes associated with GVHD, without adequate relief with intensive dry eye treatment. However, our study did not address the early treatment of patients with GVHD. Potentially, early tacrolimus intervention through T cells may lower the initial immune response and prevent future significant dry eye signs and symptoms.

Previous studies with topical tacrolimus have shown an excellent safety profile: tacrolimus ointment in GVHD,¹⁰

FIG. 3. Box plot of a number of instillations of artificial tears per day (plot 1) and Ocular Surface Disease Index (OSDI) questionnaire results (plot 2). The Wilcoxon test was used to compare the artificial tear instillation frequency and dry eye symptoms before and after lubricant and immunosuppressive topical treatment. The number of artificial tear instillations statistically lowered after 0.03% tacrolimus and 0.05% cyclosporine topical treatment (plot 1), and OSDI scores improved significantly after lubricant treatment and even more after immunosuppressive topical treatment (plot 2). No significant differences were observed between the 0.03% tacrolimus treatment group and the 0.05% cyclosporine treatment group.

tacrolimus eyedrops in allergic conjunctivitis,¹⁵ and corneal transplantation.¹⁴ However, as far as we know, no previous published studies have established the efficacy of tacrolimus eyedrops in GVHD patients and no previous published studies have compared tacrolimus eyedrops and cyclosporine eyedrops in GVHD patients. The statistically significant *P* value for the outcome variables in this study has determined improvement in both signs and symptoms. In addition, the *P* values not statistically significant between the tacrolimus and cyclosporine treatment groups suggest similar efficacy of both topical immunosuppressive drugs for treating dry eye in GVHD patients. Otherwise, the main limitation of this study is its small sample size. Although the study did not show any adverse events associated with topical tacrolimus therapy, the study is too small to determine complete safety in this group of patients with GVHD.

On the other hand, cyclosporine also blocks the T-cell immune response; thus, it has been demonstrated to be effective to treat dry eye associated with GVHD.^{8,13} Nevertheless, tacrolimus is a more potent immunosuppressive

drug than cyclosporine^{11,12}; therefore, we might assume a more intense effect on immunological ocular surface disorders, although we have observed no statistical differences between 0.05% cyclosporine and 0.03% tacrolimus eyedrops in our study.

In addition, some patients develop systemic or local intolerance, even allergy to cyclosporine, as in our study, which has demonstrated that 0.03% tacrolimus eyedrops improve the signs and symptoms of dry eye secondary to GVHD. However, we must emphasize that 0.03% tacrolimus eyedrops (12.56€ per eyedrops) is approximately 20 times more expensive than 0.05% cyclosporine eyedrops (0.62€ per eyedrops) currently in Spain; hence, this immunosuppressive drug can be a therapeutic alternative and a rescue treatment for cyclosporine-intolerant or -unresponsive dry eye patients.

In fact, topical tacrolimus ointment has already proven effective for dry eye in GVHD patients.¹⁰ Nevertheless, 0.03% tacrolimus ointment is a dermatological medication that is not prepared for ophthalmological treatment. We have obtained contradictory results in isolated experiences

FIG. 4. Patient 4. A 46-year-old female, with severe dry eye secondary to GVHD (graft versus host disease) immunosuppressed with 250 mg mycophenolate mofetil, presented severe dry eye with local intolerance to cyclosporine eyedrops. (a, a1) Basal fluorescein staining and hyperemia; (b, b1) fluorescein staining worsened after cyclosporine treatment; (c, c1) hyperemia and fluorescein staining improved after 90 days of 0.03% tacrolimus eyedrop treatment.

with 0.03% tacrolimus ointment, although we have not performed any comparative study of tolerance. We observed pruritus and hyperemia, bad tolerance, difficult instillation, and ocular surface impairment with 0.03% tacrolimus ointment in patients with severe dry eye.

Otherwise, 0.03% tacrolimus eyedrops were well tolerated in 71.4% (10/14) of the patients in our case series. Tacrolimus eyedrops have been safe and effective in our study. No statistical differences were observed between the cyclosporine-treated patients and the tacrolimus-treated patients, and the tacrolimus immunosuppressive potential is higher than cyclosporine. However, as commented above, tacrolimus is more expensive than cyclosporine. Therefore, 0.03% tacrolimus eyedrops may be a good therapeutic alternative for patients with local or systemic intolerance to cyclosporine, and it may even be a good early treatment in place of cyclosporine, especially if the therapeutic response of cyclosporine is not as good as expected.

By way of conclusion, this study shows that 0.03% tacrolimus eyedrops improve symptoms and signs of dry eye associated with GVHD in cyclosporine-intolerant patients. This study also shows that 0.03% tacrolimus is as safe and effective as 0.05% cyclosporine eyedrops; 0.03% tacrolimus eyedrops being a new therapeutic alternative for dry eye in GVHD patients. These findings should be confirmed with a randomized, double-masked, multicenter, placebo-controlled trial.

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Author Disclosure Statement

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