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Systemic Treatment with the Janus Kinase Inhibitor Baricitinib in Ocular Chronic Graft-versus-Host Disease

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Objective: To investigate the effects of oral baricitinib on ocular surface disease (OSD) in patients with chronic graft-versus-host disease (cGVHD).

Design: Prospective phase 1 to 2 single institution trial.

Subjects: Eighteen patients with ocular graft-versus-host-disease (oGVHD) and systemic steroid-refractory cGVHD.

Methods: Oral baricitinib (2 mg and 4 mg) was administered daily for up to 12 months in an intrapatient dose-escalation design. National Institutes of Health (NIH) oGVHD score, vision, corneal Oxford staining (COS), tear break-up time (TBUT), Schirmer I test (ST) without anesthesia, and microliter tear equivalent conversion were assessed at baseline, 6 months (primary efficacy end point), and 12 months if patients remained on the drug.

Main Outcome Measures: Improvement in NIH oGVHD score, COS, TBUT, and ST results in patients with and without conjunctival fibrosis at 6 months.

Results: At 6 months, the NIH oGVHD score significantly improved ($P = 0.014$) with all OSD parameters also showing improvement, though not statistically significant. COS baseline, 2.17 to 0.95; TBUT baseline, 6.66 to 8.18 seconds, Schirmer I baseline, 3.86 mm (2.6 μl) to 5.56 mm (3.9 μl). For patients continuing treatment at 12 months improvements persisted compared with the baseline but remained statistically nonsignificant. Corneal Oxford staining decreased to 0.94; TBUT increased to 8.95 seconds, and ST improved to 10.19 mm (7.2 μL). Conjunctival fibrosis was present in 39% (n = 7) of the patients at baseline. The greatest improvement was observed in the 11 patients without prior conjunctival fibrosis compared with the baseline: COS 1.84, TBUT 6.32 seconds, ST 4.07 mm (2.1 μl); 6 months: COS 0.25 ($P = 0.018$), TBUT 8.62 seconds, ST 9.12 mm (5.4 μl); 12 months: COS 0, TBUT 10.29 seconds, ST 16.88 mm (10.6 μl). Vision was stable in all groups. Two patients developed asymptomatic, self-limited conjunctival papillomas, and 1 patient developed uncomplicated bacterial conjunctivitis twice. No dose limiting toxicity was observed. Severe adverse events with hospitalizations for possible drug-related systemic infections occurred in 5 patients.

Conclusions: Systemic baricitinib was well-tolerated, improved NIH oGVHD scores and OSD parameters in patients with oGVHD, with the greatest benefits observed in patients without pre-existing conjunctival fibrosis. Conjunctival fibrosis may affect outcomes and should be considered in patient selection for clinical trials.

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Ocular graft-versus-host disease (oGVHD) is characterized by alloreactive T cell-mediated inflammation, cytokine upregulation, and pervasive immune dysregulation, affecting all structures of the ocular surface.[1,2] This constellation of pathological processes culminates in the development of chronic keratoconjunctivitis sicca, which is marked by severe dryness and inflammation of the cornea, conjunctiva, lacrimal, and meibomian glands. In addition, oGVHD is frequently accompanied by fibrotic transformation of the lacrimal gland, conjunctiva, and meibomian glands.[1] Between 60% and 90% of patients with systemic graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation develop chronic oGVHD, and the severity of dry eye symptoms is correlated with the inflammatory response and the consequential fibrotic damage inflicted on the lacrimal gland.[1] Ocular surface disease (OSD) symptoms and related vision changes can have a profound impact on every aspect of patient's lives.[3] In oGVHD there is an abundance of biomarkers implicated in ocular surface inflammation including interferon-γ, interleukin (IL)-2, and

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IL-6 found in the tears of affected patients.[4–6] Many of the inflammatory cytokines bind to receptors that utilize Janus Kinase (JAK) signaling to activate gene transcription via the STAT pathway.[7] This cascade is intricately involved in the pathogenesis of cGVHD and also oGVHD.[4] Consequently, JAK inhibitors (JAKis) are increasingly being used to modulate or mitigate disease in cGVHD.[8] For example, ruxolitinib, a JAK1/2 inhibitor, was recently approved by the United States Food and Drug Administration for the treatment of steroid-refractory systemic GVHD.[9,10] Xue et al reported a single-center retrospective study demonstrating improvement in oGVHD scores and steroid-refractory systemic disease after 6 months of treatment.[11] Similarly, Sajjan et al reported an improvement in ocular surface disease index scores in 4 patients with systemic and oGVHD following systemic therapy with ruxolitinib.[12] Baricitinib, an oral JAKi 1/2 that is United States Food and Drug Administration–approved for the treatment of rheumatoid arthritis, alopecia areata, and COVID19 pneumonia, has shown superior GVHD control in murine models and exhibits an alternate toxicity profile than ruxolitinib, with less cytopenia and preservation of the graft-versus-tumor effect, therefore garnering interest in its study for chronic graft-versus-host disease (cGVHD).[13,14]

In the present study, we report the improvement in oGVHD-associated OSD and National Institutes of Health (NIH) oGVHD scores following therapy with baricitinib. Additionally, we provide insights into the efficacy of baricitinib on oGVHD depending on the presence of preexisting conjunctival fibrosis.

Methods

Twenty-four patients with severe systemic and steroid-refractory cGVHD according to the NIH consensus criteria enrolled in this single center open-label phase 1 to 2 trial of oral baricitinib (NCT02759731), of which 18 with ocular involvement of their cGVHD were included in this analysis.[15] The systemic treatment results of the protocol are reported separately.[16] The study was approved by the NIH Institutional Review Board, and adhered to the Declaration of Helsinki, and all patients provided informed consent. After a baseline evaluation, patients were started on 2-mg baricitinib/day for 12 weeks and then escalated to 4 mg/day until the primary efficacy end point at week 24. Patients were able to remain on the study drug for an additional 6 months after the study end point if they exhibited a response and developed no significant toxicity. However, eye clinic visits were not mandatory after the baseline visit, and the NIH oGVHD score was not collected at the end of the study. During the study, patients taking concomitant systemic immunosuppressants for the control of cGVHD had to be on a stable or tapering dose preceding 4 weeks on enrollment with intent to stop if possible. No other new systemic or topical therapy for cGVHD was permitted once baricitinib was initiated. Patients could remain on systemic steroids with the intent of tapering 10% per week starting 4 weeks after starting baricitinib. Two patients remained on systemic prednisone during the course of the study: one patient on 25 mg/day and one on 2.5 mg/day.

Ophthalmic Examinations

Eye examinations after the baseline visit were not mandatory but were obtained at 6 and 12 months if patients remained on the study drug and were able to follow up. Additionally, eye examinations were performed any time to evaluate for ocular adverse events (AEs). National Institutes of Health oGVHD scores were obtained at baseline and at the study end point at 6 months. However, details of OSD parameter assessments were not prespecified in the protocol, and missing data were collected retrospectively when available through chart review at the end of the clinical trial. Data were collected on topical medication history, vision, corneal fluorescein staining using the corneal Oxford staining (COS) 0 to 5, tear break-up time (TBUT) (average of 3 consecutive measurements in seconds), conjunctival assessment for the presence or absence of subtarsal fibrosis and slit lamp examination. Additionally, a Schirmer I test (ST) (EagleVision Colorbar, Corza Medical) was performed without anesthesia and read in millimeters of moisture migration at 5 minutes. The mean moisture migration results were then converted into microliters (μl) of tears using a previously described calibration method.[17] This conversion allows for a standardized comparison of tear volume results, regardless of the specific ST brand used.

Topical medications for each patient were assessed at baseline and each response time point. Patients were asked to avoid any changes in the topical management after enrollment. After the primary end point assessment at 6 months, recommendations for topical treatment were made based on the ocular surface findings. Adverse events were monitored throughout the study and graded using the Common Terminology Criteria for AEs, version 4.0.

Statistical Analysis

Analyses were performed with SAS version 9.4. For each parameter, we computed the mean value of both eyes at each time point. Paired *t* tests or, where appropriate, Wilcoxon signed rank tests (nonparametric equivalent of a paired *t* test) were used to assess change between baseline and 6 months and change between baseline and 12 months. Results are reported as mean ± standard deviation (SD) unless specified otherwise. Snellen vision was converted to logarithmic minimum angle of resolution for analysis.

Results

Eighteen participants with symptomatic chronic oGVHD related dry eye disease were enrolled in this pilot study from 2016 to 2021. None of the patients had membranous conjunctivitis at presentation. The median time from transplant to treatment initiation was 4.8 years (range, 0.6–11.2 years) and the median time from chronic GVHD diagnosis to baricitinib initiation was 3.3 years (range, 0.3–9.1 years). Of note, the study was conducted during the severe acute respiratory syndrome coronavirus 2 pandemic, and only 15 patients (83%) completed the baseline and 6-month study end point ophthalmic evaluation, with 9 patients (50%) also completing the 12-month ophthalmic evaluation. Additionally, one patient was unable to escalate from 2-mg baricitinib per day because of a decrease in the absolute neutrophil count. Of the patients on concurrent topical treatment at baseline, 94% used artificial tears, 28% used cyclosporine 0.05%, and 11% used topical steroid drops. At the 6-month study end point, 100% of patients were using artificial tears, 28% were using cyclosporine 0.05% drops, and 7% were using topical steroids. After the primary end point assessment 3 patients were started on cyclosporine 0.05% drops. At the 12-month visit, 100% of patients were using artificial tears, 44% were using cyclosporine 0.05%

drops, and 6% were using topical steroids. Systemic immunosuppression was not added during treatment with baricitinib. The baseline demographics and disease characteristics are shown in Table 1.

Ocular GVHD NIH Score

The mean oGVHD score improved significantly at 6 months (mean ± SD: 1.35 ± 0.78; median: 2), compared with baseline (mean ± SD: 1.78 ± 0.73; median: 2; $P = 0.014$; Table 2). National Institutes of Health oGVHD score was the highest among patients with pre-existing fibrosis (n = 7) (baseline mean ± SD: 2.43 ± 0.53; 6 months mean ± SD: 1.86 ± 0.38; median: 2; $P = 0.103$; Table 2). Patients without pre-existing fibrosis (n = 11) had a mean baseline oGVHD score of 1.36 ± 0.50, which improved to 1.0 ± 0.82 at 6 months (median 1) ($P = 0.08$).

Visual Acuity

Visual acuity remained stable in all groups while on oral baricitinib compared to baseline. Mean logarithmic minimum angle of resolution vision in all groups was 0.14 ± 0.38 SD at baseline, 0.17 ± 0.39 at 6 months, and 0.03 ± 0.08 at 12 months. The change from baseline to 6 months was as follows: −0.10, $P = 0.06$; change from baseline to 12 months, −0.01, $P = 0.74$. In the patients without pre-existing fibrosis, vision was 0.04 ± 0.10 at baseline, 0.06 ± 0.09 at 6 months, and −0.01 ± 0.06 at 12 months (P values for change: 0.83 and 0.80, respectively).

Table 1. Baseline Demographics and Patient Characteristics

	All Patients (n = 18)	No Fibrosis (n = 11)	Fibrosis (n = 7)
Sex, n (%)			
Male	8 (44)	4 (36)	4 (57)
Female	10 (55)	7 (63)	3 (43)
Age (yrs)			
Mean (SD)	51.3 (12.3)	52.4 (9.3)	49.6 (16.7)
Race, n (%)			
White	17 (94)	11 (100)	7 (87.5)
Black	1 (5)	0	1 (12.5)
NIH Severity Score, n (%)			
Severe	18 (100)	11 (100)	7 (100)
Moderate	0	0	0
Mild	0	0	0
NIH oGVHD Score			
Mean (SD)	1.8 (0.7)	1.4 (0.5)	2.4 (0.5)
HSCT indication, n (%)			
AML	8 (44)	5 (45)	3 (43)
ALL	4 (22)	2 (18)	2 (29)
MDS	4 (22)	3 (27)	1 (14)
MDS/MPN	1 (6)	1 (9)	0 (0)
NHL	1 (6)	0 (0)	1 (14)
HSCT graft source, n (%)			
PBSC	16 (89)	11 (100)	5 (71)
BM	2 (11)	0 (0)	2 (29)
HSCT donor, n (%)			
MRD	7 (39)	6 (55)	1 (14)
MUD	8 (44)	5 (45)	3 (43)
mMUD	2 (11)	0 (0)	2 (29)
Haplo	1 (6)	0 (0)	1 (14)
Prior therapies, median (range)	4.5 (2-11)	5 (3-11)	4 (2-7)
Concurrent IST at enrollment, n (%)	16 (89)	10 (91)	6 (86)
Systemic steroids at enrollment, n (%)	10 (56)	7 (64)	3 (43)
Daily dose in mg pred equivalent at enrollment, median (range)	17.5 (2.5-30)	15 (2.5–25)	25 (10–30)
Organs involved			
Mean (SD)	5 (1.1)	5.2 (1.0)	4.7 (1.4)
Ocular medications, topical at enrollment			
Mean (SD)	1.3 (0.7)	1.5 (0.8)	0.9 (0.4)

ALL = acute lymphocytic anemia; AML = acute myeloid leukemia; BM = bone marrow; Haplo = haploidentical; HSCT = hematopoietic stem cell transplant; IST = immunosuppressive therapy; MDS = myelodysplastic syndrome; MDS/MPN = myelodysplastic/myeloproliferative neoplasms; mMUD = mismatched unrelated donor; MRD = minimal residual disease; MUD = matched unrelated donor; NHL = non-Hodgkin's lymphoma; NIH = National Institutes of Health; PBSC = peripheral blood stem cell; SD = standard deviation.

Table 2. Change in NIH oGVHD Score, Baseline to 6 Mos

Baseline score	N at baseline	6-Mo Score			
		0	1	2	3
1	7	3	4	0	0
2	7	0	0	7	0
3	3	0	1	2	0
Total	17	3	5	9	0

NIH = National Institutes of Health; oGVHD = ocular graft-versus-host-disease.
Of the 17 eyes with NIH oGVHD scores, 6 (35%) improved between baseline and 6 months. A total of 5 of the 6 improved scores were a 1-step improvement and 1 of the 6 improved scores was a 2-step improvement. Green: no change from baseline. Yellow: improvement from baseline (lower score at 6 months than at baseline).

Patients with fibrosis had a vision of 0.28 ± 0.59 at baseline, 0.34 ± 0.6 at 6 months, and 0.08 ± 0.09 at 12 months (*P* values for change: 0.61 and 0.85, respectively).

Conjunctival Fibrosis

Pre-existing subtarsal fibrosis was present in 7 patients (39%) (Fig 1). All cases were bilateral. Three individuals had upper and lower palpebral lid involvement, without displaying forniceal shortening. Two participants had only upper lid fibrosis while the remaining 2 displayed inferior lid involvement. No new cases of conjunctival fibrosis were observed during the study. None of the patients had lagophthalmos, entropion, ectropion, or trichiasis.

Corneal Staining Score

Mean baseline corneal staining score (COS) in all groups was 2.17 ± 1.42 SD and it improved by 0.86 grades to 0.95 ± 1.22 at the study end point of 6 months, but the difference was not statistically significant ($P = 0.09$). At 12 months, the mean score was 0.94 ± 1.24 SD (median: 0; $P = 0.39$).

In the subgroup without pre-existing fibrosis the mean score improved by 1.06 grades from 1.84 ± 1.33 at baseline (median 1.5) to 0.25 ± 0.46 at 6 months (median 0) ($P = 0.018$). At 12 months, the mean and median COS were 0, but the difference was not statistically significant. Patients with pre-existing fibrosis improved from 2.68 ± 1.49 SD at baseline (median: 3.50) to 1.88 ± 1.32 (median: 2.38) at 6 months ($P = 0.60$) and 2.12 ± 0.85 (median: 2.25) at 12 months ($P = 0.85$; Tables 3–5).

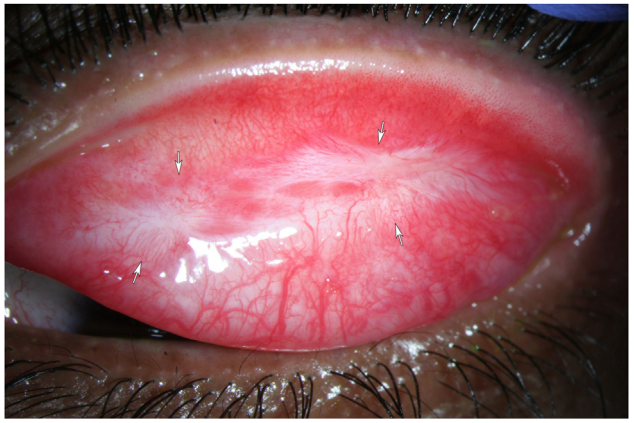

Figure 1. Representative color photograph of a subtarsal band of conjunctival fibrosis (arrows). Upper lid is everted.

Schirmer I Test

The mean Schirmer test results increased at 6 months (5.56 ± 4.95 mm; 3.1 µl) (median 5.0; 2.7 µl) and 12 months (10.19 ± 9.74 mm; 6.2 µl) (median 6.75; 3.9 µl) compared with baseline values (3.86 ± 3.97 mm; 2.0 µl) (median: 2.50;1.0 µl), but the changes were not significant ($P = 0.76$ and 0.59, respectively; Tables 3–5). Similarly, in the no fibrosis subgroup, the mean ST result increased compared to baseline (4.07 ± 5.1 mm; 2.1 µl) (median 1.5; 0.4 µl), at 6 months (9.12 ± 4.33 mm; 5.4 µl) (median 8.75; 5.2 µl) and 12 months (16.88 ± 9.63 mm; 10.6 µl; median 15.25; 9.5 µl) without reaching statistical significance ($P = 0.88$ and 0.08, respectively) (nonparametric testing result for 12 months, $P = 0.50$). The Schirmer test did not improve in patients with pre-existing fibrosis compared to baseline (3.64 ± 3.0 mm; 1.8 µl) (median: 3.0; 1.4 µl) at 6 months (2.0 ± 2.12 mm; 0.7 µl) (median: 1.25; 0.24 µl) or 12 months (3.50 ± 3.03 mm; 1.7 µl; median: 3.75; 1.9 µl) (*P* values for change, 0.60 and 0.25, respectively).

Tear Break-Up Time

Tear break-up increased at 6 and 12 months in all patients, but the changes were not significant in any groups compared to baseline. Mean TBUT was (6.66 ± 3.08 SD) (median: 6.50) seconds at baseline, 8.18 ± 4.42 (median: 6.5) at 6 months, 8.95 ± 3.76 (median: 10.15) at 12 months; *P* for change, 0.88 and 0.25, respectively). The no fibrosis subgroup showed an increase in TBUT (albeit not statistically significant) at 6 months (8.62 ± 2.01 seconds; median: 9.25) and at 12 months (10.29 ± 3.79) (median: 11.32) compared with baseline (6.32 ± 2.89; median: 6.38; *P* for change 0.30 and 0.48, respectively). There was no change in TBUT in the fibrosis group (baseline 7.22 ± 3.60; [median: 6.75]; 6 months 7.58 ± 6.66; [median: 5.50]; 12 months 7.17 ± 3.55 [median: 6.5]; *P* for change, 0.28 and 0.54, respectively; Tables 3–5). Ocular surface parameters in the different groups are shown in Figure 2.

Continuation of Oral Steroids

Two patients were undergoing systemic prednisone therapy at the time of enrollment and continued throughout the study. Patient 1, who did not have pre-existing fibrosis, was on a low dose of 2.5 mg daily, whereas patient 2, who had conjunctival fibrosis, was on 25 mg daily. Both patients exhibited notable improvement in corneal staining, with patient 1 improving from grade 1 to grade 0 and patient 2 from grade 4 to grade 0, which remained stable until 12 months. Additionally, TBUT increased by 4 seconds in both patients. No changes were observed in Schirmer test results.

Table 3. Ocular Parameters for All Groups

Parameter	Time Point	N	Mean	SD	Median	Mean Change*, Baseline Minus 6 Mos	P Value† for Change, Baseline to 6 Mos	Mean Change*, Baseline Minus 12 Mos	P Value for Change‡, Baseline to 12 Mos
Oxford corneal staining score*									
	Baseline	18	2.17	1.42	1.75				
	6 mos	14	0.95	1.22	0.25	0.86	0.091		
	12 mos	9	0.94	1.24	0			0.53	0.390
TBUT (s)									
	Baseline	16	6.66	3.08	6.5				
	6 moss	14	8.18	4.42	6.5	0.14	0.882		
	12 mo	7	8.95	3.76	10.15			2.36	0.2512
Schirmer 1 (mm)									
	Baseline	14	3.86	3.97	2.5				
	6 mos	8	5.56	4.95	5	−0.36	0.760		
	12 mos	8	10.19	9.74	6.75			0.67	0.588
NIH oGVHD score									
	Baseline	18	1.78	0.73	2.00				
	6 mos	17	1.35	0.78	2.00	0.41	**0.0144**		
VA (logMAR)									
	Baseline	18	0.136	0.376	0.050				
	6 mos	15	0.170	0.391	0.100	−0.010	0.604		
	12 mos	9	0.028	0.079	0.050			−0.011	0.738

logMAR = logarithmic minimum angle of resolution; NIH = National Institutes of Health; oGVHD = ocular graft-versus-host-disease; SD = standard deviaiton; TBUT = tear break-up time; VA = visual acuity.
Bold indicates statistical significance.
*Difference >0 indicates improvement.
†Paired *t* test.
‡For the no preexisting fibrosis group, non-parametric test results for corneal staining score.

Ocular Safety

Two individuals, while taking 4 mg of baricitinib daily, were found to have asymptomatic conjunctival papillomas, which were suspected to be caused by human papilloma virus. In one case, a patient with pre-existing scarring developed 2 papillomas in the upper palpebral conjunctiva after 8 months of baricitinib and was subsequently prescribed oral cimetidine 800 mg 3x/day (Fig 3A). The lesions resolved 11.5 months after discontinuing baricitinib. In the second case, a patient developed a small papilloma in the lower palpebral conjunctiva, which was diagnosed 7 months after starting baricitinib (Fig 3B). The lesion resolved 6 months later while the patient continued taking baricitinib without any intervention.

One patient developed *Staphylococcus aureus* conjunctivitis 3 months after starting baricitinib and purulent *Haemophilus influenzae* conjunctivitis 3 months later. Both infections were successfully treated with moxifloxacin 0.3% ophthalmic drops administered 4 times daily for 7 days, resulting in complete resolution. None of these events were considered severe adverse events.

Systemic Safety

The side effect profile of oral baricitinib was well-tolerated compared to other orally available JAKis. In our study, no dose limiting toxicity was observed at either dose level. In all 24 patients on baricitinib, the most common grade ≥2 AE (regardless of attribution to drug) included viral upper respiratory infection (42%), hypophosphatemia (21%), and lung infection (21%). Grade ≥3 AEs occurred in 15 (63%), 7 of which were possibly drug-related (29%). Twelve severe AEs occurred, of which 5 were possibly drug-related, including hospitalizations for upper respiratory infection (2), cellulitis (2), joint infection (1), and pneumonia (1). Three patients (13%) required dose-reductions due to neutropenia (2) or refractory myalgias (1). No relapsed malignancies or deaths occurred on treatment.

Of the enrolled 18 patients with oGVHD, 3 (17%) discontinued treatment before the study end point of 6 months because of pneumonia (n = 1), worsening of cGVHD (n = 1), and detection of an exclusion criterion after the first dose (n = 1). Eleven patients (61%) remained on baricitinib until cycle 12.

Discussion

This study demonstrated a significant improvement in oGVHD NIH grading after 6 months of treatment with baricitinib and highlighted the potential benefit of oral baricitinib therapy in improving symptoms in affected patients. Compared with the baseline, there was a notable improvement in corneal staining scores in individuals without preexisting fibrosis at the study end point of 6 months. Tear

Table 4. Ocular Parameters for Subgroup No Preexisting Fibrosis

Parameter	Time Point	N	Mean	SD	Median	Mean Change[‡], Baseline Minus 6 Mos	*P* Value[§] for Change, Baseline to 6 Mos	Mean Change[‡], Baseline Minus 12 Mos	*P* Value for Change[‖], Baseline to 12 Mos
Oxford corneal staining score[‡]									
	Baseline	11	1.84	1.33	1.5				
	6 mos	8	0.25	0.46	0	1.06	**0.018**		
	12 mos	5	0	0	0			1.15	0.035*
TBUT (s)									
	Baseline	10	6.32	2.89	6.38				
	6 mos	8	8.62	2.01	9.25	1.39	0.301		
	12 mos	4	10.29	3.79	11.32			1.91	0.482[†]
Schirmer 1 (mm)									
	Baseline	7	4.07	5.01	1.5				
	6 mos	4	9.12	4.33	8.75	−0.50	0.878		
	12 mos	4	16.88	9.63	15.25			4.00	0.079
NIH oGVHD score									
	Baseline	11	1.36	0.50	1.00				
	6 mos	10	1.00	0.82	1.00	0.30	0.081		
VA (logMAR)									
	Baseline	11	0.045	0.101	0.050				
	6 mos	9	0.056	0.092	0.100	−0.006	0.834		
	12 mos	5	−0.010	0.055	−0.050			−0.010	0.799

logMAR = logarithmic minimum angle of resolution; NIH = National Institutes of Health; oGVHD = ocular graft-versus-host-disease; SD = standard deviation; TBUT = tear break-up time; VA = visual acuity.
Bold indicates statistical significance.
*$P = 0.125$ if nonparametric test is used.
†$P = 0.50$ if nonparametric test is used.
‡Difference >0 indicates improvement in the corneal staining score.
§Denotes paired *t*-test analysis.
‖For the no preexisting fibrosis group, non-parametric test results for corneal staining score.

break-up time and ST were also increased in this group, but this improvement was not statistically significant. This finding suggests that, in the absence of fibrotic damage to the conjunctiva, the anti-inflammatory properties of the JAKi baricitinib can potentially improve tear film quality and quantity and help maintain the epithelial surface. Conjunctival and lacrimal gland fibrosis are common complications of chronic oGVHD and affect approximately 50% of patients.[18,19] The process of subepithelial fibrosis after allogeneic hematopoietic stem cell transplantation is believed to arise from donor T cell-mediated damage to the conjunctival basal epithelium and lacrimal gland myoepithelium, leading to disruption of the basal lamina and transformation of epithelial cells into mesenchymal phenotypes that produce aberrant collagens, ultimately resulting in scarring.[20] The degree of scar tissue is directly correlated with the extent of the resulting loss-of-function.[21] Additionally, microtrauma resulting from friction during blinking in conjunction with possible secondary inflammation may also contribute to ocular surface staining in patients with subtarsal fibrosis who often have conjunctival goblet cell loss and meibomian gland dysfunction in the presence of tear deficiency.[22-25]

In this study, we observed mild improvement of corneal staining in patients with fibrosis but no improvement in ST. This lack of tear production may suggest a dysfunction in both the accessory and main lacrimal glands due to the existing scarring, preventing them from producing aqueous tears despite the systemic anti-inflammatory therapy with baricitinib. Conversely, the average ST increased in patients who did not exhibit pre-existing conjunctival fibrosis at 6 months and continued to improve in those who continued to take the medication for 12 months (Fig 2). Although this increase was not statistically significant it could be clinically significant as the combination of increased ST and TBUT with a decreased corneal staining indicates a healthier ocular surface. Conversion of ST results from millimeters into microliters were performed to allow for universal interpretation of tear volume changes independent of brand of Schirmer strips used as this can significantly affect the results.[17] Previous studies have shown that ST did not exhibit progressive improvement over time in patients with oGVHD and consequently is not regarded as a therapeutic biomarker in this particular context.[26,27] However, it is important to mention that the presence or absence of conjunctival fibrosis was not documented in these studies. Based on our study, we suggest that the efficacy of therapy for oGVHD and the restoration in function may be contingent upon the degree of pre-existing conjunctival and lacrimal gland fibrosis. This is different from other forms of dry eye disease where fibrosis is not typically present. Therefore, in oGVHD early

Table 5. Ocular Parameters for Subgroup Preexisting Fibrosis

Parameter	Time Point	N	Mean	SD	Median	Mean Change*, Baseline Minus 6 Mos	P Value† for Change, Baseline to 6 Mos	Mean Change*, Baseline Minus 12 Mos	P Value for Change‡, Baseline to 12 Mos
Oxford corneal staining score*									
	Baseline	7	2.68	1.49	3.5				
	6 mos	6	1.88	1.32	2.38	0.58	0.600		
	12 mos	4	2.12	0.85	2.25			−0.25	0.848
TBUT (s)									
	Baseline	6	7.22	3.60	6.75				
	6 mos	6	7.58	6.66	5.5	−1.60	0.276		
	12 mos	3	7.17	3.55	6.5			3.25	0.545
Schirmer 1 (mm)									
	Baseline	7	3.64	3.00	3				
	6 mos	4	2	2.12	1.25	−0.25	0.604		
	12 mos	4	3.5	3.03	3.75			−1.00	0.252
NIH oGVHD score									
	Baseline	7	2.43	0.53	2.00				
	6 mos	7	1.86	0.38	2.00	0.57	0.103		
VA (logMAR)									
	Baseline	7	0.278	0.588	0.050				
	6 mos	6	0.342	0.597	0.075	−0.017	0.611		
	12 mos	4	0.075	0.087	0.050			−0.012	0.854

logMAR = logarithmic minimum angle of resolution; NIH = National Institutes of Health; oGVHD = ocular graft-versus-host-disease; SD = standard deviation; TBUT = tear break-up time; VA = visual acuity.
*Difference >0 indicates improvement.
†Paired *t* test.
‡For the no preexisting fibrosis group, non-parametric test results for corneal staining score.

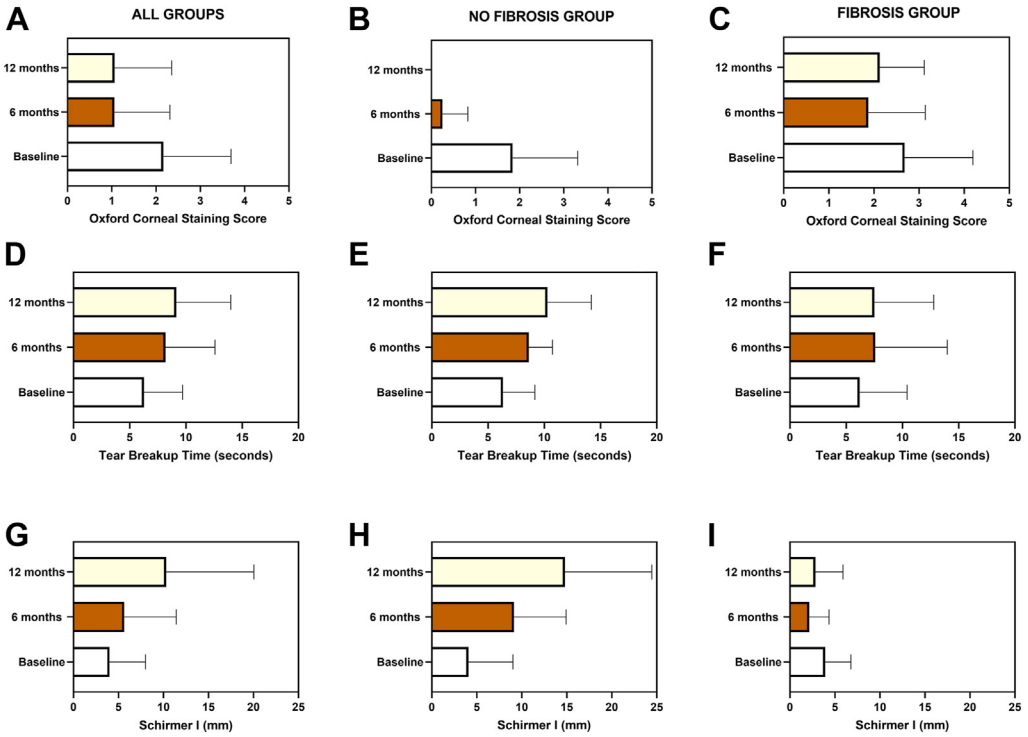

Figure 2. Column graphs of mean and standard deviation values for the ocular surface parameters at baseline, 6 months (study end point), and 12 months for each group. Corneal oxford staining for all patients, no pre-existing fibrosis subgroup, and fibrosis subgroup is shown in **A, B,** and **C,** respectively. **D, E,** and **F** show tear breakup time in the 3 different groups. The figures in the bottom row **(G, H, I)** show the Schirmer I test results in the 3 groups.

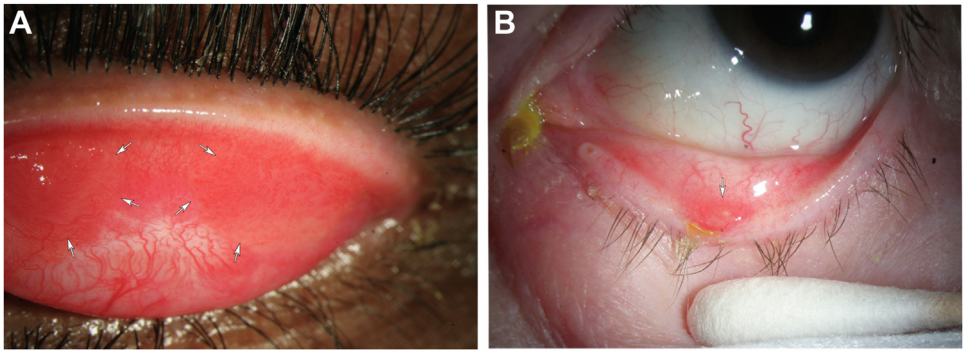

Figure 3. **A** Color photograph of asymptomatic conjunctival papillomas (arrows) observed in 2 patients. One patient developed 2 upper lid papillomas 8 months after starting baricitinib (**A**), and one patient was diagnosed with a lower lid papilloma 7 months after starting medication (**B**).

intervention with topical and systemic immunomodulatory therapies should be considered to prevent inflammatory tissue fibrosis.

Topical immunosuppressive therapy is currently the primary treatment option for oGVHD related dry eye disease. Previously, topical administration of a JAKi 1/3 and a spleen tyrosine kinase inhibitor to patients with oGVHD resulted in a significant improvement in corneal fluorescein staining. However, this improvement in corneal surface staining was not reflected in the ST results, and the study was not designed to investigate the influence of subtarsal fibrosis on the treatment outcomes.[18] Similarly, topical tofacitinib, a JAK 1/3 inhibitor was studied in (non oGVHD) dry eye disease.[28,29] The results showed an improvement in ocular surface index scores, decrease in ocular surface staining, TBUT, and tear inflammatory biomarkers, such as matrix metalloproteinase -9, IL-1b, IL-12p70, IL-15, and IL-17A, with a modest increase in ST.[28,29] These findings suggest that relying on topical JAKi therapy for the treatment of oGVHD or dry eye disease, which typically does not exhibit fibrosis, may not be sufficient to mitigate inflammation and improve tear production. Although topical tofacitinib and the combined JAKi/ spleen tyrosine kinase inhibitor treatments caused only mild side effects such as ocular discomfort without systemic side effects, oral baricitinib therapy had a greater impact on the immune system, and we observed a few systemic and ocular conjunctival infections (*H influenza* conjunctivitis).[18,29] Despite the AEs, 83% of patients with oGVHD were able to complete the study end point evaluation. Close monitoring and a multidisciplinary management approach are essential for patient safety during systemic JAKi therapy, which may effectively control systemic and ocular cGVHD.

The limitations of this study include its open-label single-arm design and a relatively small sample size, which limited the statistical power of analyses. Additionally, the protocol was primarily focused on systemic GVHD and did not include mandatory eye exams after the BL although 83% of patients had an eye examination at the study end point at 6 months. Also, NIH oGVHD scores beyond the 6-month primary efficacy end point or assessments of conjunctival redness were not included in the data collection. Finally, the study was conducted during the severe acute respiratory syndrome coronavirus 2 pandemic, further limiting visits and assessments. Nevertheless, this report provides initial findings on the use of baricitinib in treating oGVHD. Results indicate that systemic therapy with baricitinib was effective in improving NIH oGVHD scores, reducing ocular surface inflammation, as evidenced by decreased staining, improved TBUT, and increased tear volume. The most significant effects were observed in patients who did not have pre-existing conjunctival fibrosis, highlighting the importance of assessing its presence prior to enrolling patients in interventional trials, as the extent of fibrosis may affect outcomes. Future studies are necessary to fully assess the potential benefits of baricitinib and other JAKi in the treatment of oGVHD.

Footnotes and Disclosures

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Abbreviations and Acronyms:

AE = adverse event; **cGVHD** = chronic graft-versus-host disease; **COS** = corneal Oxford staining; **GVHD** = graft-versus-host-disease; **IL** = interleukin; **JAK** = Janus kinase; **JAKi** = Janus kinase inhibitor; **NIH** = National Institutes of Health; **oGVHD** = ocular graft-versus-host-disease; **OSD** = ocular surface disease; **SD** = standard deviation; **ST** = Schirmer I Test; **TBUT** = tear break-up time.

Keywords:

Baricitinib, Conjunctival fibrosis, Ocular graft versus host disease, Ocular surface, Volume calibration of Schirmer strip.

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