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Effect of Ruxolitinib on lung function after allogeneic stem cell transplantation

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Abstract

Ruxolitinib, a selective Janus kinase (JAK)1/2 inhibitor, has recently been proposed for steroid refractory chronic graft-versus host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation (HSCT), particularly in severe skin cGVHD. Lung function impairment is common in severe skin cGVHD through concomitant bronchiolitis obliterans syndrome (BOS) or restrictive lung disease (RLD) from skin sclerosis. No treatment to date has shown benefit on lung function in this context. We retrospectively assessed the effect of ruxolitinib on lung function in a cohort of patients treated for sclerotic-type skin cGVHD. Between March 2015 and April 2018, 70 patients were diagnosed with sclerotic-type skin cGVHD. Amongst those, 36 received ruxolitinib. To handle confounding by indication bias, exposure groups were matched on the propensity score to receive ruxolitinib incorporating age, myeloablative conditioning, total body irradiation, bronchiolitis obliterans (BOS), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and tobacco at the time of cohort entry, as well as the time from transplantation. Matching 1:1 used a greedy-matching algorithm with replacement, using a caliper of 0.10. We compared both FVC and FEV1 trajectories during the follow-up on the matched samples, using linear mixed effects models. Median follow-up of the 46 matched patients was 58 months (IQR, 32 to 84). Ten patients had a RLD (6 exposed; 4 unexposed) while 13 patients were diagnosed with BOS (8 exposed, 5 unexposed). FEV1 significantly decreased over time independently of exposure to ruxolitinib ($p < 0.0001$). FEV1 trajectory was similar in exposed and unexposed patients ($p = 0.11$). In conclusion, ruxolitinib administration did not demonstrate any improvement in the course of respiratory function in allogeneic HSCT recipients with sclerotic-type skin cGVHD.

Word count: 267

Key words: bronchiolitis obliterans; sclerodermatous chronic graft versus host disease; sclerotic type skin cGVHD; pulmonary graft versus host disease; restrictive lung disease

Introduction

Despite major improvements in allogeneic hematopoietic stem cell transplantation (HSCT) over the past decades, graft-versus-host disease (GVHD) remains a frequent complication associated with both high morbidity and mortality ¹. First-line treatment of GVHD relies on steroids with reported response rates ranging from 50 to 70% ². In case of steroid-refractory cGVHD, several second-line treatments have been studied, such as extracorporeal photopheresis (ECP), mycophenolate mofetil, rituximab, sirolimus, IL2 mimetics or imatinib ³. To date, no consensus has been reached regarding the optimal choice between those agents.

Ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor, currently approved for the treatment of myeloproliferative neoplasms, was found to be associated with suppression of proinflammatory signaling that mediates tissue damage in acute GVHD and promotion of tolerogenic Treg cells ⁴. Based on the results of an open-label, single-arm, multicenter study of ruxolitinib that enrolled patients with steroid-refractory acute GVHD ⁵ ruxolitinib was recently approved by the Food and Drug Administration (FDA) for the treatment of corticosteroid-refractory acute GVHD⁶. The efficacy of ruxolitinib in glucocorticoid-refractory acute GVHD was further confirmed⁷. Data suggest that ruxolitinib may also be an effective drug for corticosteroid-refractory chronic GVHD (cGVHD) ^{5,8-11}. Among these data, we previously found that ruxolitinib was effective in severe skin sclerotic-type cGVHD ¹². Otherwise, recent observational retrospective studies suggest a moderate effect for ruxolitinib on lung GVHD, while no specific data on the pulmonary function trajectory were available^{11,13}.

Pulmonary function is frequently impaired in the course of severe skin sclerotic type cGVH. Alteration of the pulmonary function can present as airflow obstruction from concomitant bronchiolitis obliterans syndrome (BOS, recognized as lung cGVHD)¹⁴ or/and as restrictive lung disease (i.e. decreased lung volumes) ¹⁵(RLD) from lung parenchymal abnormalities, pleural effusion, diaphragmatic dysfunction or/and skin sclerosis limiting chest expansion ^{16,17}. Monitoring forced expiratory volume in one second (FEV1) and vital capacity (VC) after allogeneic HSCT, especially in the setting of cGVHD, allows the detection of pulmonary involvement and the assessment of its severity¹⁸.

Most studies have evaluated the effect of ruxolitinib on overall GVHD but few have focused on its effect in the lung. Zeiser et al. found that ruxolitinib improved lung GVHD in a mouse model ⁸. In

humans, case series have shown a positive effect of ruxolitinib on FEV1 trajectory in children with BOS¹⁹. Some data suggests that ruxolitinib could also act as a steroid sparing agent in adults with BOS^{11,13,20}.

Because lung function impairment, whatever the cause, is associated with both morbidity and mortality after HSCT²¹, we focused on a specific relevant population of patients with high incidence of lung function impairment during their follow-up, i.e. those with severe skin GVHD. The aim of the present study was to address a pragmatic question about the effect of ruxolitinib on pulmonary function trajectory in patients who were treated with ruxolitinib for extensive skin sclerotic-type steroid-refractory cGVHD compared to unexposed patients.

Patients and Methods

Study population

We conducted a retrospective single center study from March 2015 to April 2018. All consecutive HSCT recipients who were diagnosed with an extensive skin sclerotic-type (grade 3) steroid-refractory cGVHD at Saint-Louis hospital (Paris, France) with a modified Rodnan skin score ≥ 10 were included. Diagnosis and severity of skin cGVHD were based on clinical assessment by dermatologists in our center using the NIH 2014 criteria¹⁴. Extensive skin cGVHD was defined as sclerotic features extending to more than 50% of the body surface area.

Patients were then categorized based on their exposition to ruxolitinib (“exposed” vs “unexposed”). Ruxolitinib was initiated at a dose of 5, 10 or 15 mg twice daily based on the physician’s discretion. To avoid introducing an immortality bias, given death shortly after diagnosis of sclerotic-type skin cGVHD would be considered “unexposed”, we began enrollment from the time of the first prescription for exposed patients. For unexposed patients, follow-up was defined from a randomly selected time from the set of prescription times of the exposed patients (so-called the “index date”). This method has been shown to avoid the imbalance of the prescription time distribution between the two groups, and thus controlling for survival bias²².

Pulmonary function test analysis

In our center, pulmonary function tests (PFT) are systematically performed before HSCT, at day 100, 6, 12, 18 and 24 months after HSCT. In patients who developed sclerotic-type GVHD, PFT were performed each 6 months. BOS was diagnosed as previously defined with either an FEV₁ <75% of predicted and decline ≥10% of FEV₁ from the pre-transplant value; and either FEV₁/vital capacity (VC) <0.7 or a concomitant decrease in both FEV₁ and forced VC (FVC) <80% of predicted, with a total lung capacity (TLC) >80% of predicted^{14,15,23–25}. RLD was defined as a TLC <80% of predicted¹⁸. Of note, FEV₁ is often impaired in both obstructive and restrictive patterns. VC is systematically decreased in RLD and it is occasionally impaired in BOS.

Outcomes and measurements

Primary outcome was the evolution of FEV₁ from the index date. Secondary outcome was that of FVC. Demographic and clinical data were collected at baseline. PFT were collected at the time of skin cGVHD diagnosis, and in the follow-up period. PFT data included FEV₁ (ml), FVC (ml), FEV₁/FVC ratio (%), and predictive values were determined as previously described²⁶. Other treatments received for cGVHD were also collected. The evolution of skin sclerosis following ruxolitinib initiation was evaluated by dermatologists (C.H and J.D. B).

Data analyses

Categorical and ordinal variables were presented as frequencies, and continuous variables were presented as mean ± SD or median [interquartile range, IQR].

Owing to the nonrandom assignment of ruxolitinib, propensity score matching was used to reduce confounding by indication bias, based on the following steps. Details are reported in the Supplementary materials.

First, a multivariate logistic regression model was fitted to estimate the propensity score (PS) for the use of ruxolitinib, including prognostic covariates measured before or at the index time, namely age, myeloablative conditioning, FEV₁, FVC, Tobacco, index time, BOS and total body irradiation (TBI). Given missing data in covariates, multiple imputation were first performed, with propensity score defined as the average PS across 30 imputed datasets²⁷.

Secondly, propensity score matching was performed, where exposed patients were individually matched to unexposed patients on the pooled score, allowing replacement and using a caliper of 0.10²⁸.

Third, pre- and post-matching standardized mean differences (SMD), c-statistic and overlapping coefficient (OVL), were computed as balance metrics to check the reduction in imbalances on potential confounders²⁹.

Last, once balance was achieved, both FVC and FEV1 trajectories across exposed groups in the matched sample were compared using generalized linear mixed effects models.

Two sensitivity analyses were performed. The first analysis further adjusted the estimated treatment effect on residual imbalances (if any). The second sensitivity analysis avoided replacement of controls in matching on PS.

All statistical analyses were conducted using R (R Project for Statistical Computing). Propensity score matching procedures were conducted using the Matching package. Two-tailed $P < .05$ was considered statistically significant.

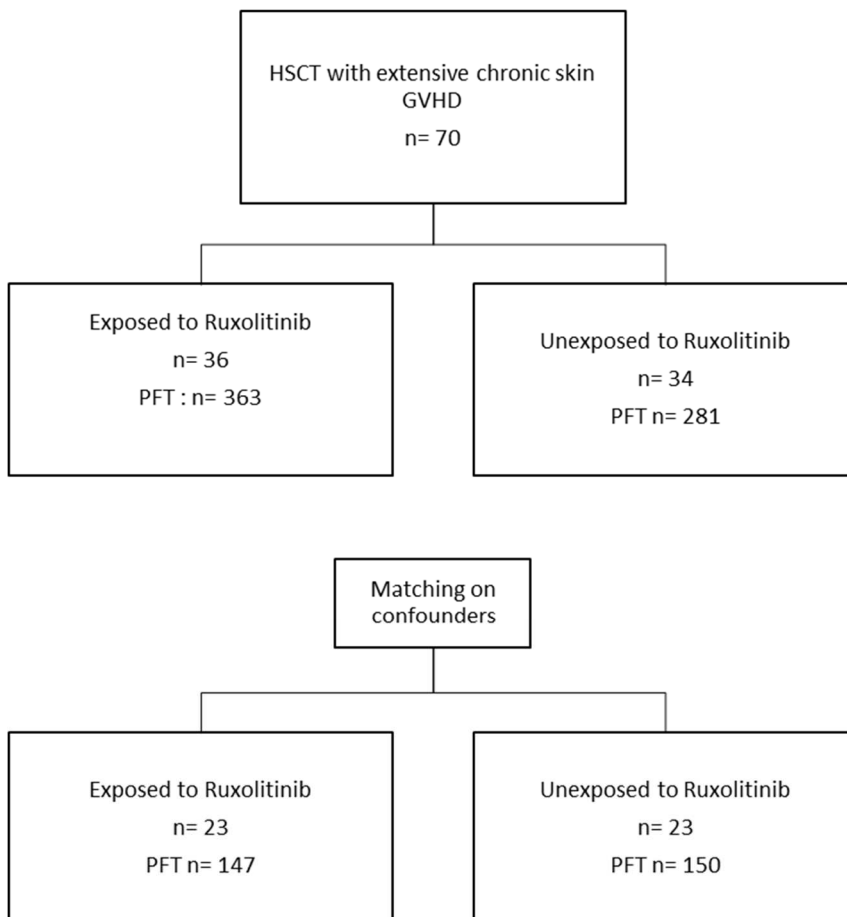
This retrospective cohort study was approved by the Institutional Review Board of the French Learned society for respiratory medicine (CEPRO 2018-022).

Results

Patients and GVHD Characteristics

A total of 70 HSCT patients, median age 45 years [IQR, 33 to 52], who developed an extensive sclerotic-type skin cGVHD from March, 2015 to April, 2018, were consecutively enrolled in the study (**Figure 1**).

Figure 1: Flow chart



Following cGVHD diagnosis, 36 (51%) patients received ruxolitinib after a median time of 35.2 months [IQR, 18.3 to 58.9], and 34 (49%) patients were unexposed to ruxolitinib. The median number of previous lines of cGVHD treatments before the index date was 3 [IQR, 2 to 3] in both groups, including corticosteroids for all patients in both groups, extracorporeal photopheresis (n=20 (55.6%) in patients who received ruxolitinib and n=16 (47%) in those who were unexposed, p=0.63), mycophenolate mofetil (n=21 (58%) in patients who received ruxolitinib and n=11 (32%) in those who were unexposed, p=0.034), cyclosporine (n=2 (5.6%) in patients who received ruxolitinib and n=1 (3%) in those who were unexposed, p=1.00), methotrexate (n=8 (22.2%) in patients who received ruxolitinib and n=7 (20.6%) in those who were unexposed, p=1.00), rituximab (n=1 (2.8%) in patients who received ruxolitinib and n=1 (2.9%) in those who were unexposed, p=1.00), tyrosine kinase inhibitors (n=7 (19.4%) in patients who received ruxolitinib and n=6 (17.7%) in those who were unexposed, p=1.00) and IL2 (n=3 (8.8%) in patients who received ruxolitinib and n=3 (8.8%) in those who were unexposed, p=1.00). Dosing of ruxolitinib was 15 mg twice daily (BID) for 2 patients, 10 mg BID for 7 patients and 5 mg BID for 14 patients

Median follow-up after the index time was 58 months [IQR, 32 to 84], with no difference in exposed (median 49 months [IQR, 29 to 87]) and unexposed patients (median 59 months, [IQR, 46 to 76]) (p=0.43). A total of 181 PFTs were performed after the index date, including 109 in exposed and 72 in unexposed patients.

Table 1 reports the patient characteristics among the two groups of patients. Patients who received ruxolitinib were older, received less frequently total body irradiation, myeloablative conditioning, and were more likely to have a history of acute GVHD; they had lower FEV1 and FVC. Eighteen patients were diagnosed with BOS, including 10 patients who received ruxolitinib after a median time from BOS diagnosis of 11 [IQR, 5 to 27] months, ranging from 1 to 46 months, and 8 unexposed patients. Eleven patients were diagnosed with RLD; they were treated with ruxolitinib at a median time of 21 months after RLD [IQR, 11.1 to 44.3], ranging from 6.7 months before RLD to 89 months after RLD. Median dose for steroids at the time of ruxolitinib initiation was 15 mg/d [IQR, 7 to 21]. Amongst the 36 exposed patients, 23 (64%) could be matched with 23 unexposed patients on the estimated propensity score, with improved balances in confounders (Table 1; Supplementary Fig S1).

Table 1: Comparison of pre-treatment characteristics across exposed groups, before and after matching. Standardized mean differences (SMD) are used as balance metrics across exposure groups

	Original Sample			Matched sample		
	Unexposed (n=34)	Exposed (n=36)	SMD*	Unexposed (n=23)	Exposed (n=23)	SMD*
Male	18 (53%)	19 (53%)	0.003	7 (30%)	10 (43%)	0.27
Age at HSCT	41.3 ±13.3	46.4 ± 11.6	0.40	45.6 ±12.1	47.1 ±11.9	0.12
Active smoker	11 (32%)	15 (42%)	0.19	6 (26%)	7 (30%)	0.09
Hematologic disease						
Lymphoid malignancy	9	7		3	6	
Acute leukemia	15	15		9	10	
Myelodysplastic syndrome	2	4		1	0	
Myeloproliferative	3	8		6	4	
Others	5	2		4	3	
Myeloablative conditioning	16 (48%)	9 (26%)	0.46	6 (26%)	5 (24%)	0.05
Total Body irradiation	22 (67%)	8 (24%)	0.96	7 (30%)	7 (33%)	0.06
GVHD prophylaxis						
CSA/MMF	18 (54%)	24 (71%)	0.34	18 (78%)	16 (73%)	0.13
CSA/MTX	15 (45%)	10 (29%)		5 (22%)	6 (27%)	
After allograft						
Acute GVHD grade ≥ 2	23 (70%)	25 (76%)	0.135	17 (74%)	16 (76%)	0.05
Lines of treatment before index, median, IQR	2.4 ± 1.2	2.6 ± 1.4	0.20	2.4 ± 0.8	2.6 ± 1.5	0.17
BOS diagnosis	8 (24%)	10 (29%)	0.11	8 (35%)	5 (23%)	0.26
RLD diagnosis	8 (24%)	11 (30.5%)#	0.25	4 (17%)	6 (26%)	0.21
Baseline PFTs						
FEV1, % Predicted	77 ± 27	67 ± 26	0.38	70 ± 37	73 ± 26	0.08
FVC, % Predicted	81 ± 26	71 ± 25	0.37	76 ± 31	77 ± 24	0.03

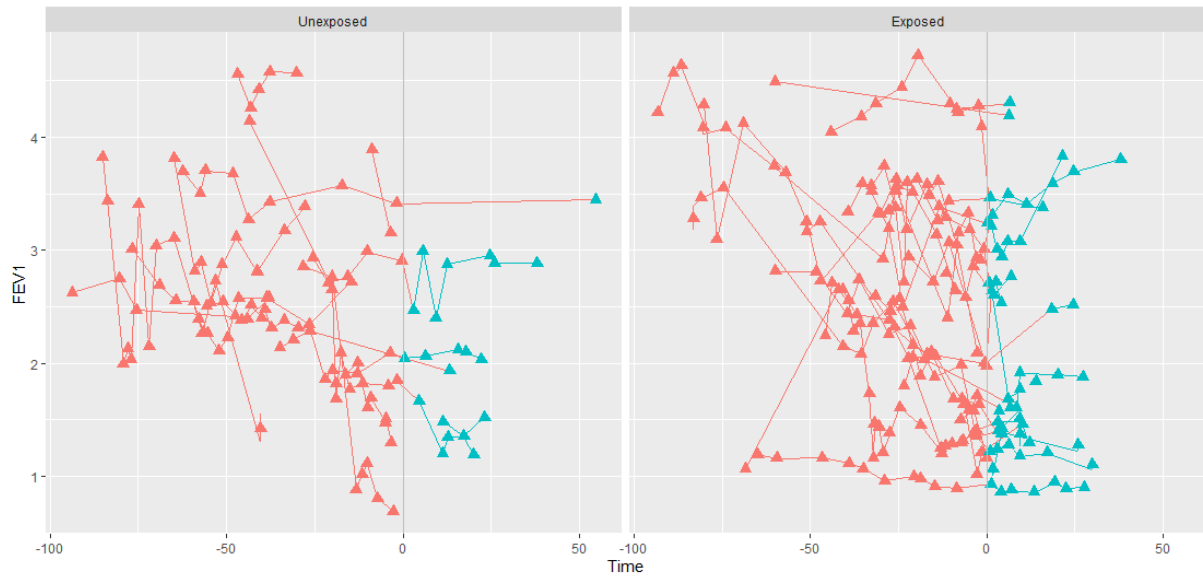
SMD, standardized mean difference; HSCT, hematopoietic stem cell transplantation; GVHD, graft versus host disease; IQR, Interquartile range; BOS bronchiolitis obliterans syndrome; RLD: Restrictive lung disease; CSA, cyclosporine; MMF mycophenolate mofetil; MTX, methotrexate; PFT, pulmonary function test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity

*SMD, standardized mean difference, is a measure of difference on each variable between groups, expressed in terms of difference in means relative to the variability observed in the sample. # Including two patients with parenchymal abnormalities (one with pleuroparenchymal fibroelastosis and one with organizing pneumonia)

Effect of Ruxolitinib on PFTs

Based on the matched sample, 147 PFTs were available in the 23 exposed patients, and 150 in the 23 matched unexposed patients, with 70 and 40 measurements after the index date, respectively. The median number of PFTs per patient was 7.5 [IQR, 6 to 12], ranging from 1 to 22, with a median time frame of 13 months post Index/ruxolitinib initiation (IQR, 1 to 35), ranging from 25 months before exposure/index up to 106 months after. **Figure 2** displays the time course of FEV1 in both exposed and unexposed patients. Since pretransplant PFT measurement, FEV1 significantly decreased over time whether or not the patients were exposed to ruxolitinib ($p < 0.0001$). The decline in FEV1 was less pronounced after the index date ($p < 0.0001$). However, the FEV1 trajectory was similar in exposed and unexposed patients, so as the interaction of exposure with time elapsed since the index date ($p = 0.11$).

Figure 2: Spaghetti Plot of the FEV1 trajectory over time in the 23 matched patients unexposed (left plot) or exposed (right plot) to ruxolitinib.



Time is measured in months from the index date. Red points indicate measurements before the index date while blue points indicate measurements after the index date.

Similar results were found for FVC trajectory. Indeed, no evidence of any effect of ruxolitinib exposure was observed on the time course of FVC ($p= 0.47$) (**Figure3**).

Figure 3: Spaghetti Plot of the FVC trajectory over time in the 23 matched patients unexposed (left plot) or exposed (right plot) to ruxolitinib.



Time is measured in months from the index date. Red points indicate measurements before the index date while blue points indicate measurements after the index date.

Sensitivity Analyses. Further adjustment on BOS diagnosis did not modify these findings, although it exhibited an effect of BOS on the FEV1 trajectory ($p < 0.0001$; Supplementary Figure 2). In fact, FEV1 declined more importantly in patients with BOS compared to other patients. Based on matching with no replacement, only 17 exposed patients could be matched. Balance was checked with c-index at 0.50 and the overlapping coefficient (OVL) at 0.98. Results regarding the decreased shape of FEV1 and FVC over time, were still not affected by the exposure to Ruxolitinib ($p = 0.24$ and $p = 0.19$, respectively).

Discussion

This retrospective study is the largest series to date of HSCT recipients with cGVHD treated with ruxolitinib for whom respiratory function was assessed compared to match unexposed patients over a long period of time. In these patients treated for severe sclerotic-type skin cGVHD, no effect of ruxolitinib on the course of respiratory function was observed. Until now, only two case series have evaluated the effects of ruxolitinib on respiratory function in patients with BOS; one in 5 children¹⁹ and the other in 6 adult patients²⁰. Both studies concluded on a steroid sparing effect of ruxolitinib, although its effect on pulmonary function varied. Most patients had multi-organ cGVHD and the decision to decrease steroids was based on overall cGVHD, rather than BOS alone, at the discretion of the treating physician. That said, no studies have demonstrated the efficacy of steroids on BOS in adult allogeneic HSCT recipients. In fact, we previously reported a deleterious effect of systemic corticosteroids on survival in patients with BOS²³. Thus, steroid sparing effect is relative to its overall effect on cGVHD burden and cannot be based on respiratory function alone. Most of the 11 patients studied for ruxolitinib efficacy had BOS refractory to several previous lines of immunosuppressive treatment^{19,20}. In the adult series, the pooled FEV1 values for the 6 patients did not significantly change over time after ruxolitinib initiation. However, FEV1 trajectory from BOS diagnosis was not compared pre and post ruxolitinib initiation²⁰. In the children study, the two patients who had ruxolitinib initiated later following BOS diagnosis (15 and 28 months post), both following a sudden decline in FEV1, saw their lung function improve significantly. On the other hand, two children who had earlier initiation of ruxolitinib following BOS diagnosis had stable FEV1 without drastic change over time.

A phase III randomized open-label multi-center study (REACH3) of ruxolitinib versus best available therapy in patients with corticosteroid-refractory cGVHD is currently ongoing (NCT03112603). However, the endpoints of this study are based on the overall response of GVHD and not on the specific effects on each organ. The recent retrospective observational studies evaluating the efficacy of ruxolitinib in patients with chronic GVHD, provided data on each organ, including lung GVHD, but they do not provide lung function parameters trajectory^{11,13}. A phase II open label non-randomized study of ruxolitinib for new-diagnosed BOS after allogeneic HSCT has also recently started with an expected study completion date of 2023 (NCT03674047).

Although the natural history of BOS is poorly understood, there is evidence to suggest that the decline in FEV1 is initially abrupt with subsequent stabilization regardless of treatment, making it difficult to

assess the effect of treatment on lung function without a control group^{30,31}. This trajectory of lung function makes early diagnosis of BOS challenging as one could postulate that the effect of immunosuppressive therapy is better in the early inflammatory phase of BOS than in the late fibrotic phase¹⁷. Lastly, given the various events that can affect breathing (such as intercurrent infection or fatigue), the evolution of lung function over time is key. Hence, multiple values must be taken into account to draw any conclusions.

In our study, we focused on a specific population of patients with sclerotic-type skin cGVHD whose PFT are frequently impaired both because of associated BOS or restrictive lung defect secondary to skin involvement. We found a significant impairment in lung function over time for all patients regardless of the treatment received. Due to the small number of patients with BOS (i.e., 8 and 10 patients in each group) we could not draw any conclusion on the effect of ruxolitinib in BOS. However, adjustment for BOS did not modify our results.

Although the true effect of a drug can only be asserted on the basis of a randomized placebo-controlled study, which is difficult to conduct in the context of GVHD, our study provides a methodology with a higher level of evidence than prior reported case series on the topic. Indeed, by accounting for the covariates that predict receiving the treatment, propensity-score matching attempts to reduce the bias due to confounding variables that could be found in an estimate of the treatment effect obtained from simply comparing outcomes among patients who received the treatment versus those who did not³². Moreover, we used an approach that was shown to control for survival bias associated with time-to-treatment initiation²².

Our study has several limitations. Although it is the largest available study, it was a single-center study and the number of patients remains relatively low. It is a retrospective cohort study, and one may not exclude some biases. However, we used medical and administrative data files to ensure the selection of consecutive patients with cGVHD. Propensity score matching was used, that resulted in smaller matched samples, could be questionable in small samples; nevertheless, we carefully selected the confounders and assessed the balance in matched treatment groups, then performed sensitivity analyses to assess the robustness of our estimates, as recommended in this setting³³. Otherwise, the outcomes were based on PFT measurements which exclude information bias. Last, ruxolitinib was

used late after the diagnosis of cGVHD. Hence, we cannot predict the effect of ruxolitinib if used earlier after diagnosis.

In conclusion, our study did not find a significant effect of ruxolitinib on the FEV1 and FVC of patients with sclerotic-type skin cGVHD. Further studies are required to establish the true effect of ruxolitinib on lung function in patients with cGVHD.

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