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Characterization of Spirometric Response to Standard-of-care Treatment in Lung Allograft Recipients With Bronchiolitis Obliterans and the Utility of Spirometric Criteria for Rescue Therapy: Implications for the Design of Risk-stratified Clinical Trials

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Background. The spirometric response to standard-of-care (SOC) immunosuppressive therapy for the management of bronchiolitis obliterans syndrome (BOS) has been sparsely reported in the literature. Data from a Medicare-approved Registry were analyzed to characterize the effectiveness/durability of a wide range of SOC interventions to manage the decline of lung function and to validate the study spirometric criteria for initiation of rescue therapy. **Methods.** Lung transplant recipients with refractory BOS at 21 US collaborating centers were enrolled in the Registry. Data included both nonspirometric (eg, demographic, Immunosuppressive Regimens for management of BOS) and spirometric parameters (ie, forced expiratory volume in 1 s [FEV₁] measurements and derived indices). The utility of study FEV₁ criteria for treatment (ie, statistically significant rate of FEV₁ decline >30 mL/mo) was evaluated by comparing the spirometric course between participants who met or did not meet this criterion. **Results.** Only 21% of participants treated with SOC therapy had >50% decrease (76 ± 25% decrease) in the rate of FEV₁ decline. Although 51% of participants had a partial response (rate of FEV₁ decline decreased on average 71%), 49% of participants had a substantial increase (mean increase 224%). The FEV₁ criterion for treatment was able to identify 19% of participants (48/258) who achieved durable stabilization (ie, nonsignificant rate of FEV₁ <30 mL/mo) with SOC therapy. **Conclusions.** Patients with BOS have a widely variable response to SOC therapy. Our findings support the use of FEV₁ rate of decline to assess response to SOC therapy and to ensure appropriate assignment of participants with refractory BOS to rescue therapy treatment cohorts.

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INTRODUCTION

Chronic lung allograft dysfunction represents the leading cause of morbidity and mortality in recipients of lung allografts beyond the first year,¹ with an annual incidence of 7%–8% in the first 10 y after transplantation,² despite routine usage of multiagent immunosuppressive regimens. The obstructive form of chronic lung allograft dysfunction, bronchiolitis obliterans syndrome (BOS), results in an obstructive ventilatory defect due to an irreversible fibroproliferative immune-mediated process, which results in progressive narrowing of bronchial lumens.³ Although early studies reported a mortality rate of 51%–54% within 3 y after BOS diagnosis,^{4,5} a more recent analysis involving more than several thousand patients outlined median survival of 2.6–3.1 y versus 3.1–4.3 y for single versus bilateral lung transplant recipients, respectively.⁶

Although several single-center retrospective analyses have described the course of the rate of decline of lung function in this population with BOS treated with extracorporeal photopheresis (ECP),^{7–9} prospective data on spirometric outcomes remain sparse. After approval from US Centers for Medicare and Medicaid (CMS) in 2014,¹⁰ we launched a prospective, multicenter Registry (ie, hereafter referred to as Registry) under the auspices of Medicare's Coverage and Evidence Development program. The Registry component of this CMS-approved study achieved its target enrollment of 258 participants in April 2022.¹¹ The main focus of the Registry was to document the spirometric

outcomes of patients treated with ECP, which will be submitted subsequently as a separate article for peer review.

Randomized controlled trials (RCTs) are the established gold standard for validation of effective therapeutic interventions, but the feasibility of such studies in lung transplant recipients with BOS is challenging. Medicare subsequently approved expansion of the study to include an RCT component based on the lack of a standard-of-care (SOC) comparator for the Registry and our early findings.¹²

Therefore, our study team is considering the following 2 initiatives: (1) generation of a SOC comparator for the Registry via retrospective collection of data from our 21 enrolling sites and/or (2) reinitiation of a revised RCT that is restructured to enhance feasibility with a robust spirometric biomarker of survival. Both of these approaches should conclusively confirm that the previous observations of a change in rate of FEV₁ decline after ECP were in fact due to the effect of ECP rather than to other factors.

Hypothesis generation and study design for randomized and nonrandomized comparative studies would benefit from robust characterization of the natural history of patients who receive SOC immunosuppressive therapy to manage BOS. Accordingly, there is a paucity of published data that characterizes the response to a diverse array of SOC immunosuppressive regimens that are used to manage BOS and that formally validate the use of specific Spirometric Criteria for treatment of BOS refractory to SOC agents. Spirometric

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Criteria for treatment of refractory BOS (ie, a statistically significant rate of FEV₁ decline that exceeds 30 mL/mo) within the Registry were based on a previous analysis¹³ to facilitate achievement of major advantages cited by the Food and Drug Administration¹⁴: (1) increased study efficiency and (2) an enhanced benefit-risk relationship for the patients compared with overall population.

Although a preliminary analysis supported the use of these criteria,¹² this analysis was limited to data from 44 enrolled participants.

To address these issues, this analysis was initiated to assess the suitability of our published Spirometric Criteria to (1) augment the clinical definition of BOS refractory to SOC therapy using the entire data set ($n = 258$) and (2) also describe the observed outcomes of SOC therapy in a subset of enrolled patients with refractory BOS by comparing spirometric data before and after initiation of SOC therapy, with the goal of aiding researchers in developing comparative studies of new therapies for BOS.

MATERIALS AND METHODS

Registry

This CMS-approved, multicenter Registry involved enrollment of Medicare-covered lung allograft recipients from April 2015 to April 2022 who were eligible to be treated with ECP if BOS was refractory to conventional SOC therapy based on the study Spirometric Criteria.¹¹ This study protocol (NCT 02181257) was initially approved by the Washington University Human Research Protection Office and subsequently by all local institutional review boards at each of 21 enrolling centers. Informed consent was obtained from all participants.

Diagnosis of BOS and Refractory BOS

Participants enrolled in this study received prophylactic standard immunosuppressive therapy as dictated by local practices at enrolling institutions. Pulmonary function was monitored by serial spirometry after lung transplant in accordance with guidelines issued by the American Thoracic Society.¹⁵ BOS diagnoses were rendered using clinical criteria predicated on FEV₁ values (ie, >20% reduction from baseline, posttransplant values) as defined by the International Society for Heart and Lung Transplantation.¹⁶

Clinicians at enrolling sites had full discretion to manage BOS with any currently available therapy and/or to augment or change the current immunosuppressive regimen (ie, discontinue any current agents or either add or replace with alternative agents) after diagnosis of BOS under their local practice. Refractory BOS was defined as a progressive decline in FEV₁ unresponsive to all local interventions as determined by the enrolling investigator.

Study enrollees, who were followed clinically and with spirometry, were eligible to be treated with ECP if BOS was refractory to SOC therapy predicated on previously defined^{12,13} study FEV₁ Spirometric Criteria (ie, hereafter referred to as FEV₁ criteria) specifically defined as a statistically significant ($P < 0.05$) FEV₁ rate of decline >30 mL/mo over a period of 6 to 9 mo prior to enrollment.¹¹

The data in this report include spirometry data (1) for patients who did not receive ECP therapy and (2) for

patients who were subsequently treated with ECP therapy (ie based on attainment of the defined FEV₁ criteria); however, only FEV₁ values obtained during the preceding period of time when they were only receiving SOC therapy were used.

Registry Study Design

Assessment of FEV₁ Criteria for Treatment of Refractory BOS

To evaluate the utility of the FEV₁ criteria for treatment of refractory BOS with ECP, cohorts were generated on the basis of whether the FEV₁ criteria cutoff (>30 mL/mo, $P < 0.05$) was met either at enrollment (AE) or post-enrollment (PE) and these FEV₁ criteria cohorts were compared using the following analytic approaches.

Assessment of the Spirometric Course After SOC Therapy

Enrolled participants were included on the basis of sequential application of the following criteria (this approach was used to facilitate the availability of an adequate number of FEV₁ to be obtained after BOS diagnosis, at least 4, and to provide a more accurate assessment of the impact of SOC therapy within the 9-mo period based on a multivariate analysis which revealed that response to SOC was not influenced by the time interval from BOS diagnosis to first ECP when it was limited to <9 mo):

1. Limiting the interval between BOS diagnosis and enrollment to <9 mo.
2. Limiting the interval of the last measured FEV₁ to within 2 d after the first ECP treatment. To prevent a potential confounding effect of ECP treatment, the time period between the last FEV₁ value and first ECP treatment was limited to within 2 d after the first ECP treatment (only 2 participants had FEV₁ values after the first ECP treatment: at day 1 and day 2 after ECP).

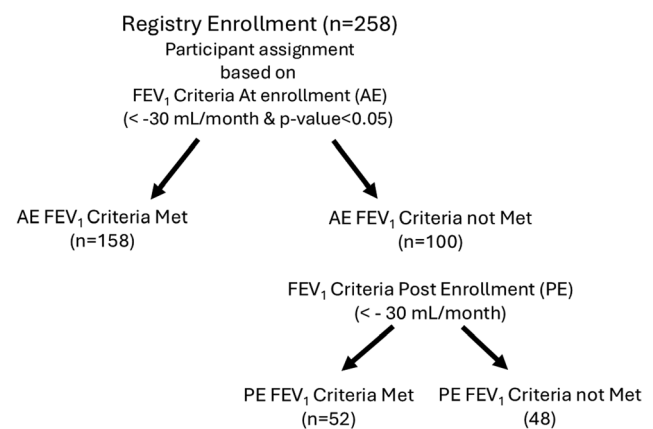


FIGURE 1. Enrollment into the Registry. At enrollment, participants were segregated on the basis of FEV₁ criteria (ie, <-30 mL/mo, $P < 0.05$). Participants were then segregated on the basis of meeting (AE FEV₁ criteria met) vs not meeting (AE FEV₁ criteria not met) FEV₁ criteria AE. Similarly, participants who initially did not meet AE FEV₁ criteria were segregated on the basis of either meeting (PE FEV₁ criteria met) vs not meeting FEV₁ criteria PE (PE FEV₁ criteria not met). AE, at enrollment; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment.

3. To permit precise estimation of the rate of FEV₁ decline, at least 4 FEV₁ values 6 mo before and after the diagnosis of BOS were required.

Data Included in the Analyses

Nonspirometric Data

- 1. Demographic: age and sex
- 2. Pretransplant primary pulmonary diagnosis
- 3. Operative procedural factors: single versus double lung transplant and heart-lung transplant
- 4. BOS stage AE
- 5. Immunosuppressive treatment regimen(s) used for maintenance and/or for active management of BOS
- 6. Enrolling site as a separate covariate

Spirometric Data

FEV₁ data used for analysis were recorded at the following time periods predicated on the availability of measurements: at baseline (as defined by ISHLT guidelines), at BOS diagnosis, before enrollment and AE, and after BOS diagnosis up to 2 d after the first ECP treatment.

Spirometric Indices

Indices were generated using FEV₁ values as follows: percentage of baseline FEV₁ values, difference in FEV₁ values,

difference in percentage of baseline FEV₁ values, and FEV₁ rate of decline (FEV₁ versus time slopes using linear regression) were calculated at the following time periods:

- 1. At BOS diagnosis: with at least 4 FEV₁ values obtained 6 mo before BOS, inclusive of values used for BOS diagnosis.
- 2. AE: with at least 5 FEV₁ values obtained from up to 9 mo before enrollment.
- 3. After BOS diagnosis: with at least 5 FEV₁ values obtained between BOS diagnosis and the first ECP treatment (ie, with the last FEV₁ within 2 d of the first ECP treatment).

Characterization of the Effect of SOC Therapy After BOS Diagnosis With Regression-derived FEV₁ Versus Time Slopes

Quantification of the Impact of SOC Therapy

The impact of SOC therapy on the spirometric progression of BOS was quantified using the change in regression slope (FEV₁ versus time) trajectory between the before (pre) and after (post) BOS periods using the following 2 mathematical conventions:

- 1. Slope difference values: the difference in slope values (ie, FEV₁ versus time) obtained after (post-BOS) BOS diagnosis, for example, up to 2 d after the first ECP treatment, and FEV₁ slope values obtained before (pre-BOS) BOS diagnosis (slope_{post-BOS} – slope_{pre-BOS}).

TABLE 1. Demographics, indications for transplant, type of transplant, and BOS staging AE

	All participants (N = 255/258)	FEV ₁ criteria met AE/PE (N = 210)	FEV ₁ criteria not met AE/PE (N = 45)	P
Age, y	65 (58/70)	65 (58/70)	67 (62/70)	0.38
Sex				
Male	62	62	60	
Female	38	38	40	0.87
Pretransplant diagnosis				
Interstitial lung disease	36	38	31	
COPD	25	26	20	
Idiopathic pulmonary fibrosis	15	13	22	
Cystic fibrosis	7	8	2	
α-1-antitrypsin deficiency	4	4	4	
Repeat lung transplant	2	1	2	
Bronchiectasis	2	2	2	
Pulmonary hypertension	1	1	0	
Sarcoidosis	1	1	0	
Pulmonary venous occlusive disease	1	1	0	
Other ^a	6	4	15	0.22
Type of transplant (n = 253)				
Bilateral lung	79	82	66	
Single lung	21	18	34	0.02
BOS stage ^b				
1	21	19	3	
2	35	37	25	
3	39	43	22	<0.001

Categorical data are expressed as percentage or mean (SD), whereas continuous variables are expressed as median and interquartile range. Data are summarized in all participants and in participants who met or did not meet FEV₁ criteria (statistically significant rate of FEV₁ decline <–30 mL/mo) AE or PE

^aOther indications included the following: CREST syndrome, eosinophilic granulomatous disease, hypersensitive pneumonitis, Langerhans cell histiocytosis, lymphangioleiomyomatosis, nonspecific interstitial pneumonia, primary ciliary dyskinesia, scleroderma, diabetes mellitus, usual interstitial pneumonia, and aspergilloma.

^bComparison in 245 participants who were stage 1 or greater.

AE, at enrollment; BOS, bronchiolitis obliterans syndrome; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment.

2. Slope percent change values (% change): the aforementioned slope difference values were adapted by dividing the slope difference values by the pre-BOS slope values and then multiplying by 100.

Categorization of Response to SOC Therapy

Response to SOC therapy was categorized using the following 2 definitions:

- 1. Partial response was defined as any decrease in the rate of FEV₁ decline, as defined as a positive numeric value obtained from the difference between rate of FEV₁ decline slopes at as follows: BOS diagnosis slope subtracted from slope at the first ECP treatment.
- 2. Fifty percent response was defined as a cutoff of >50% reduction in the rate of FEV₁ decline in participants with a positive difference value (first ECP – BOS).

Statistical Methods

Chi-square and Fisher exact tests were used to compare categorical variables. Either the 2-sample Wilcoxon rank-sum test or 1-way ANOVA was used for comparison of continuous variables at ≥1 time period. In circumstances where there were missing data, the number of data points for each condition was included when mean values were described in tables.

Univariate linear regression was used to evaluate the degree and trajectory of decline in lung function via generation of FEV₁ versus time (slope) values using time (independent variable) and FEV₁ values (dependent variable) at several different time periods predicated on the availability of spirometry results based on the respective, aforementioned criteria.

Multivariate linear and logistic regression analyses were performed to potentially identify variables associated with response to SOC therapy. A stepwise elimination process was used for multivariate models that involved 2 steps for sequential removal of covariates based on (1) the level of significance (ie, the covariate with the highest nonsignificant *P* value that exceeded 0.05 until all remaining variables were significant at the *P* < 0.05.) and (2) collinearity assessment using a variance inflation factor analysis was used to characterize the degree of collinearity (ie, values with high variance inflation factor values of >2 were considered for preferential removal). Statistical analyses were performed using Stata version 14 software (StataCorp, College Station, TX).

RESULTS

Of 258 patients enrolled in the ECP Registry Study, 158 met FEV₁ criteria AE, whereas 100 did not meet FEV₁

TABLE 2.
Demographics, indications for transplant, type of transplant, and BOS staging AE in participants who met FEV₁ criteria at AE vs PE

	All participants (N = 258)	FEV ₁ criteria met AE (N = 158)	FEV ₁ criteria met PE (N = 52)	<i>P</i>
Age, y	65 (58/ 70)	65 (57/ 69)	67 (60/ 71)	0.14
Sex				
Male	62	62	60	0.87
Female	38	38	40	
Pretransplant diagnosis (255/258)				
Interstitial lung disease	36	39	33	0.69
COPD	25	27	23	
Idiopathic pulmonary fibrosis	15			
Cystic fibrosis	7	7	10	
α-1-antitrypsin deficiency	4	4	6	
Repeat lung transplant	2	2	0	
Bronchiectasis	2	3	2	
Pulmonary hypertension	1	1	4	
Sarcoidosis	1	1	2	
Pulmonary venous occlusive disease	1	1	0	
Other ^a	6	4	6	
Type of transplant (n = 253)				
Bilateral lung	79	86	71	0.02
Single lung	21	14	29	
BOS stage ^b				
1	21	13	35	0.003
2	35	37	37	
3	39	48	29	

Categorical data are expressed as percentage or mean (SD), whereas continuous variables are expressed as median and interquartile range. Data are summarized in all participants and in participants who met or did not meet FEV₁ criteria (statistically significant rate of FEV₁ decline <–30 mL/mo) AE or PE.
^aOther indications included the following: CREST syndrome, eosinophilic granulomatous disease, hypersensitive pneumonitis, Langerhans cell histiocytosis, lymphangioliomyomatosis, nonspecific interstitial pneumonia, primary ciliary dyskinesia, scleroderma, diabetes mellitus, usual interstitial pneumonia, and aspergilloma.
^bComparison in 245 participants who were stage 1 or greater.
AE, at enrollment; BOS, bronchiolitis obliterans syndrome; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment.

TABLE 3.**Regimens used for maintenance immunosuppression before BOS diagnosis**

Maintenance immunosuppression	All participants (N = 255/258)	FEV ₁ criteria met AE/PE (N = 210)	FEV ₁ criteria not met AE/PE (N = 45)
Prednisone, tacrolimus, mycophenolate	122 (47%)	104	18
Prednisone, tacrolimus	33 (13%)	25	8
Prednisone, tacrolimus, azathioprine	29 (11%)	25	4
Prednisone, tacrolimus, sirolimus	14 (5%)	14	0
Prednisone, mycophenolate, CSA	13 (5%)	10	3
Prednisone, tacrolimus, mycophenolate, sirolimus	10 (4%)	8	2
Prednisone, everolimus, tacrolimus	8 (3%)	5	3
Prednisone, CSA	4 (2%)	4	0
Prednisone, tacrolimus, mycophenolate, everolimus	5 (2%)	3	2
Tacrolimus, mycophenolate	3 (1%)	3	0
Prednisone, tacrolimus, mycophenolate, azathioprine	3 (1%)	2	1
Prednisone, tacrolimus, azathioprine, sirolimus	2 (1%)	1	1
Prednisone, sirolimus, mycophenolate	2 (1%)	1	1
Prednisone, CSA, sirolimus	2 (1%)	1	1
Prednisone, tacrolimus, azathioprine, everolimus	1 (0.5%)	1	1
Prednisone, sirolimus	1 (0.5%)	1	0
Prednisone, mycophenolate, CSA, sirolimus	1 (0.5%)	1	0
Prednisone, mycophenolate	1 (0.5%)	1	0
Azithromycin use	219 (86%)	177 (84%)	42 (93%)
Antithymocyte globulin use	3 (1%)	3 (1%)	0 (0%)

Data are expressed as number (%). Data are summarized in all participants and in participants who met or did not meet FEV₁ criteria (statistically significant rate of FEV₁ decline <−30 mL/mo) AE or PE. AE, at enrollment; BOS, bronchiolitis obliterans syndrome; CSA, cyclosporine A; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment.

criteria (see Figure 1). An additional 52 participants met FEV₁ criteria PE.

Demographics, Indication for and Type of Lung Allograft Transplantation, and BOS Stage AE

Demographic and primary disease indication for transplant were similar between the 2 FEV₁ criteria cohorts AE (Table 1). A higher percentage of participants who met FEV₁ criteria received a double lung transplant. A substantial percentage of participants were in advanced BOS stages (stage II/III: 74%) AE with a higher percentage observed in participants meeting FEV₁ criteria (80% versus 4% in stage II/III in those meeting and not meeting FEV₁ criteria, respectively, $P < 0.001$). Similarly, a higher percentage of participants who initially met treatment criteria AE received a double lung transplant and were in a more advanced stage (Table 2).

Maintenance Immunosuppressive Regimens and SOC Changes at BOS Diagnosis

Maintenance immunosuppressive therapy regimens up to the time of BOS diagnosis are summarized in Table 3. A variable distribution of 18 different immunosuppressive regimens was observed that involved various combinations of 7 agents. Eighty-six percent of participants received azithromycin, with a similar percentage of participants between the 2 FEV₁ criteria cohorts.

Changes in ≥ 1 of 11 agents used for active management of BOS (eg, azithromycin, antithymocyte globulin, adding of another agent, or increases in steroid dose) are summarized in Table 4. The most common change involved an increase in the prednisone dose in 96% of participants,

TABLE 4.**Changes in immunosuppression usage to manage BOS**

Immunosuppression agents	Before BOS (N = 253/258)	After BOS Dx (N = 248/258)
Prednisone	234 (94%)	234 (94%)
Prednisone dose (mg QD)	8.8 (7.3)	19 (22.3)
Tacrolimus	231 (91%)	203 (79%)
Sirolimus	33 (13%)	39 (15%)
Everolimus	16 (6%)	16 (6%)
Azathioprine	45 (17%)	36 (14%)
Cyclosporine A	20 (8%)	19 (7%)
Methotrexate	1 (0.5%)	2 (1%)
Mycophenolate	160 (63%)	163 (63%)
No. of agents added		
None ^a		137 (53%)
1		93 (36%)
2		19 (7%)
3		5 (2%)
4		3 (1%)
No. of agents deleted		
None ^a		154 (60%)
1		55 (21%)
2		26 (10%)
3		15 (6%)
≥ 4		7 (3%)
Antithymocyte globulin	3 (1%)	89 (35%)
Alemtuzumab	0	15 (6%)
Azithromycin use	219 (86%)	214 (83%)

^aLimited to a change in steroid dose.

BOS, bronchiolitis obliterans syndrome; Dx, diagnosis.

followed by the use of azithromycin and antithymocyte globulin in 83% and 35% of participants, respectively. The number of additional agents added involved 1–4 agents,

TABLE 5.
Spirometry values at BOS diagnosis and AE between criteria cohorts

Time periods	FEV ₁ measurements and indices			
	All participants (N = 258)	AE FEV ₁ criteria met (N = 158)	AE FEV ₁ criteria not met (N = 100)	
			PE FEV ₁ criteria met (N = 52)	PE FEV ₁ criteria not met (N = 48)
Baseline ^a after transplantation				
FEV ₁	2.7 ± 0.8 (n = 254)	2.8 ± 0.8 (n = 157)	2.7 ± 0.9 (n = 52)	2.6 ± 0.8 (n = 45)
BOS diagnosis				
FEV ₁ ^b	1.9 ± 0.6	1.9 ± 0.6	1.8 ± 0.6	1.9 ± 0.5
% Baseline	69 ± 11 (n = 251)	69 ± 11 (n = 156)	66 ± 13 ^c (n = 52)	70 ± 10 (n = 43)
AE				
First screening FEV ₁	1.9 ± 0.7	2.1 ± 0.7	1.7 ± 0.6 ^c	1.7 ± 0.6 ^c
FEV ₁ AE	1.5 ± 0.5	1.4 ± 0.5	1.5 ± 0.6	1.6 ± 0.6 ^b
% Baseline FEV ₁ AE	54 ± 15	51 ± 14	57 ± 13 ^b	63 ± 16 ^b
FEV ₁ rate of decline, mL/mo	−88 ± 104	−132 ± 108	−37 ± 48 ^c	0.5 ± 31 ^{c,d}
PE at 1st ECP ^e				
FEV ₁	1.4 ± 0.5 (n = 100)	1.4 ± 0.5 (n = 90)	1.4 ± 0.6 ^b (n = 10)	

Data are expressed as mean ± SD. Data are summarized in all participants and in participants who met or did not meet FEV₁ criteria (rate of FEV₁ decline <−30 mL/mo and *P* < 0.05) AE or PE.

^aBaseline is defined as the average of the 2 highest values after transplantation.

^b*P* < 0.05 when compared with FEV₁ criteria met AE cohort.

^c*P* < 0.0001 when compared with FEV₁ criteria met AE cohort.

^d*P* < 0.0001 when compared with FEV₁ criteria PE cohort.

^eCriteria used to identify a subset of participants who met FEV₁ criteria (n = 196) for this comparison are as follows:

1. Interval between BOS diagnosis and enrollment <9 mo (n = 116; time from BOS to enrollment = 110 ± 65 d).
2. Enrollment slope <−30 mL/mo (n = 113) and *P* < 0.05.
3. At least 4 FEV₁ values 6 mo before and after BOS Dx (n = 100).

Comparisons of FEV₁ values and indices were not significant when the study site was factored into the comparison, except for the comparison of FEV₁ % baseline between participants who met treatment criteria between AE vs PE (cell at row 9, fourth column from left).

AE, at enrollment; BOS, bronchiolitis obliterans syndrome; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment.

36%–1%, respectively, whereas 1 versus ≥4 were deleted, 21%–3%, respectively.

Spirometric Analyses

FEV₁ and Derived Values at Various Periods Between Cohorts

Table 5 summarizes FEV₁ values in all participants and within each FEV₁ criteria cohort (as previously defined) at 5 time points (ie, at baseline, at BOS diagnosis, AE, and at the first ECP treatment) while the rate of FEV₁ decline was also summarized AE. Mean FEV₁ values at first screening were lower, whereas mean FEV₁ values AE were slightly higher in participants who never met FEV₁ criteria (ie, those participants who stayed in observation and did not initiate treatment) compared with participants who met FEV₁ criteria AE. These findings can be explained by the substantially lower (ie, less negative values of −37 mL/mo) rates of FEV₁ decline that were observed in participants who did not meet FEV₁ criteria AE and to a greater extent (ie, mean FEV₁ value of 0.5 mL/mo) in participants who never met FEV₁ criteria when compared with participants who did meet FEV₁ criteria AE (ie, mean FEV₁ value of −132 mL/mo).

Evaluation of the Trajectory of FEV₁ Rate of Decline Between Cohorts

To characterize the severity of BOS between cohorts before and after BOS diagnosis, the trajectory of FEV₁ rate

of decline after BOS diagnosis was compared in a subset of participants (n = 113) between the FEV₁ criteria assignment cohorts (ie, those who met or did not meet FEV₁ criteria, either AE or PE). Table 6 summarizes linear regression output (ie, slope and R² values) for the FEV₁ versus time relationship at each of 3 time points: at BOS diagnosis, AE, and after BOS diagnosis up to 2 d after the first ECP treatment. Based on the observed FEV₁ rates of decline in both Tables 5 and 6 and as illustrated in Figure 2, participants who met FEV₁ criteria had a more aggressive disease state that tended to accelerate after SOC therapy in the majority of participants (ie, trend observed for higher rates of decline at first ECP treatment, *P* = 0.057). The rate of decline in FEV₁ was attenuated by SOC therapy in both subcohorts of participants who did not meet FEV₁ criteria AE, with a greater reduction in the subcohort who did not meet FEV₁ criteria PE, 81% versus 42% decrease, respectively. Accordingly, the response in the subcohort who met FEV₁ criteria PE was not durable in approximately 43% (ie, 10/23 included in the analysis) of participants who did not meet FEV₁ criteria AE.

Spirometric Characterization of “Response” to SOC therapy

Categorization of the Effect of SOC Therapy After BOS Diagnosis

Tables 6 and 7 details an analysis from a subcohort of 116 participants who met the following criteria: (1) enrollment within 9 mo of BOS diagnosis and (2) availability of

TABLE 6.
Comparison of the rate of FEV₁ decline at 3 time points in a subset of participants (N = 113)

	Participants who met FEV ₁ criteria at either AE or PE	FEV ₁ criteria met AE	FEV ₁ criteria not met AE	
			FEV ₁ criteria met PE (N = 52)	FEV ₁ criteria not met PE (N = 48)
Subset of participants included that met specific criteria ^a	(n = 100/196)	(n = 90/158)	(n = 10/52)	(n = 13/48)
Time periods				
At BOS Dx				
FEV ₁ rate of decline	-136 ± 109	-138 ± 113	-116 ± 57	-72 ± 59
R ² value	0.72 ± 0.25	0.75 ± 0.22	0.48 ± 0.37 ^b	0.56 ± 0.32
AE				
FEV ₁ rate of decline	-145 ± 116	-153 ± 118	-67 ± 40 ^b	-14 ± 29 ^b
R2 value	0.78 ± 0.18	0.82 ± 0.12	0.39 ± 0.20 ^b	0.13 ± 0.13 ^b
At 1st ECP				
FEV ₁ rate of decline	-173 ± 218 ^c	-182 ± 226	-88 ± 79	-1 ± 25 ^b
R ² value	0.73 ± 0.29	0.76 ± 0.27	0.46 ± 0.3 ^b	0.28 ± 0.28 ^b

Linear regression-derived values (slope and r2 values) from FEV₁ vs time relationship are summarized at 3 time periods (ie, at BOS Dx, AE, and between BOS Dx and within 2 d of the first ECP treatment). Data summarized in participants who met (n = 100) or did not meet (n = 13) FEV₁ criteria (rate of FEV₁ decline <-30 mL/mo and P < 0.05) AE or PE. Inclusion of participants in this analysis was predicated on meeting the following criteria: participants in whom spirometry results were available and the period between BOS Dx and enrollment was restricted to <9 mo (ie, based on multivariate analysis that revealed that response to SOC was not influenced by time from BOS Dx to first ECP when it was limited to <9 mo). Slopes (mL/mo) and R² values are expressed as mean ± SD.

^aCriteria used to identify a subset of participants who met FEV₁ criteria (n = 196) for this comparison as follows:

1. Interval between BOS diagnosis and enrollment <9 mo (n = 116; time from BOS to first ECP treatment = 126 ± 67 d).
2. Enrollment slope <-30 mL/mo (n = 113) and P < 0.05.
3. At least 4 FEV₁ values 6 mo before and after BOS Dx (n = 100).

Participants who did not meet FEV₁ criteria (n = 48) but who did meet the criterion (3) as described above (n = 13).

^bP < 0.05 when compared with the cohort who met FEV₁ criteria AE.

^cP = 0.057 when compared with the rate of FEV₁ decline at BOS Dx.

AE, at enrollment; BOS, bronchiolitis obliterans syndrome; Dx, diagnosis; ECP, extracorporeal photophoresis; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment; SOC, standard of care.

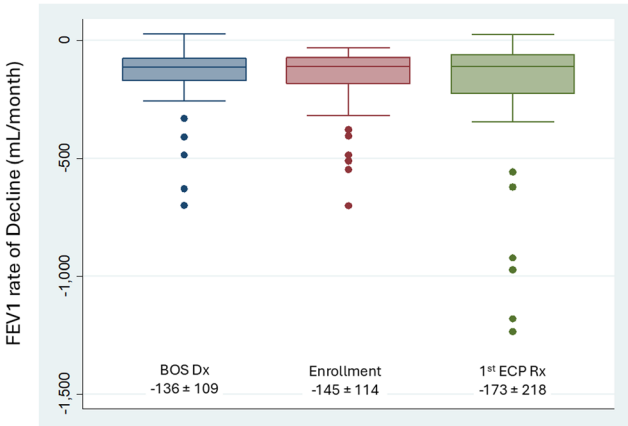


FIGURE 2. Box whisker plots showing the rate (mL/mo) of FEV₁ decline in participants who met criteria obtained at 3 separate time points (BOS Dx, AE, and within 2 d after the first ECP treatment), with values expressed as mean and SD detailed at the bottom of the graph. AE, at enrollment; BOS, bronchiolitis obliterans syndrome; Dx, diagnosis; ECP, extracorporeal photophoresis; FEV₁, forced expiratory volume in 1 s.

requisite data for evaluation of the course of FEV₁ rate of change over time between BOS diagnosis and up to 2 d after the first ECP treatment. In the entire subset series (n = 116) with a partial response, some improvement was observed in 51% of participants with slope difference and % change values (79 mL/mo, -71%, respectively). However, the remaining 49% (all participants who met FEV₁ criteria) with a partial response had a profound increase in the rate of FEV₁ decline (-150 mL/mo, a 224% increase).

Approximately 49% of participants who met FEV₁ criteria AE demonstrated a partial response (see Table 6, third data column from left), in contrast to 69% of participants who met FEV₁ criteria PE (Table 7, fifth data column from left). Similarly, 54% of participants who met FEV₁ criteria PE, when compared with only 21% of participants who initially met FEV₁ criteria AE, attained a 50% response (ie, 50% decrease in the rate of FEV₁ decline). Overall, in all participants who met FEV₁ criteria AE or PE, a 133% increase (-80 mL/mo) was observed in 75% of the participants who did not sustain a 50% response (see Table 7). Nevertheless, approximately 19% (48/258) of all enrolled participants did not meet FEV₁ criteria AE or PE, which suggests that at least a small subset of participants may have achieved a reasonable degree of stabilization by SOC therapy.

Figure 3 graphically illustrates these findings by plotting the change in slope difference values (first ECP - BOS diagnosis along the y-axis) relative to the initial rate of FEV₁ decline at BOS diagnosis (x-axis); positive slope difference values (that are above the green horizontal line along y-axis) in this figure reflect a “partial response” (positive values). This graph specifically facilitates direct comparison of the spirometric response to SOC therapy (ie, via the slopes of the predicted linear regression lines) within each of the 2 subcohorts involving participants who met FEV₁ criteria, either AE (black circles) or PE (red triangles). Figure 4 shows the linear relationship between the % change in FEV₁ slopes (y-axis) versus the time from BOS diagnosis to the first ECP treatment (x-axis); the inverse relationship depicted in this graph suggests that clinicians most likely sped up enrollment and treatment for participants who had spirometric evidence of aggressive disease

TABLE 7.
Characterization response to SOC treatment based on the change in FEV₁ rate of decline

	All participants who met FEV ₁ criteria at either AE or PE (n = 116/210)		Participants who met FEV ₁ criteria AE (n = 103/158)		Participants who met FEV ₁ criteria PE (N = 13/52)	
Partial response	Yes	No	Yes	No	Yes	No
Any decrease in FEV ₁ rate of decline with SOC treatment, %	51%	49%	49%	51%	69% ^a	31%
Slope at BOS Dx	-155 ± 96	-114 ± 115 ^a	-158 ± 103	-119 ± 117	-136 ± 38	-46 ± 25 ^a
Slope at 1st ECP ^b	-75 ± 58	-261 ± 258 ^a	-80 ± 61	-269 ± 265 ^a	-49 ± 27	-148 ± 96 ^a
Difference in slope (1st ECP – BOS)	79 ± 69	-150 ± 194 ^a	78 ± 74	-154 ± 201 ^a	87 ± 26	-101 ± 75 ^a
% Change in slope (1st ECP – BOS)	-71 ± 157	224 ± 463 ^a	-72 ± 170	223 ± 479 ^a	-66 ± 16	244 ± 156 ^a
50% response						
>50% decrease in FEV ₁ rate of decline (%)	25%	75%	21%	79%	54% ^a	46%
Slope at BOS Dx	-161 ± 119	-124 ± 100	-169 ± 134	-128 ± 102	-136 ± 42	-76 ± 51 ^a
Slope at 1st ECP	-46 ± 55	-204 ± 222 ^a	-48 ± 62	-210 ± 228 ^a	-40 ± 23	-125 ± 83 ^a
Difference in slope (1st ECP – BOS)	115 ± 77	-80 ± 184 ^a	121 ± 87	-83 ± 188 ^a	96 ± 21	-49 ± 100 ^a
% Change in slope (1st ECP – BOS)	-115 ± 217	133 ± 390 ^a	-129 ± 250	132 ± 401 ^a	-72 ± 9	149 ± 190 ^a
Time BOS Dx to 1st ECP Rx, mo	5.3 ± 2.3	4.0 ± 2.0 ^a	4.8 ± 2.3	4.0 ± 2.0	6.6 ± 1.7	3.5 ± 1.8 ^a

FEV₁ rate of decline (slope) values (mL/mo) and difference/percent change in slope values expressed as mean ± SD.
Response to SOC therapy is characterized and defined by the 2 categories:
1. Partial response: defined as a positive difference value when the rate of FEV₁ change (slope) measured at BOS is subtracted from the rate of FEV₁ change (slope) measured using FEV₁ values from enrollment to first ECP.
2. 50% response: in participants with a positive difference value (first ECP – BOS) as described above, 50% response is defined as >50% reduction in the rate of FEV₁ decline.
Time period from BOS Dx to first ECP treatment: AE FEV₁ criteria met (4.1 ± 2.1 mo) vs PE FEV₁ criteria were met (5.2 ± 2.3 mo).
^aP < 0.05 when compared between response and nonresponse participants.
^bRepresents slopes generated within 2 d of the first ECP treatment (only 2 participants had FEV₁ values obtained after the first ECP treatment, 1 at 1 d and the second after 2 d).
AE, at enrollment; BOS, bronchiolitis obliterans syndrome; Dx, diagnosis; ECP, extracorporeal photophoresis; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment; SOC, standard of care.

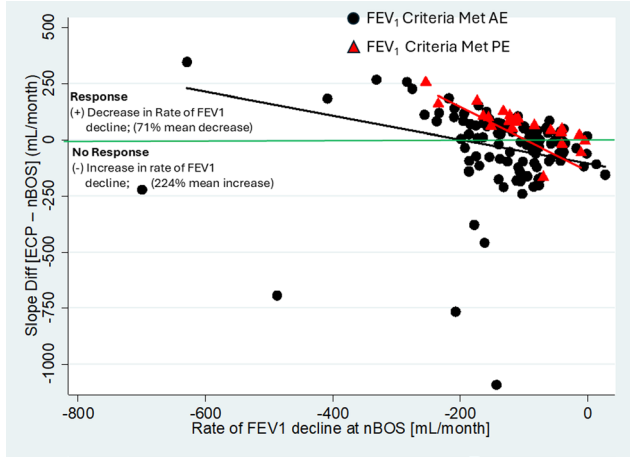


FIGURE 3. The relationship of FEV₁ rate of decline (mL/mo) and slope difference (ie, first ECP – BOS Dx) values (y-axis) as related to FEV₁ rate of decline (mL/mo) at BOS Dx (x-axis) in participants who met FEV₁ criteria AE (black circles) vs participants who met FEV₁ criteria PE (red triangles). Linear regression was used to generate predictive lines for each cohort (ie, red line for participants who met FEV₁ criteria PE vs black line for participants who met FEV₁ criteria AE). The green horizontal line demarcates a decrease in the rate of FEV₁ decline (response: +ve value; above green line) vs an increase in the rate of decline (no response: –ve value; below green line). The percentage of participants and the percent change in FEV₁ rate of decline are summarized within the figure for participants who met FEV₁ criteria AE relative to either a response (+ difference values) or a 50% response. AE, at enrollment; BOS, bronchiolitis obliterans syndrome; Dx, diagnosis; ECP, extracorporeal photophoresis; FEV₁, forced expiratory volume in 1 s; PE, post-enrollment.

(participants who met FEV₁ criteria AE with greater rates of FEV₁ decline). Figures 5 and 6 illustrate the change in FEV₁ versus time at BOS diagnosis (left side) versus at

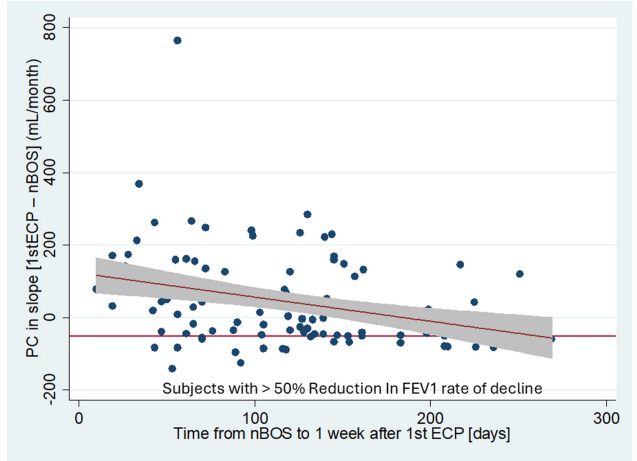


FIGURE 4. The indirect relationship between the PC in FEV₁ rate of decline between 2 time points (BOS Dx and within 2 d after the first ECP) vs the time (in days) from BOS diagnosis until the first ECP for participants who met FEV₁ criteria AE (n = 103). The horizontal red line represents the cutoff for response, defined as >50% decrease in the rate of FEV₁ decline, with 22 of 103 cases depicted below the red line. AE, at enrollment; BOS, bronchiolitis obliterans syndrome; Dx, diagnosis; ECP, extracorporeal photophoresis; FEV₁, forced expiratory volume in 1 s; PC, percent change.

first ECP treatment (right side) for individual participants, in “nonresponders” and “responders,” respectively. No agent or combination of agents had an association with either FEV₁ values (percent change or difference values) or any (partial response) or 50% decrease (50% response) in the rate of FEV₁ decline via multivariate linear or logistic regression, respectively. In summary, these findings characterize the marginal efficacy of SOC therapy to durably

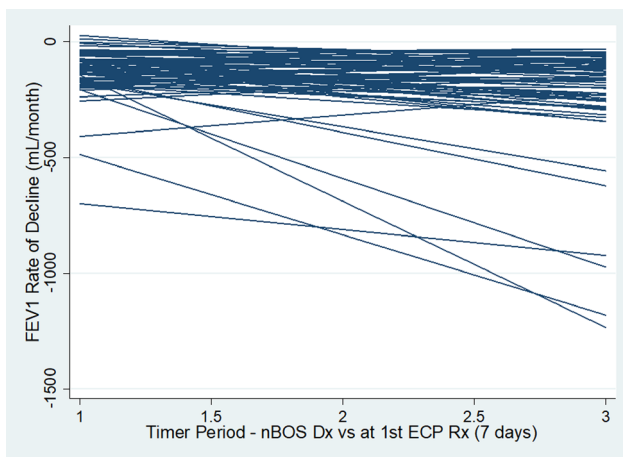


FIGURE 5. The degree of increase in the FEV₁ rate of decline (mL/mo) between the 2 time periods (BOS Dx to left; within 2 d of the first ECP treatment to right) in nonresponders to SOC therapy (ie, <50% drop in the rate of FEV₁ decline). BOS, bronchiolitis obliterans syndrome; Dx, diagnosis; ECP, extracorporeal photophoresis; FEV₁, forced expiratory volume in 1 s; SOC, standard of care.

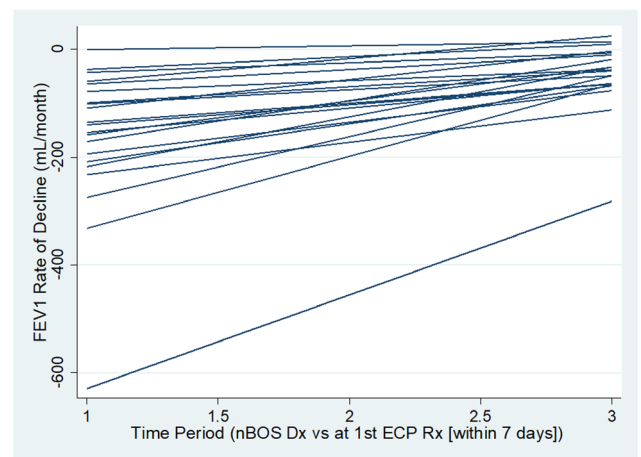


FIGURE 6. The degree of decrease in the FEV₁ rate of decline (mL/mo) between the 2 time periods (BOS Dx to left; within 2 d of the first ECP treatment to right) in responders to SOC therapy (ie, >50% drop in the rate of FEV₁ decline). BOS, bronchiolitis obliterans syndrome; Dx, diagnosis; ECP, extracorporeal photophoresis; FEV₁, forced expiratory volume in 1 s; SOC, standard of care.

arrest BOS in this series of participants, especially in those participants with an aggressive level of BOS pathology.

DISCUSSION

The present analysis, involving data from participants enrolled in the largest prospective series to date, was designed to (1) describe the wide range of SOC interventions used to manage BOS at our 20 enrolling centers, (2) characterize the spirometric course after initiation of SOC therapy, and (3) evaluate the suitability of our FEV₁ criteria for management of refractory BOS and by doing so, to enhance design of comparative therapeutic studies.

We had previously observed a significant relationship between the decline in the rate of FEV₁ decline and early mortality in lung transplant recipients with BOS.¹² Based on the observed trajectory of FEV₁ rate of decline at several time periods and the differential response to SOC therapy stratified by our FEV₁ criteria, these findings support the use of this FEV₁ cutoff to initiate rescue therapy for a revised RCT pursuant to a previous Food and Drug Administration guidance document.¹⁴ Although additional validation of the FEV₁ criteria used in this study would be useful, it is expected that this should be a reasonable cutoff based on the substantial variability in FEV₁ values (ie, 2 SD coefficient of variation of 17%) observed in patients in surveillance for BOS.¹⁷

Although SOC interventions resulted in a partial response in up to 51% of participants who met slope criteria AE or PE (Table 7) and as illustrated in Figure 3 (data points above the green horizontal line), only 19% (48/258) of all enrolled participants (ie, those who did not meet FEV₁ criteria) had evidence of complete stabilization of BOS. Alternatively, this stabilization may have represented a mischaracterization of BOS (ie, acute cellular rejection). In contrast, only 25% of participants who met FEV₁ criteria AE or PE had ≥50% reduction in the rate of decline by SOC therapy (Table 7). The enhanced SOC response profile, that is, the steeper predicted linear regression line

(red line) the response region (above green line) in Figure 3 that was observed for participants who met FEV₁ criteria PE may be explained by the lower severity of BOS in these participants based on FEV₁ rate of decline (ie, 50% lower slope values AE within Table 6). However, the SOC effect was not durable because >50% of participants who did not meet FEV₁ criteria AE met these criteria PE (Figure 1). The observed progressive decline in lung function after SOC therapy in the majority of participants facilitates the use of mathematical constructs to predict survival (ie, more rapid rates of FEV₁ decline that require less time to reach a previously defined terminal FEV₁ of 700 mL).¹⁷ These findings align with the well-documented poor prognosis of lung transplant recipients after development of BOS.⁴⁻⁶

The substantial loss of lung capacity observed AE (ie, FEV₁ values at 54% of baseline values AE in Table 5) is consistent with previously described variable and prolonged intervals (ie, between every 3 and 12 mo) for FEV₁ measurements between institutions,¹⁸ reinforces the importance of early detection and frequent monitoring of pulmonary function for patients under surveillance for BOS is critically important especially for patients with higher observed rates of decline in FEV₁.¹²

Generally, earlier detection of BOS via frequent spirometry coupled with earlier use of effective therapy may result in better functional status and prolonged survival for either primary or refractory BOS. However, compliance with a frequent monitoring schedule (every 4–8 wk) via conventional laboratory spirometry for long surveillance periods (ie, up to 15 y) based on a fairly consistent annual BOS incidence of 8% per year² may not be feasible for many patients. Since home spirometry monitoring systems can lead to early detection of acute rejection and infection in lung transplant recipients,¹⁹⁻²² it offers clear advantages for optimizing management of either infections versus rejection. Therefore, we have developed and validated (in a series of 9 volunteers) a novel home spirometry system that results in automated generation and transmission of reports with spirometry, oximetry, and survey data. Use of this system will facilitate earlier

detection and treatment of BOS and will enhance enrollment into a revised RCT.

In summary, the findings in the present study illustrate that the vast array of SOC interventions implemented at our 21 enrolling sites had a modest effect on attenuation of the rate of FEV₁ decline, especially in participants who met FEV₁ criteria AE with more aggressive disease. However, because 19% of all enrolled participants did not meet FEV₁ criteria AE or PE based on stable FEV₁ values, this finding supports that validated Spirometric Criteria should be used to assess response to SOC before rescue therapy options are considered. In addition, our findings support stratification of participants (ie, either via retrospective data capture or random assignment in RCTs) based on validated spirometric biomarkers after SOC therapy to ensure that there is an equal distribution of high- and low-risk participants assigned to comparator cohorts.

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