

ORIGINAL ARTICLE

Extracorporeal photopheresis to attenuate decline in lung function due to refractory obstructive allograft dysfunction

The EPI Study Group | Chadi A. Hage¹ | Julia Klesney-Tait² | Keith Wille³ | Selim Arcasoy⁴ | Gordon Yung⁵ | Marshall Hertz⁶ | Kevin M. Chan⁷ | Matt Morrell⁸ | Hilary Goldberg⁹ | Suresh Vedantham¹⁰ | Mary Clare Derfler¹⁰ | Paul Commean¹¹ | Keith Berman¹² | Ed Spitznagel¹³ | Jeff Atkinson¹⁴ | George Despotis¹⁵

¹Department of Medicine, Division of Pulmonology, Indiana University, Bloomington, Indiana, USA

²Department of Medicine, Division of Pulmonology, University of Iowa, Iowa City, Iowa, USA

³Department of Medicine, Division of Pulmonology, University of Alabama, Tuscaloosa, Alabama, USA

⁴Department of Medicine, Division of Pulmonology, Columbia University of Alabama, Orange Beach, Alabama, USA

⁵Division of Pulmonary, Critical Care, and Sleep Medicine, University of California San Diego, La Jolla, California, USA

⁶Department of Medicine, Division of Pulmonology, University of Minnesota, Minneapolis, Minnesota, USA

⁷Department of Medicine, Division of Pulmonology, University of Michigan, Ann Arbor, Michigan, USA

⁸Department of Medicine, Division of Pulmonology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁹Harvard Medical School, Department of Medicine, Division of Pulmonology, Brigham and Women's Hospital, Boston, Massachusetts, USA

¹⁰Clinical Coordinating Center, Washington University School of Medicine, Mallinckrodt Institute of Radiology, St. Louis, Missouri, USA

¹¹Data Coordinating Center, Washington University School of Medicine, Mallinckrodt Institute of Radiology, St. Louis, Missouri, USA

¹²Health Research Associates, Mountlake Terrace, Washington, USA

¹³Department of Mathematics, Washington University, St. Louis, Missouri, USA

¹⁴Department of Internal Medicine, Division of Pulmonary Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

¹⁵Department of Pathology & Immunology, Division of Laboratory & Genomic Medicine, Department of Anesthesiology, Division of Cardiothoracic Anesthesiology, Washington University School of Medicine, St. Louis, Missouri, USA

Correspondence

George Despotis, Department of Pathology & Immunology, Division of Laboratory & Genomic Medicine, Washington University School of Medicine, 425 S. Euclid Avenue, Campus Box 8118, Saint Louis, MO 63110, USA.
Email: gidespotis@wustl.edu

Funding information

US Centers for Medicare and Medicaid Services (CMS), Grant/Award Number: CAG-00324R2; Therakos®, Inc., Grant/Award Number: NCT02181257

Abstract

Background: This study was designed to prospectively evaluate the efficacy of extracorporeal photopheresis (ECP) to attenuate the rate of decline of FEV₁ in lung transplant recipients with refractory bronchiolitis obliterans. Due to an observed higher than expected early mortality, a preliminary analysis was performed.

Study Design and Methods: Subjects from 10 lung transplant centres were assigned to ECP treatment or to observation based on spirometric criteria, with potential crossover for those under observation. The primary endpoint of this study was to assess response to ECP (i.e., greater than a 50% decrease in the rate of FEV₁ decline) before and 6 months after initiation of ECP. Mortality was also evaluated 6 and 12 months after enrolment as a secondary endpoint.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Transfusion Medicine* published by John Wiley & Sons Ltd on behalf of British Blood Transfusion Society.

Results: Of 44 enrolled subjects, 31 were assigned to ECP treatment while 13 were initially assigned to observation on a non-random basis using specific spirometric inclusion criteria (seven of the observation patients subsequently crossed over to receive ECP). Of evaluable patients, 95% of patients initially assigned to treatment responded to ECP with rates of FEV₁ decline that were reduced by 93% in evaluable ECP-treated patients. Mortality rates (percentages) at 6 and 12 months after enrolment was 32% and 41%, respectively. The most common (92%) primary cause of death was respiratory or graft failure. Significantly ($p = 0.002$) higher rates of FEV₁ decline were observed in the non-survivors (-212 ± 177 ml/month) when compared to the survivors (-95 ± 117 ml/month) 12 months after enrolment. In addition, 18 patients with bronchiolitis obliterans syndrome (BOS) diagnosis within 6 months of enrolment had lost 38% of their baseline lung function at BOS diagnosis and 50% of their lung function at enrolment.

Conclusions: These analyses suggest that earlier detection and treatment of BOS should be considered to appreciate improved outcomes with ECP.

KEYWORDS

bronchiolitis obliterans syndrome, extracorporeal photopheresis, forced expiratory volume in 1 s, lung transplantation

1 | INTRODUCTION

Chronic lung allograft dysfunction (CLAD), predominantly related to bronchiolitis obliterans syndrome (BOS) represents the leading cause of morbidity and mortality in recipients of lung allografts beyond the first year¹ with an annual incidence that exceeds 7%–8% in the first 10 years after transplantation.² BOS is an irreversible fibroproliferative immune process that results in progressive narrowing of bronchial lumens, ultimately resulting in complete airway occlusion.³ Despite current clinical use of one or more on or off-label treatment options, no immunosuppressive regimen has been shown to consistently prevent BOS.^{4,5}

Extracorporeal photopheresis (ECP), a pheresis-based therapeutic immunomodulatory intervention, was approved by the FDA in 1987 for the management of cutaneous T-cell lymphoma.⁶ ECP is additionally covered by Medicare for two off-label uses: management of GVHD after bone marrow transplantation^{7,8} and for cellular rejection of orthotopic heart transplants.⁹

Since the early 1990s, ECP has also been used on an off-label basis for treatment of BOS refractory to the currently available armamentarium of immunosuppressive agents in lung transplant recipients.^{10–16} Three retrospective analyses have demonstrated a reduction in the rate of decline of lung function in ~80% of lung transplant recipients with BOS.^{14–16} Based on these findings, we submitted a formal request to the US Centres for Medicare and Medicaid (CMS) to revise its ECP National Coverage Determination (NCD) to cover this treatment for patients with refractory BOS.

Pursuant to concerns raised by CMS regarding the study design for a prospective trial, we pursued a follow-up analysis of our

previously published 60-patient database¹⁶ to address these issues. In this re-analysis, FEV₁ was the only parameter that correlated with outcome (e.g., 50% survival at 1 year for patients with an FEV₁ < 1.25 L when compared to 85% survival at 1 year for patients with an FEV₁ > 1.25 L, $p < 0.0001$).¹⁷ In addition, two parameters associated with response to ECP were identified in this analysis: patients with an FEV₁ rate of decline that exceeded 40 ml/month were 12 times more likely to respond to ECP and patients who had a statistically significant ($p < 0.05$) rate of FEV₁ decline over time (via linear regression analysis) were 10 times more likely to respond to ECP when compared to those patients whose rate of FEV₁ decline over time was not statistically significant ($p > 0.05$).

Under its Medicare Coverage and Evidence Development (CED) authority, CMS published a Decision Memo¹⁸ authorising use of ECP for treatment of Medicare patients with BOS in the setting of an approved research protocol. In September 2012, CMS approved our prospective, multi-centre registry study with a target enrolment of 160 patients over 5 years to attain our primary spirometric rate of decline endpoint (50% decrease in the rate of decline in FEV₁ between a 6-month period before and after enrolment).¹⁹ After 1 year of enrolment ($n = 44$), despite improvement in rate of decline in FEV₁ observed in the entire cohort, a higher than expected mortality rate was also observed within the first year after enrolment. Therefore, a preliminary analysis was performed with the primary aim of assessing the factors associated with early mortality before completion of the 6-month ECP regimen. Since the protocol construct did not allow patients to receive ECP treatment unless they met defined spirometric criteria, we also wanted to compare the survival between patients who were non-randomly assigned to either the ECP treatment versus Observation cohorts.

2 | MATERIALS AND METHODS

2.1 | Subjects

Subjects were enrolled in an ongoing, multicentre, study involving Medicare lung transplant recipients diagnosed with BOS that was refractory to conventional therapy, and therefore eligible to be treated with ECP. Subjects were recruited from nine centres from April 2015 to July 2016.¹⁹ This study protocol (NCT 02181257) was initially approved by the Washington University Human Research Protection Office and subsequently by all local IRBs at enrolling centres.

2.2 | Refractory BOS diagnosis and treatment regimens

All subjects enrolled in this study received prophylactic standard immunosuppressive therapy pursuant to local practices at enrolling institutions. Pulmonary function was monitored by serial spirometry following lung transplant in accordance with guidelines issued by the American Thoracic Society (ATS).²⁰ BOS diagnoses were rendered using clinical criteria predicated by FEV₁ values as defined by the International Society for Heart and Lung Transplantation.²¹ Enrolling sites had full discretion to administer any new therapy and/or augment the current immunosuppressive regimen after diagnosis of BOS. Refractory BOS was defined as a progressive decline in FEV₁ unresponsive to all interventions as determined by the enrolling investigator.

2.3 | Registry study design

2.3.1 | Subject assignment and crossover

Enrolled subjects were initially assigned to one of two (ECP vs. Observation) cohort on a non-randomised basis predicated on the spirometric criteria previously described¹⁷; subjects who met the spirometric criteria (i.e., a statistically significant rate of FEV₁ decline that exceeded 10 ml/month if the most recent pre-ECP FEV₁ was <1200 or 30 ml/month if FEV₁ > 1200 ml) were assigned to the ECP Treatment cohort. Subjects who were enrolled in the study but who did not initially meet these spirometric criteria were assigned to the Observation cohort. For subjects in the Observation cohort who continued to have FEV₁ values regularly monitored after enrolment, ECP treatment could be initiated when the subject's FEV₁ values subsequently met the aforementioned spirometric criteria; these Observation cohort subjects were designated post hoc as a "Crossover."

2.3.2 | ECP regimen and instruments utilised

Subjects that met the enrolment spirometric rate of decline criteria either initially (ECP Treatment cohort) or with Crossover (Observation cohort) were scheduled to receive 24 ECP

treatments over a period of 6 months, using a regimen previously described.⁹ In summary, treatment centres performed ECP using the intravenous formulation of 8 methoxy psolarin (UVADEX™) with either the UVAR XTS or CELLEX instruments (Therakos, Exton, PA) predicated on instrument availability, patient-specific indications or operator experience.

2.4 | Spirometry data (FEV₁) between cohorts

2.4.1 | FEV₁

Spirometry was performed in clinical laboratories at each enrolling site according to ATS guidelines. FEV₁ data for enrolled subjects were summarised for assigned cohorts at several time points: baseline (as defined by ISHLT guidelines), 1st screen (the first of at least 5 FEV₁ values measured 6 months prior to ECP), enrolment, and monthly (when available) up to 12 months after ECP initiation.

2.4.2 | FEV₁ rate of decline

To assess the relative efficacy of ECP to arrest the rate of decline in lung function, the rate of decline in FEV₁ was calculated via linear regression using five FEV₁ values obtained 6 months prior to enrolment, and using at least four FEV₁ values obtained at 6 and 12 months after ECP initiation predicated on availability of FEV₁ values 2 months after the first ECP procedure. Only patients who had at least three monthly FEV₁ values after the first ECP treatment were included in the comparative analysis. The change in rate of decline between the pre and post-ECP periods was calculated as the difference between the slope of FEV₁ decline post-ECP (e.g., 3, 6 or 12 months) and the rate of decline just prior to ECP initiation ($\text{slope}_{\text{post-ECP}} - \text{slope}_{\text{pre-ECP}}$).

2.5 | Primary efficacy outcome

The primary endpoint of the Registry study was the change in rate of FEV₁ decline with "response" defined as a 50% or greater decrease in the rate of FEV₁ decline between pre-ECP and 6 months post-ECP treatment.

2.6 | Secondary outcomes

2.6.1 | Relationship between initial rate of FEV₁ decline and response to ECP

To assess the ability of our spirometric enrolment criteria to identify subjects who respond to ECP, "response" at 3 or 6 months after ECP was summarised for ECP and Observation Crossover Cohort subjects; predictive indices with respect to the ability of spirometric enrolment criteria to identify response were derived using Bayes' Theorem.



2.6.2 | Mortality assessment

As part of our DSMB safety assessment functions, mortality was adjudicated with respect to relatedness to ECP by our DSMB while causality was assessed by local managing physicians. Time to mortality was determined for all subjects who expired within 12 months of enrolment and early mortality was defined as death prior to completion of the 6-month ECP regimen (i.e., 24 ECP procedures). The following factors were assessed with respect to a potential association with early mortality: demographics, indication, and type of transplant, the rate and degree of decline of pulmonary function at enrolment. In addition, response to ECP and study design-related factors (i.e., spirometric enrolment criteria) were also evaluated.

2.7 | Requisite time for BOS diagnosis on enrolment FEV₁ values

To characterise the impact of the requisite time for BOS on the magnitude of decline in FEV₁ at enrolment, % change from baseline FEV₁ values were summarised at various times point in a subset ($n = 18$) of patients who were initially assigned to ECP treatment whose BOS diagnosis was made within 6 months prior to enrolment.

2.8 | Statistical methods

Chi square and Fischer's exact test were used to compare orical variables. Either two-sample Wilcoxon rank-sum or one-way analysis of variance was used for comparison of continuous variables at one or more time periods. In circumstances where there were missing data (in part related to early mortality), specific data points were displayed in distribution plots rather than mean values and when data were expressed as mean values in tables, the number of data points for each condition was included.

Univariate linear regression was used to evaluate the decline in lung function via generation of slope values using time (independent variable) and FEV₁ values (dependent variable) at multiple different time periods. Univariate and multivariate linear regression analyses were performed to identify potential covariates that may be associated with mortality at either 6 or 12 months after enrolment and with response to ECP therapy; only variables that had a p value <0.1 with univariate analyses were included in multivariate models. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using STATA14 software (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Subject enrolment and assignment

Of 44 patients enrolled in the ECP Registry Study, 31 were initially assigned to the ECP cohort while 13 were assigned to the Observation cohort in a non-randomised fashion based on spirometric enrolment

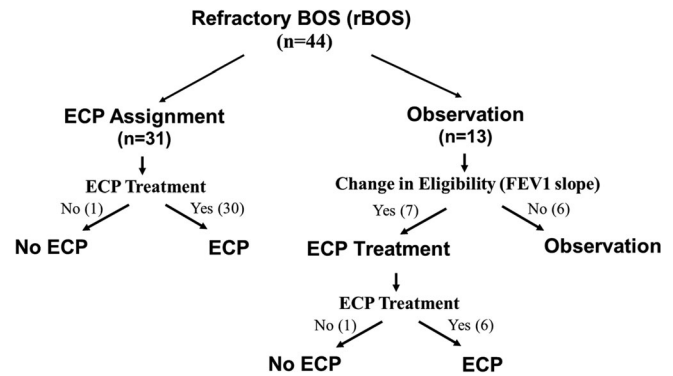


FIGURE 1 A flow diagram that illustrates patient enrolment on a non-random basis using spirometric enrolment criteria, assignment and crossover to extracorporeal photopheresis (ECP) treatment

criteria. Thirty-seven subjects received ECP as follows: 30 of 31 ECP Treatment cohort patients received ECP (one excluded due to venous access issues) while 6 of 7 observation cohort subjects who crossed over received ECP therapy (Crossover Cohort) (see Figure 1). The average number of days between enrolment and the first ECP treatment was 10 days for ECP cohort subjects while Crossover subjects received ECP on average 28 days after observation cohort enrolment; this 18 day difference translated into an average loss of 51 ml in FEV₁.

3.2 | Patient demographics, indication for lung transplant and immunosuppressive regimen

Demographic, primary disease indication for transplant, type of lung transplant (i.e., single vs. bilateral), and stage of BOS at enrolment were similar between the two cohorts (Table 1). A substantial percentage of patients were in advanced stages (58% vs. 50% in Stage II/III in the ECP and Observation cohorts, respectively).

A similar overall distribution of maintenance immunosuppressive medications was observed between cohorts (Table 2). Accordingly, similar percentages of patients had received either Azithromycin or anti-thymocyte globulin between the two cohorts, with p values of 0.3 and 1.0, respectively (Table 2).

3.3 | Spirometric analyses: FEV₁ and FEV₁ rates of decline

Table 3 summarises FEV₁ values at four time points in each cohort (ECP vs. observation vs. crossover). When compared to the ECP cohort, the screening FEV₁ was statistically lower ($p < 0.01$) in the observation subjects who did not cross-over to ECP treatment.

Table 4 summarises rates of FEV₁ decline and p values (i.e., values derived from the FEV₁ versus time plots and slopes expressed in ml/month) between cohorts at two time points (before and 6 months after enrolment); the number of data points included was predicated on availability of FEV₁ measurements as detailed at the bottom of the table. As expected based on the spirometric criteria for cohort

	ECP arm (n = 31)	Observation arm (n = 13)	p value
Age, years	57 (13)	61 (8)	0.36
Gender			
Male	53	42	
Female	47	58	0.73
Pre-transplant diagnosis ^a			
COPD	34	17	
Cystic fibrosis	10	8	
Interstitial lung disease	38	43	
α -Antitrypsin deficiency	7	8	
Primary pulmonary hypertension	0	8	
Sarcoidosis	0	8	
Pulmonary venous occlusive disease	4	0	
Other	7	8	0.67
Type of transplant			
Bilateral lung	83	64	
Single lung	17	36	0.22
BOS stage ^b			
1	42	50	
2	29	33	
3	29	17	1.0

Abbreviations: BOS, bronchiolitis obliterans syndrome; ECP, extracorporeal photopheresis.

^aComparison in 41 subjects (ECP = 29, Observation = 12).

^bComparison in 35 subjects (ECP = 28, Crossover = 6, ECP (non-treated) = 1).

TABLE 1 Demographics, indications for transplant, type of transplant and BOS staging at the time of photopheresis initiation, data expressed as % or mean (SD)

TABLE 2 Current immunosuppressive regimens at the time of extracorporeal photopheresis initiation—data expressed as %

Maintenance immunosuppression ^a	ECP cohort	Observation cohort
Prednisone, mycophenolate, CSA	4	10
Prednisone, tacrolimus, azathioprine	10	10
Prednisone, tacrolimus, mycophenolate	45	30
Prednisone, tacrolimus, mycophenolate, azathioprine	21	0
Prednisone, tacrolimus, mycophenolate, CSA	7	0
Prednisone, tacrolimus, mycophenolate, everolimus	4	10
Prednisone, tacrolimus, mycophenolate, sirolimus	4	30
Prednisone, tacrolimus, mycophenolate, sirolimus, azathioprine	7	0
Prednisone, tacrolimus, sirolimus	0	10
Azithromycin use	79	100
Anti-thymocyte globulin use	41	40

Abbreviation: ECP, extracorporeal photopheresis.

^a $p = 0.11$ when comparing treatment regimens between cohorts.

assignment, the slopes of FEV1 decline pre-enrolment were much steeper ($p = 0.004$) in the ECP cohort (-192 ± 167 ml/month) when compared to the observation cohort (-46 ± 46 ml/month).

3.4 | Outcomes

3.4.1 | Primary outcome: Assessment of spirometric “response”

The primary outcome of the registry study with respect to the change in the rate of FEV1 decline could only be assessed in a subset of enrolled patients that had at least six monthly FEV1 values after ECP treatment as follows: 63% (19 of 30) of ECP cohort subjects and 71% (5 of 7) Crossover subjects. At 6 months, 19 evaluable ECP cohort subjects demonstrated a 93% decrease (from -136 to -10 ml/month, $p = 0.0002$) in the mean rate of FEV1 decline after ECP (Table 4, Figure 2). In contrast, only a trend ($p = 0.29$) in reduced mean rate of FEV1 decline (65%) 6 months after ECP was observed in 5 initially assigned Observation patients who crossed over to ECP treatment (Table 4).

Using a 50% or more decrease in the rate of FEV1 decline as a response criteria, 95% (18 of 19 evaluable subjects) of subjects initially assigned to ECP treatment responded to ECP. A statistically ($p = 0.001$) lower percentage (25% or 2 of 8 evaluable subjects) of Observation subjects responded to ECP. Of six Observation subjects who crossed over and received ECP treatment, only five were evaluated as one subject did not have enough FEV1 values after crossover due to early mortality. Of these 5 evaluable Crossover subjects, two demonstrated no change in the rate of FEV1 decline at 6 months after ECP (Table 4, see Figures E2 and E3 for Crossover subjects). Of three evaluable non-



TABLE 3 Spirometry FEV₁ values prior to and after enrolment between non-randomised cohorts allocated to either ECP treatment or observation based on spirometric criteria

	All patients (n = 44)	ECP cohort (n = 31)	Observation cohort (n = 13)	
			Crossover (n = 7)	No crossover (n = 6)
Baseline FEV1 after transplant ^a	2.7 ± 0.9	2.8 ± 0.9	2.7 ± 0.5	1.7 ± 0.7
First screening FEV1	2.0 ± 0.8	2.2 ± 0.8	1.8 ± 0.8	1.2 ± 0.4 ^b
Enrolment	1.4 ± 0.6	1.4 ± 0.6	1.6 ± 0.6	1.2 ± 0.4
Last FEV1 after enrolment	1.0 ± 0.5	1.0 ± 0.6	1.0 ± 0.4	1.2 ± 0.4

Note: FEV1 in L and data expressed as mean ± SD.

Abbreviation: ECP, extracorporeal photopheresis.

^aBaseline values based on data from 40 subjects.

^bp < 0.01 when compared to ECP cohort.

TABLE 4 Rates of FEV₁ decline prior to and after enrolment between non-randomised cohorts allocated to either ECP treatment or observation based on spirometric criteria

Time after enrolment	ECP cohort (n = 30)	Observation cohort (n = 13)	
		Crossover (n = 6) ^a	No Crossover (n = 6)
0 (ECP: n = 30, CO: n = 7, No CO: n = 6)			
FEV1 rate of decline	-148 ± 154	-38 ± 51	-1.2 ± 18 ^{b,c}
p value	0.009 ± 0.01	0.12 ± 0.08 ^b	0.32 ± 0.15 ^{b,c}
0+ months (ECP: n = 19, CO: n = 5) ^d			
FEV1 rate of decline	-136 ± 117	-81 ± 36	
p value	0.01 ± 0.01	0.08 ± 0.11	
6 months (ECP: n = 19, CO: n = 5) ^d			
FEV1 rate of decline	-10 ± 58 ^e	-28 ± 98	
p value	0.18 ± 0.13 ^e	0.1 ± 0.12	

Note: Linear regression derived values (slope and p values) from FEV₁ versus time relationship. Slopes (ml/month) and p values expressed as mean ± SD. 0+ refers to either at enrolment (ECP cohort) or at Crossover (observation cohort).

Abbreviations: CO, observation patients who cross over to ECP treatment; ECP, extracorporeal photopheresis.

^aOnly 6 of 7 crossover subjects included since one did not receive ECP.

^bp < 0.05 when compared to ECP arm.

^cp < 0.05 when compared to Crossover.

^dOnly 19 of 30 ECP subjects and 5 of 7 crossover subjects included based on available FEV₁ values at 6 months for calculation of FEV₁ rate of decline.

^ep < 0.05 when compared to Time 0.

crossover Observation cohort subjects, no patient (0%) had a change in their FEV1 rate of decline as they continued to have a stable FEV₁ pattern for at least 3 months after enrolment (i.e., no change in FEV1 rate of decline – see Figure E4 for all non-Crossover subjects).

3.5 | Secondary outcomes

3.5.1 | Assessment of spirometric enrolment criteria to identify patients who responded to ECP

Of 36 patients who received ECP (30 ECP and 6 Crossover), 24 patients (19 ECP Treatment and 5 Observation with crossover) had six monthly post-enrolment FEV₁ values. Of six Observation patients, three had at least three monthly post-enrolment FEV₁ values. Data

from these 27 patients were used to assess the predictive capacity (using Bayes Theorem derived predictive indices like sensitivity) of the spirometric enrolment criteria to identify response to ECP (the spirometric primary endpoint). Predictive indices for a response to ECP using the initial assignment as directed by the spirometric enrolment criteria are as follows: Sensitivity: 90%, Specificity: 85%, Positive Predictive Value: 94%, and Negative Predictive Value: 75% (see Figure 3).

3.5.2 | Mortality analysis

Of 44 subjects, 32% (12 ECP and 2 Crossover) expired within 6 months of enrolment while 43% (15 ECP and 3 Crossover and one Observation) expired within 12 months of enrolment. There were no treatment related deaths as adjudicated by our DSMB; a complete

description of the etiology of mortality between cohorts at various time periods is summarised in Table 5. The most common primary cause of death among all non-survivors (both ECP cohort and Observation cohort subjects) was respiratory or graft failure (90%). There was no difference in mortality between the two cohorts ($p = 0.2$). Although a higher numeric percentage of subjects initially assigned to ECP treatment ($n = 31$) expired at both 6 (ECP: 39% vs. Obs: 23%) and 12 (ECP: 48% vs. Obs: 31%) months after enrolment when compared to subjects initially assigned to Observation ($n = 13$), these trends were not significant $p = 0.49$ and $p = 0.34$, respectively. These findings were not unexpected as they were most likely related to subject assignment in a non-random fashion using spirometry-based

criteria which assigned subjects to ECP treatment based on higher rates of FEV1 decline.

3.5.3 | Comparison of spirometry between survivors and non-survivors

To evaluate the potential effects of reduced lung function on survival, FEV₁ values were compared at several time points between patients who survived for either 6 or 12 months (Survivors) versus those who expired in that period of time (Non-survivors). Specifically, 14 and 19 subjects who expired had higher mean FEV₁ at the first screening FEV₁ prior to enrolment when compared lower mean FEV₁ in 40 and 36 subjects who survived ($p = 0.01$) 6 and 12 months after enrolment, respectively. (Table S1, Figure E1). However, similar mean FEV₁ values were observed at baseline and at enrolment between Survivors and non-survivors (Table S1). These findings were explained by the comparison of rate of decline in FEV₁ between survival cohorts. Significantly ($p = 0.009$) higher rates of FEV₁ decline were observed in the non-survivors (-232 ± 195 ml/month) when compared to the survivors (-101 ± 110 ml/month) at 6 months and similarly at 12 months after enrolment ($p = 0.002$) (Table S1). When all relevant covariates were included in a multivariate logistic regression analysis to identify potential variables associated with either early mortality or 12 month mortality, only pre-enrolment FEV₁ rate of decline in lung function was associated with both early (6 month) ($p = 0.005$) and 12 month mortality ($p = 0.005$).

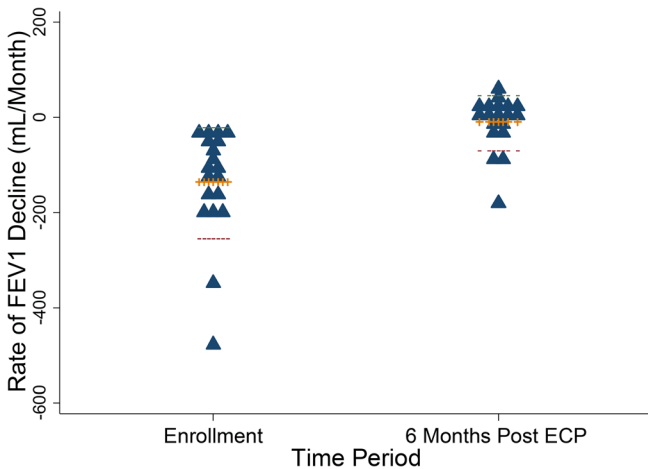


FIGURE 2 Illustrates a density distribution of FEV₁ rate of decline (slope in ml/month) values along the y-axis for the 20 extracorporeal photopheresis (ECP) Treatment cohort patients before and after ECP treatment at the following monthly time periods (x-axis): at enrolment prior to ECP and 6 months after Enrolment [Color figure can be viewed at wileyonlinelibrary.com]

3.6 | The impact of requisite time for BOS diagnosis on enrolment FEV₁

To assess the impact of the requisite time for BOS diagnosis on lung function at enrolment, mean FEV₁ values obtained during the 6 month

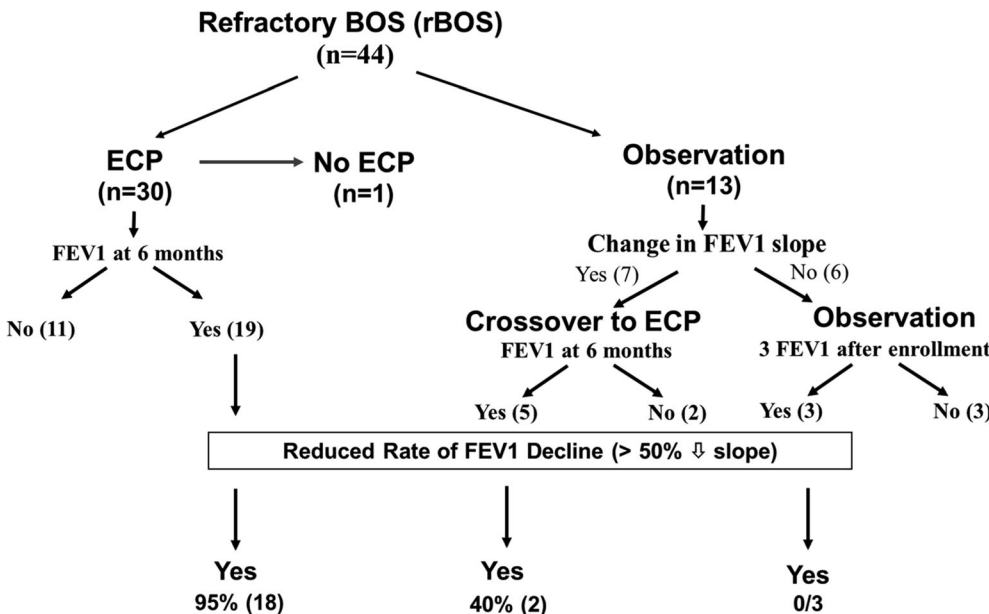


FIGURE 3 A flow diagram that illustrates patient enrolment, assignment and crossover to extracorporeal photopheresis (ECP) treatment. It also designates how many patients an adequate number of FEV₁ values to enable calculation of rates of decline



TABLE 5 Mortality after enrolment between non-randomised cohorts allocated to either ECP treatment or observation based on spirometric criteria

Months from enrolment	FEV1 decline (ml/month) ^a	Terminal FEV1	Mortality (days after enrolment)	Mortality ^c	ECP cohort (n = 31) ^b	Obs cohort (n = 13)
6	-246 ± 194	805 ± 182	86 (17-182)	Respiratory failure Pneumonia CVC sepsis Total	11 (36%) 1 (3%) 1 (3%) 12 (39%)	3 (23%) 3 (23%)
6-12	-117 ± 58	868 ± 365	235 (213-268)	Respiratory failure Pneumonia CVC sepsis Total	2 (7%) 1 (3%) 1 (3%) 3 (10%)	1 (8%) 1 (8%)
12	-212 ± 177	819 ± 223	118 (17-268)	Respiratory failure Pneumonia CVC sepsis Total	13 (42%) 1 (3%) 1 (3%) 15 (48%)	4 (31%) 4 (31%)

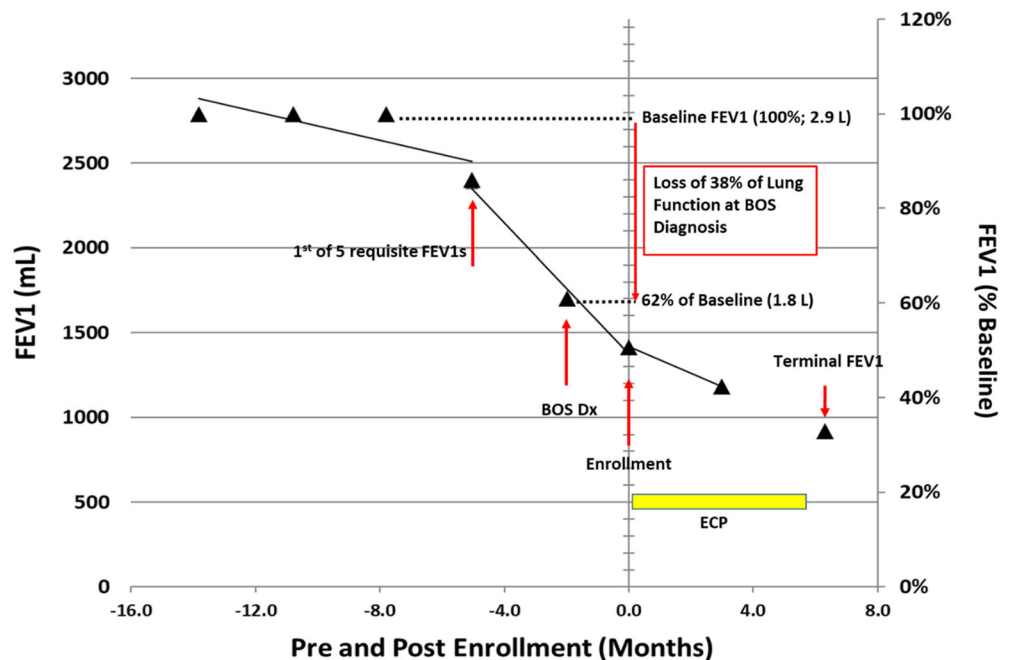
Abbreviations: ECP, subjects assigned to extracorporeal photopheresis; Obs, subjects assigned to observation with potential for crossover to ECP.

^aRate of FEV1 decline calculated at enrolment. Terminal FEV1 (ml) was defined as last measured FEV1 before expiration in 18 patients (results do not include the FEV1 in the subject who expired from Sepsis who had a 2400 ml FEV1).

^bOne subject did not receive ECP and the mean # ECP procedures performed in 30 patients was 12 (range 7-20).

^cMortality was categorized into three etiologic categories as related to pneumonia, central venous catheter (CVC) related sepsis, and/or respiratory failure which included either acute or chronic designations by enrolling physicians while one patient had pneumonia concurrent with respiratory failure—the % values were calculated using the # of patients in the respective cohort as the denominator. The most common primary cause of death among all non-survivors (both ECP cohort and observation cohort subjects) was respiratory or graft failure (17/19 or 90%).

FIGURE 4 Plots mean FEV1 values obtained during the peri-enrolment period for a series of 18 patients extracorporeal photopheresis (ECP) cohort subjects who were treated with ECP and who had a diagnosis of bronchiolitis obliterans syndrome (BOS) within the 6 month FEV1 screening period revealed that patients had lost 38% of their lung function by the time that BOS was diagnosed with even further reduction by the time of ECP initiation [Color figure can be viewed at wileyonlinelibrary.com]



period prior to and at enrolment were calculated for 18 patients who had a diagnosis of BOS within the 6 month FEV₁ screening period. Figure 4 illustrates that patients had lost an average of 38% of their lung function at the time of BOS diagnosis (on average at 2 months prior to enrolment), with further reduction to an average of 50% of baseline lung function by enrolment. Accordingly, the mean time for diagnosis on average ~3-

4 months. This information prompted us to send a survey to our enrolling centres requesting the typical institutional frequency for laboratory spirometry for the BOS surveillance population. A review of responses from 6 of 10 enrolling centres revealed a median spirometry monitoring frequency of 3 months (range: 1-6 months) for enrolled patients after the first year of transplant at our enrolling centres.

4 | DISCUSSION

Although ECP was associated with a 93% reduction in the rate of decline in FEV₁ at 6 months after ECP initiation in our non-randomised registry study, we also observed a concerning early mortality rate. Safety of the ECP procedure was assessed by our DSMB which adjudicated that none of the fatal outcomes were related to ECP and local investigators characterised that 92% were due to end-stage pulmonary dysfunction. Although higher than expected mortality was observed after enrolment in patients non-randomly assigned to ECP Treatment based on spirometry criteria, these findings were related to the more aggressive nature of BOS in patients assigned to ECP treatment (i.e., statistically significant fourfold greater rate of FEV₁ decline in patients assigned to ECP treatment) which was shown to be the most important and only factor associated with mortality; this artefact was clearly related to the study design since spirometric criteria were used to assign patients to treatment in a non-randomised fashion with those assigned to ECP having a resultant much greater rate of FEV₁ decline. With respect to our study design, our current analysis revealed that our spirometric criteria enabled accurate identification of responders to ECP. In the Observation cohort involving patients with low rates of FEV₁ decline, only two subjects (25%) of eight evaluable subjects (crossover and non-crossover) had a 50% change in the enrolment FEV₁ rate of decline. Poor treatment response in a slow FEV₁ decline phenotype was originally described by Jackson et al. in a large series of patients with BOS²² and more recently confirmed with another analysis.¹⁷ We also confirmed that the current spirometric enrolment criteria can detect patients who respond to ECP and should not have a substantial clinical impact with respect to delay in ECP treatment since the time for crossover was nominal (18 days) with minimal loss of FEV₁ volume in that period.

The findings of low FEV₁ values at BOS diagnosis (Figure 4) and the higher rates of decline in FEV₁ in non-survivors highlights the potential importance of early detection and expedited management of BOS with ECP as first line therapy rather than use for refractory disease to arrest disease progression before lung function reaches a critically low level. Accordingly, we have modified our CMS approved study to now include a randomised controlled trial (RCT) arm that involves use of ECP as first line therapy when compared to local standard of care management of BOS.

Delays in detection of BOS may also be an important factor that led to higher early mortality in our series. Generally, FEV₁ measurements are made biweekly or monthly during the first year following lung transplant, with variable extension to every 3, 6, or 12 months between institutions,²³ despite a fairly consistent annual BOS incidence of at least 7%–8% per year.² Data from our previous publication¹⁶ demonstrate that this approach results in loss of up to 1 L of FEV₁ volume at the diagnosis of BOS as well as a prolonged delay (mean = 401 days) for ECP initiation at our institution.

Accordingly, earlier detection of BOS via frequent spirometry coupled with earlier use of ECP or other new therapies may result in better functional status and prolonged survival for either primary or refractory BOS. However, use of a frequent monitoring schedule

(every 4–8 weeks) for conventional laboratory spirometry over a long surveillance period (i.e., up to 15 years) may not be feasible for many patients, especially for patients who live far from their treatment or diagnostic facilities or who are not compliant with laboratory-based spirometry predicated on safety concerns in the setting of the current COVID-19 pandemic. Home Spirometry monitoring systems can lead to early detection of acute rejection and infection in lung transplant recipients,^{24–27} and may also be preferable if these systems can automatically transmit spirometric²⁶ and symptom^{26,28} data to facilitate discrimination of variance results between infections versus rejection.

Despite our findings that support use of ECP in lung transplant recipients with BOS, there were several limitations to our registry study. The most notable involved the use of ECP for refractory BOS rather than at initial diagnosis of BOS, but also includes lack of a control comparator cohort to assess important outcomes, premature assessment of efficacy of ECP to attenuate the rate of decline of lung function, lack of uniform prophylactic and BOS treatment anti-rejection regimens, the lack of use of a standardised approach for early detection of BOS, and the inclusion of only Medicare patients. Although Medicare patients are typically older aged, age was not identified as a confounder with respect to attenuation of the rate of FEV₁ decline by ECP or survival. These limitations and our preliminary analyses prompted us to revise the study to promote early detection (i.e., with use of an automated Home Spirometry Method) and treatment of refractory BOS at early stages and to evaluate all of the outcomes CMS had previously outlined: the impact of ECP on rate of decline in FEV₁, survival and quality of life in a RCT arm using ECP as first-line therapy when compared to local Standard of Care.

In summary, these preliminary analyses support earlier detection and treatment of BOS especially in patients who have a rapid decline in lung function. In light of the preliminary suggestion of ECP's efficacy in reducing the rate of decline of lung function, we are modifying our study to add an RCT arm that will enrol patients with newly diagnosed BOS. Based on these findings, we will continue to utilise our spirometric criteria to enrol patients who are more likely to respond to ECP.

ACKNOWLEDGMENTS

Funded by Therakos[®], Inc., a Mallinckrodt Pharmaceuticals company (NCT02181257). The US Centers for Medicare and Medicaid Services (CMS) reimbursed costs of extracorporeal photopheresis therapy for enrolled participants in this CMS-approved study under its Coverage with Evidence Development authority (CAG-00324R2).

CONFLICT OF INTEREST

Relationships with entities related to the topic listed below: Chadi Hage, MD—None. Julia Klesney-Tait, MD—None. Keith Wille, MD—None. Selim Arcasoy, MD, MPH—None. Gordon Yung, MD—Financial interest that exceeds \$5000 with Industry sponsor. Marshall Hertz, MD—None. Kevin Chan, MD—None. Matt Morrell, MD—None. Hilary Goldberg, MD—Subcontract for CMS and Therakos, Inc sponsored study. Suresh Vedantham, MD—Investigator of study funded by both Medicare and Therakos/Mallinckrodt (outlined above). Mary Clare

Derfler RN—Project Leader of study funded by both Medicare and Therakos/Mallinckrodt (outlined above). Paul Commean, BEE—Investigator of study funded by both Medicare and Therakos/Mallinckrodt (outlined above). Keith Berman, MPH/MBA—None. Edward Spitznagel, PhD—Statistician and Investigator of study funded by both Medicare and Therakos/Mallinckrodt (outlined above). Jeff Atkinson, MD—None. George Despotis, MD—PI of study funded by both Medicare and Therakos/Mallinckrodt (outlined above).

AUTHOR CONTRIBUTIONS

Chadi Hage MD: Participated in performance of the research, enrollment of patients, review and editing of the paper. **Julia Klesney-Tait, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Keith Wille, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Selim Arcasoy, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Gordon Yung, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Marshall Hertz, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Kevin Chan, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Matt Morrell, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Hilary Goldberg, MD:** Participated in performance of the research, enrollment of patients, review and editing of the paper. **Suresh Vedantham, MD:** Participated in research design, editing of the paper. **Clare Derfler, RN:** Participated in performance of the research, review and editing of the paper. **Paul Commean, BEE:** Participated in data management, performance of the research, review and editing of the paper. **Keith Berman, MPH/MBA:** Participated in guidance for data analysis, editing of the paper. **Edward Spitznagel, PhD:** Participated performance of the research, in editing of the paper, data analysis. **Jeff Atkinson, MD:** Participated in review and editing of the paper. **George Despotis, MD:** Participated in research design, performance of the research, data analysis, writing of the paper.

REFERENCES

- Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment—a consensus report from the pulmonary council of the ISHLT. *J Heart Lung Transplant.* 2019;38(5):493-503.
- Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-second official adult lung and heart-lung transplantation report—2015; focus theme: early graft failure. *J Heart Lung Transplant.* 2015;34(10):1264-1277.
- Verleden SE, Vasilescu DM, McDonough JE, et al. Linking clinical phenotypes of chronic lung allograft dysfunction to changes in lung structure. *Eur Respir J.* 2015;46(5):1430-1439.
- Heng D, Sharples LD, McNeil K, Stewart S, Wreghitt T, Wallwork J. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. *J Heart Lung Transplant.* 1998;17(12):1255-1263.
- Finlen Copeland CA, Snyder LD, Zaas DW, Turbyfill WJ, Davis WA, Palmer SM. Survival after bronchiolitis obliterans syndrome among bilateral lung transplant recipients. *Am J Respir Crit Care Med.* 2010;182(6):784-789.
- Edelson R, Facktor M, Andrews A, Lutzner M, Schein P. Successful management of the Sézary syndrome. Mobilization and removal of extravascular neoplastic T cells by leukapheresis. *N Engl J Med.* 1974;291(6):293-294.
- Foss FM, DiVenuti GM, Chin K, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplant.* 2005;35(12):1187-1193.
- Greinix HT, Volc-Platzer B, Kalhs P, et al. Extracorporeal photochemotherapy in the treatment of severe steroid-refractory acute graft-versus-host disease: a pilot study. *Blood.* 2000;96(7):2426-2431.
- Barr ML, Meiser BM, Eisen HJ, et al. Photopheresis for the prevention of rejection in cardiac transplantation. Photopheresis transplantation study Group. *N Engl J Med.* 1998;339(24):1744-1751.
- Slovic BS, Loyd JE, King LE. Photopheresis for chronic rejection of lung allografts. *N Engl J Med.* 1995;332(14):962.
- O'Hagan AR, Stillwell PC, Arroliga A, Koo A. Photopheresis in the treatment of refractory bronchiolitis obliterans complicating lung transplantation. *Chest.* 1999;115(5):1459-1462.
- Salerno CT, Park SJ, Kreykes NS, et al. Adjuvant treatment of refractory transplant rejection with extracorporeal photopheresis. *J Thorac Cardiovasc Surg.* 1999;117(6):1063-1069.
- Villanueva J, Borhade SM, Robinson JA, Husain AN, Garrity ER. Extracorporeal photopheresis for the treatment of lung allograft rejection. *Ann Transplant.* 2000;5(3):44-47.
- Benden C, Speich R, Hofbauer GF, et al. Extracorporeal photopheresis after lung transplantation: a 10-year single-center experience. *Transplantation.* 2008;86(11):1625-1627.
- Jaksch P, Scheed A, Keplinger M, et al. A prospective interventional study on the use of extracorporeal photopheresis in patients with bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant.* 2012;31(9):950-957.
- Morrell MR, Despotis GJ, Lublin DM, Patterson GA, Trulock EP, Hachem RR. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant.* 2010;29(4):424-431.
- Karnes HE, Schindler EI, Morrell M, et al. Factors associated with mortality and response to extracorporeal photopheresis in lung allograft recipients with bronchiolitis obliterans syndrome. *Transplantation.* 2019;103(5):1036-1042.
- CMS Transmittal. <https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R2551CP.pdf>. Accessed October 1, 2012.
- CMS Protocol Number CAG-00324R2; ClinicalTrials.gov identifier: NCT02181257.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-338.
- Welsh CH, Wang TS, Lyu DM, et al. An international ISHLT/ATS/ERS clinical practice guideline: summary for clinicians. Bronchiolitis obliterans syndrome complicating lung transplantation. *Ann Am Thorac Soc.* 2015;12(1):118-119.
- Jackson CH, Sharples LD, McNeil K, Stewart S, Wallwork J. Acute and chronic onset of bronchiolitis obliterans syndrome (BOS): are they different entities? *J Heart Lung Transplant.* 2002;21(6):658-666.
- Robson KS, West AJ. Improving survival outcomes in lung transplant recipients through early detection of bronchiolitis obliterans: daily home spirometry versus standard pulmonary function testing. *Can J Respir Ther.* 2014;50(1):17-22.
- Bjørntuft O, Johansen B, Boe J, Foerster A, Holter E, Geiran O. Daily home spirometry facilitates early detection of rejection in single lung transplant recipients with emphysema. *Eur Respir J.* 1993;6(5):705-708.

25. Kugler C, Fuehner T, Dierich M, et al. Effect of adherence to home spirometry on bronchiolitis obliterans and graft survival after lung transplantation. *Transplantation*. 2009;88(1):129-134.
26. Finkelstein SM, Scudiero A, Lindgren B, Snyder M, Hertz MI. Decision support for the triage of lung transplant recipients on the basis of home-monitoring spirometry and symptom reporting. *Heart Lung*. 2005;34(3):201-208.
27. Wagner FM, Weber A, Park JW, et al. New telemetric system for daily pulmonary function surveillance of lung transplant recipients. *Ann Thorac Surg*. 1999;68(6):2033-2038.
28. Wang W, Finkelstein SM, Hertz MI. Automatic event detection in lung transplant recipients based on home monitoring of spirometry and symptoms. *Telemed J E Health*. 2013;19(9):658-663.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: The EPI Study Group, Hage CA, Klesney-Tait J, Wille K, et al. Extracorporeal photopheresis to attenuate decline in lung function due to refractory obstructive allograft dysfunction. *Transfusion Medicine*. 2021; 31:292-302. <https://doi.org/10.1111/tme.12779>