Original Research Article

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Significance of autoimmune disease in severe pulmonary hypertension complicating extensive pulmonary fibrosis: a prospective cohort study

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Abstract

The association of autoimmune disease (AI) with transplant-free survival in the setting of *severe* Group 3 pulmonary hypertension and *extensive* pulmonary fibrosis remains unclear. We report cases of severe pulmonary hypertension (mean pulmonary artery pressure $\geq$35 mmHg *and* right ventricular dysfunction) and extensive pulmonary fibrosis after pulmonary arterial hypertension-specific therapy. We used multivariate regression to determine the clinical variables associated with transplant-free survival. Of 286 screened patients, 55 demonstrated severe pulmonary hypertension and extensive pulmonary fibrosis and were treated with parenteral prostacyclin therapy. The (+)AI subgroup (n = 34), when compared to the (–)AI subgroup (n = 21), was more likely to be female (77% versus 19%) and younger (58.7 ± 12.1 versus 66.0 ± 10.7 years), and revealed lower forced vital capacity (absolute) (1.9 ± 0.7 versus 2.9 ± 1.1 L), higher D_LCO (% predicted) (31.1 ± 15.2 versus 23.2 ± 8.0), and increased unadjusted transplant-free survival (1 year (84.6 ± 6.3% versus 45 ± 11.1%)), 3 years (71 ± 8.2% versus 28.6 ± 11.9%), and 5 years (47.6 ± 9.6% versus 6.4 ± 8.2%); (p = 0.01)). Transplant-free survival was unchanged after adjusting for age and gender. The pulmonary hemodynamic profiles improved after parenteral prostacyclin therapy, independent of AI status. The baseline variables associated with mortality included age at pulmonary hypertension diagnosis (heart rate (HR) 1.23 (confidence interval (CI) 1.03–1.47); p = 0.02) and presence of AI (HR 0.26 (confidence interval (CI) 0.10–0.70); p < 0.01). Gas exchange was not adversely affected by parenteral prostacyclin therapy. In the setting of *severe* Group 3 pulmonary hypertension and *extensive* pulmonary fibrosis treated with pulmonary arterial hypertension-specific therapy, AI is independently associated with increased transplant-free survival. Pulmonary hypertension/pulmonary fibrosis associated with AI should be considered in future clinical trials of pulmonary arterial hypertension-specific therapy in Group 3 pulmonary hypertension.

Keywords

pulmonary fibrosis, pulmonary hypertension, autoimmune disease

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Introduction

Pulmonary hypertension (PH) can complicate pulmonary fibrosis (PF) and is an independent risk factor for mortality. The mortality in PH/PF patients is greater when compared to other PH groups.[1] Despite this association, clinical trials targeting PH in the setting of PF have either failed to show

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efficacy[2–5] or have demonstrated increased morbidity and/or mortality.[2,6,7] Several potential explanations for the uniformly negative results have been proposed,[8] including patient selection, severity of PH, trial design, and choice of pulmonary arterial hypertension (PAH)-specific therapy. In addition, worsening gas exchange due to PAH-specific therapy remains a concern in the setting of PH/PF where hypoxemia is almost uniformly present at baseline.[8]

Within the broad group of PF etiologies, autoimmune disease (AI) is unique in that (i) it may be associated with either Group 1 PAH or Group 3 PH/PF and (ii) Group 1 PAH associated with AI generally demonstrates a favorable responsive to PAH-specific therapy.[9] However, it is unknown whether AI itself is a prognostic variable in PH/PF. The purpose of this study was to determine if AI is associated with the transplant-free survival of a severe Group 3 PH cohort with right ventricle (RV) dysfunction and extensive PF after systematic PAH-specific therapy.

Patients and methods

This prospective cohort study was approved by the Institutional Review Board at our University (IRB# 12-000738). PH/PF patients referred to the University of California Los Angeles (UCLA), Pulmonary Vascular Disease clinic between 6 January 2011 and 6 January 2017 were considered for study enrollment. Based on clinical experience[10] at the time, the UCLA PH program (prior to the study enrollment period) began prospectively offering systematic treatment with a parenteral prostacyclin (treprostinil), irrespective of PF etiology or extent of background PAH-specific (non-prostanoid) therapy. Parental prostacyclin therapy for PH/PF was only offered in the context of all of the following: (i) severe precapillary PH (mean pulmonary artery pressure (mPAP) $\geq$35 mmHg, pulmonary artery wedge pressure (PAWP) $\leq$15 mmHg); (ii) extensive PF as previously defined[11] (based on high resolution chest tomography (HRCT) chest performed within three months of the enrollment date); and (iii) echocardiographic RV dysfunction (defined as tricuspid annular planar systolic excursion (TAPSE) <1.8 cm; right ventricle fractional area of change (RV-FAC) <35%; *and* flattening of the interventricular septum during systole and/or diastole[12]). The screening echocardiogram was performed within one month of study enrollment. All patients were diagnosed with Group 3 PH[13] after a comprehensive evaluation based on the recommended diagnostic algorithm.[14] PH diagnosis was the date of the historical right heart catheterization (RHC) which first demonstrated any degree of precapillary PH (mPAP $\geq$25 mmHg, PAWP $\leq$15 mmHg, and pulmonary vascular resistance (PVR) $\geq$3 Wood units), and this RHC may or may not have been performed at our institution. Study enrollment was defined as the date of the RHC demonstrating severe PH (mPAP $\geq$35 mmHg[13] and PAWP $\leq$15 mmHg with or without background PAH-specific therapy), thus qualifying the patient for parenteral prostacyclin therapy at our institution. Patients were classified by time from PH diagnosis to study enrollment as either incident ($\leq$6 months) or prevalent (>6 months). Patients were followed at least every three months, or earlier based on clinical status until either death, lung transplantation, or censor date (5 January 2018). Causes of death (including autopsy data if available) are reported in the context of a prior classification scheme.[15] A comprehensive list of inclusion and exclusion criteria can be found in the Supplementary file. The PH/PF cohort was divided into two groups for subsequent analyses, based on the presence or absence of AI using standard definitions[16,17] (Supplementary file).

Statistical analysis

This prospective cohort design study follows the recommended guidance on reporting results and controlling for confounding variables in causal inference studies[18] (Supplementary file). Univariate and multivariate Cox proportional hazard modeling was used to determine which baseline variables were associated with transplant-free survival. Time from initiation of parenteral prostacyclin to either transplant, death, or censor date (5 January 2018) were used as endpoints. There were no missing data with regard to any of the baseline variables used in the regression analyses. The assumption of proportional hazards was confirmed graphically by the analysis of Schoenfeld residuals.[19] Unadjusted Kaplan–Meier plots were constructed for the entire cohort, and for the subgroups with and without AI. Since gender and age were disparate between AI subgroups, a weighted Cox proportional hazards model was fit in order to estimate transplant-free survival curves for the (+)AI and (–)AI subgroups, adjusting for age and gender confounding (Supplementary file). When available, hemodynamic parameters from first and second RHCs were compared using Student's paired t-test. No imputation was performed for missing data with regard to follow-up RHC data. Comparison of (+)AI and (–)AI subgroups was done using a Chi-square test and a two-tailed Student's t-test for categorical and continuous variables, respectively. No patients were lost to follow-up. p-Values <0.05 were considered statistically significant. The adjusted survival curves were computed in R[20] using the R package survival.[21,22] All other statistical analyses were performed using SAS.

Results

A total of 286 subjects with extensive PF and a positive screening echocardiogram for PH were referred to the UCLA PH clinic over a six-year period. After appropriate exclusions (Fig. 1), 55 subjects with extensive PF and severe precapillary PH (mPAP $\geq$35 mmHg) with RV dysfunction remained eligible for enrollment.

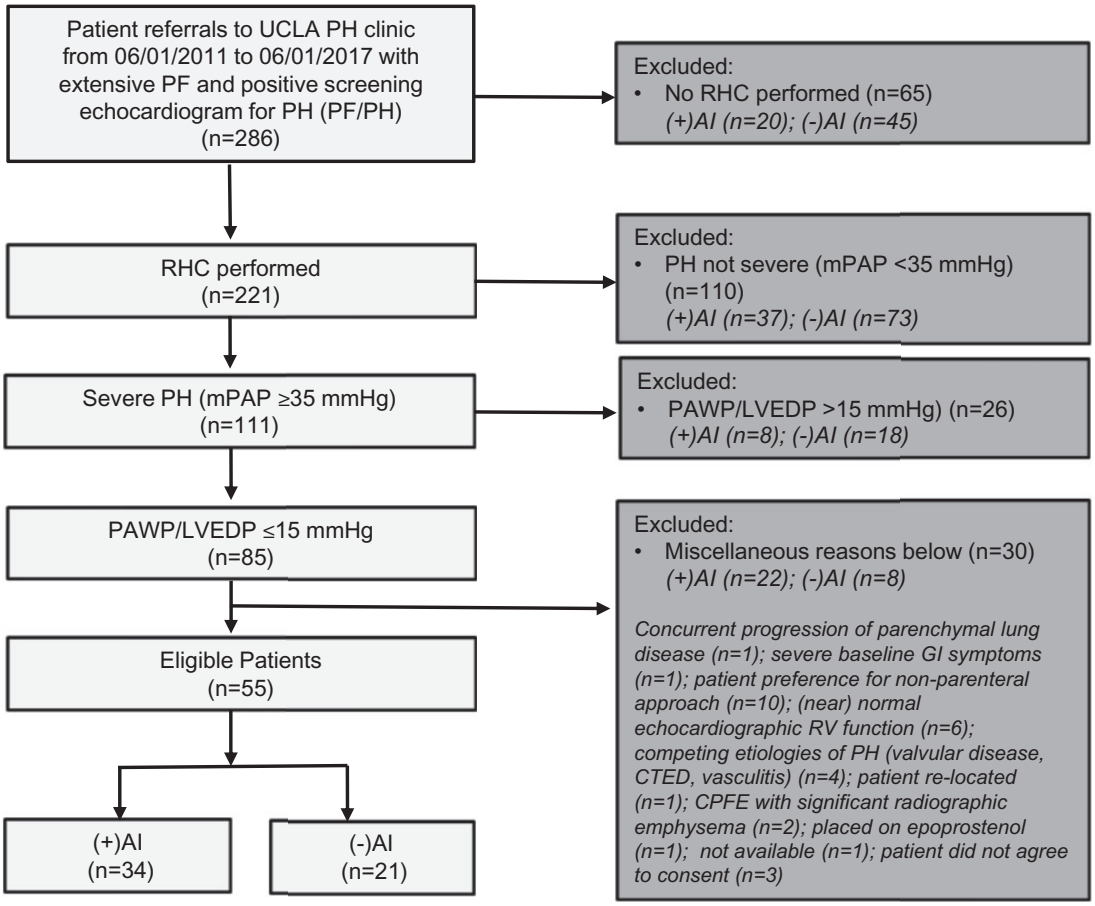

Fig. 1. Patient selection flow diagram. PF: pulmonary fibrosis; PH: pulmonary hypertension; PH/PF: combined pulmonary hypertension and pulmonary fibrosis; (+)AI: pulmonary hypertension and pulmonary fibrosis with autoimmune disease; (–)AI: pulmonary hypertension and pulmonary fibrosis without autoimmune disease; RHC: right heart catheterization; PAWP: pulmonary artery wedge pressure; LVEDP: left ventricular end-diastolic pressure; mPAP: mean pulmonary arterial pressure; IPAF: interstitial pneumonia with autoimmune features; CTED: chronic thromboembolic disease; CPFE: combined pulmonary fibrosis and emphysema.

Study cohort demographics

This PH/PF cohort (n = 55) had the following baseline characteristics: mean age (±SD) 61.5 ± 12.1 years, female-predominant (55%; n = 30), primarily incident cases (n = 40; 73%), and the majority (n = 38; 69%) were on oral background PAH-specific therapy (monotherapy (n = 28); dual therapy (n = 10)) at the time of study enrollment. The majority of subjects (89%) required oxygen supplementation at baseline (5.0 + 8.3 L/min (mean+SD)). Pulmonary function demonstrated moderate restriction (forced vital capacity (FVC) 62 ± 21(% predicted)), severe loss of diffusing capacity (28 ± 13(% predicted)), and increased FVC/D_LCO ratio (2.6 ± 1.2). The baseline pulmonary hemodynamics showed severe precapillary PH with mPAP 48 ± 9 mmHg and PVR 9.9 ± 5.3 Wood units. All baseline demographic, hemodynamic, pulmonary function, gas exchange, and background PAH therapy data are available in Table 1. The median patient follow-up was 2.2 years.

Autoimmune disease

The entire cohort (n = 55) was divided into (+)AI (n = 34) and (–)AI (n = 21) subgroups (Table 1). Supplement Table 1 outlines the types of PF[23] which comprised the (–)AI subgroup. Of the (+)AI subgroup (n = 34), the majority had an established AI[16] (n = 27) comprised of the following diagnoses: systemic sclerosis spectrum of disease (n = 21); mixed connective tissue disease (n = 2); rheumatoid arthritis (n = 3); and dermatomyositis/polymyositis (n = 1). The remaining subjects (n = 7) met ATS/ERS criteria for interstitial pneumonia with autoimmune features (IPAF)[17] (Supplement Table 2). When compared to the (–)AI subgroup, the (+)AI subgroup were younger (58.7 ± 12.1 versus 66 ± 10.7 years; $p = 0.02$), female predominant (77% versus 19%; $p < 0.01$), lower hemoglobin (12.5 ± 2.1 versus 14.3 ± 2.4; $p = 0.02$), and more background PAH-specific therapy (85% versus 43%). Pulmonary function tests in the (+)AI group demonstrated lower FVC (absolute) (1.9 ± 0.7 versus 2.9 ± 1.1 L; $p < 0.01$), lower forced expiratory volume in 1 s

Table 1. Baseline demographics, hemodynamics, and pulmonary function for entire pulmonary hypertension with pulmonary fibrosis (PH/PF) cohort (n = 55) and the subgroups with and without autoimmune disease (AI).

Variable	Entire Cohort (n = 55)	(+)AI (n = 34)	(–)AI (n = 21)	p-Value
Age, years	61.5 ± 12.10	58.67 ± 12.12	66.08 ± 10.71	**0.02**
Gender – n (%)				**<0.01**
Male	25 (45.4)	8 (23.54)	17 (80.95)	
Female	30 (54.6)	26 (76.47)	4 (19.05)	
FEV1 (L)	1.75 ± 0.61	1.54 ± 0.43	2.09 ± 0.72	**<0.01**
FEV1 (% predicted)	61.6 ± 21.4	58.18 ± 21.95	67.19 ± 19.58	0.12
FVC (L)	2.25 ± 0.96	1.88 ± 0.66	2.86 ± 1.07	**<0.01**
FVC (% predicted)	62.0 ± 20.7	58.28 ± 19.71	68.05 ± 21.27	0.08
FEV1/FVC ratio	86.7 ± 14.5	89.98 ± 13.60	81.33 ± 14.75	**0.03**
D_LCO (mL/min/mmHg)	6.77 ± 3.04	7.34 ± 3.41	5.87 ± 2.14	0.06
D_LCO (% predicted)	28.0 ± 13.4	31.10 ± 15.24	23.21 ± 7.96	**0.01**
FVC/D_LCO ratio	2.57 ± 1.20	2.17 ± 1.00	3.21 ± 1.24	**<0.01**
mRAP (mmHg)	9.93 ± 4.89	9.85 ± 5.14	10.05 ± 4.59	0.88
sPAP (mmHg)	80.3 ± 17.5	81.65 ± 19.23	78.19 ± 14.34	0.48
dPAP (mmHg)	32.2 ± 7.8	31.68 ± 7.19	33.10 ± 8.79	0.51
mPAP(mmHg)	48.05 ± 9.16	48.24 ± 9.52	47.76 ± 8.77	0.85
PAWP (mmHg)	11.9 ± 3.1	12.0 ± 3.45	11.81 ± 2.58	0.82
PA elastance (mmHg/mL)	1.03 ± 0.48	1.11 ± 0.49	0.90 ± 0.44	0.14
SVI (mL/m^2)	0.03 ± 0.01	0.0274 ± 0.01	0.0283 ± 0.01	0.76
Ea (mmHg/mL)	1845.20 ± 830	1817.9 ± 767	1625.7 ± 870	0.43
Cardiac output (L/min)	4.21 ± 1.29	3.97 ± 1.11	4.59 ± 1.47	0.08
Cardiac index (L/min/m^2)	2.25 ± 0.59	2.23 ± 0.53	2.28 ± 0.67	0.77
PVR (Wood units)	9.89 ± 5.29	10.29 ± 4.82	9.26 ± 6.02	0.49
PA Saturation (%)	63.6 ± 9.8	64.63 ± 10.29	61.66 ± 8.68	0.34
Hemoglobin (gm/dL)	13.2 ± 2.4	12.45 ± 2.13	14.28 ± 2.38	**0.02**
Oxygen supplementation (L/min)	5.0 ± 8.3	2.1 ± 3.6	8.4 ± 12.7	0.06
Background therapy (%)				**<0.01**
Dual (ERA+PDE5-I)	10 (18.18)	6 (17.64)	4 (19.04)	
Mono (ERA or PDE5-I)	28 (50.90)	23 (67.64)	5 (23.80)	
None	17 (30.90)	5 (14.70)	12 (57.14)	

Data are presented as mean ± SD; p-value calculated using Chi-square test and a two-tailed Student's t-test for categorical and continuous variables, respectively. (+)AI: pulmonary hypertension and pulmonary fibrosis with autoimmune disease; (–)AI: pulmonary hypertension and pulmonary fibrosis without autoimmune disease; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_LCO: diffusing capacity for carbon monoxide; mRAP: mean right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PA elastance: pulmonary artery elastance = [Pulmonary artery systolic pressure minus PA diastolic pressure]/SV; SV: stroke volume; SVI: stroke volume index; Ea: arterial elastance = (sPAP/SV); SV: stroke volume; PVR: pulmonary vascular resistance; ERA: endothelin receptor antagonist; PDE5-I: phosphodiesterase 5 inhibitor. p-Values in bold represent significantly different values that are <0.05. p-Values less than 0.01 are presented as "<0.01".

(FEV1) (absolute) (1.5 ± 0.4 versus 2.1 ± 0.7 L; p <0.01), higher FEV1/FVC ratio (90 ± 13.6 versus 81.3 ± 14.8; p = 0.03), lower FVC/D_LCO ratio (2.17 ± 1.0 versus 3.2 ± 1.2; p = 0.03), and higher diffusing capacity for carbon monoxide (D_LCO) (% predicted) (31.1 ± 15.2 versus 23.2 ± 8.0; p < 0.01), respectively (Table 1).

Transplant-free survival

The transplant-free survival for the entire PH/PF cohort was 72% (one year), 57% (three years), and 32% (five years). The (+)AI subgroup demonstrated increased transplant-free survival at one year (84.6 ± 6.3% versus 45 ± 11.1%), three years (71 ± 8.2% versus 28.6 ± 11.9%), and five years (47.6 ± 9.6% versus 6.4 ± 8.2%) compared to the (–)AI subgroup (p = 0.01, Fig. 2). The weighted Cox proportional hazards model (accounting for age and gender) determined that the transplant-free survival distributions remained different when comparing the (+)AI and (–)AI subgroups, respectively (HR 0.33 (CI 0.14–0.74); log-rank p = 0.02, Fig. 3). The adjusted survival probabilities (95% CI) for the (+)AI group compared to the (–)AI group were 0.79 (0.67–0.93) versus 0.48 (0.31–0.76) (one year), 0.69 (0.56–0.86) versus 0.33 (0.16–0.67) (three years), and 0.4 (0.26–0.63) versus 0.06 (0.01–0.46) (five years), respectively. This survival advantage persisted after the separate comparisons of the established AI (n = 27, Fig. 4) and the IPAF subgroups (n = 7; Supplement Figure 1) to the (–)AI cohort. The distribution of outcomes (death, lung transplantation, or censorship) based on AI

Table 2. Distribution of outcome events (death, lung transplantation, or censorship) for the entire cohort based on AI status.

Patient outcomes and causes of death			
	(+)AI (n=34)	(–)AI (n=21)	Total
Patient outcomes n(%)			
Lung transplantation	7 (21)	7 (33)	14
Censored	14 (41)	6 (29)	20
Death	13 (38)	8 (38)	21
Causes of death			
Death directly related to PH	11	6	Right heart failure/Sudden death (17)
PH contributed to death	2	2	Septic shock (1); Respiratory (non-PH) (3)
PH was not related to death	0	0	

Note: Of the 21 total deaths, 9 patients had autopsy data which were reviewed to help identify cause of death.
(+)AI: pulmonary hypertension and pulmonary fibrosis with autoimmune disease; (–)AI: pulmonary hypertension and pulmonary fibrosis without autoimmune disease.

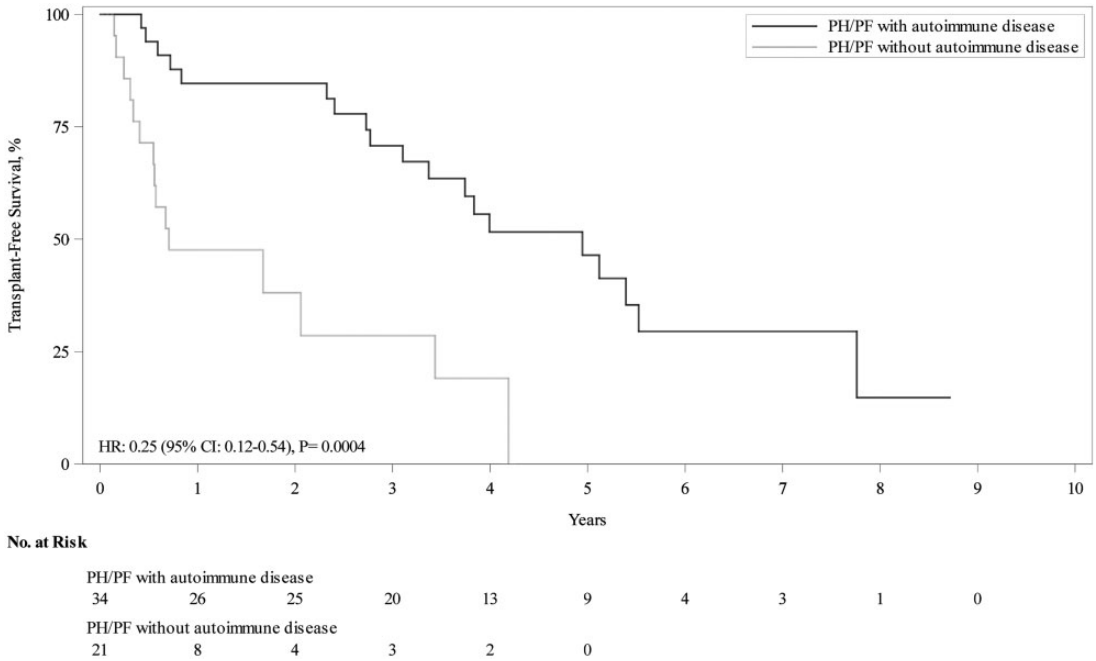

Fig. 2. Kaplan–Meier estimates of survival for pulmonary hypertension and pulmonary fibrosis (PH/PF) with autoimmune disease versus PH/PF without autoimmune disease.

status and the causes of death are outlined in Table 2. The majority of deaths (81%) were directly related to PH in the context of right heart failure/sudden death.

Pulmonary hemodynamics and gas exchange before and after parenteral prostacyclin therapy

There were no significant differences in baseline pulmonary and systemic hemodynamics between the (+)AI and (–)AI subgroups (Table 1). A repeat RHC was performed in 31/55 patients ((+)AI (n = 22); (–)AI (n = 9)) at a median of 253 ± 614 days after the enrollment RHC (Tables 3A and 3B). After treatment with parenteral prostacyclin therapy, pulmonary hemodynamics were improved in both the (+)AI and (–)AI groups, with no change in systemic hemodynamics (Tables 3A and 3B). The oxygen requirements were unchanged after three months of parenteral prostacyclin therapy (5.0 ± 8.3 (baseline) versus 4.4 ± 5.8 (3 months) L/min; $p = 0.48$).

Predictors of mortality

In the univariate analysis, four variables ($p < 0.05$) predicted mortality and included age at PH diagnosis, AI, gender, and diffusing capacity (D_LCO). Using multivariate regression, the baseline variables that remained independently associated with mortality for the entire cohort included age at PH diagnosis (five-year increment) (HR 1.23

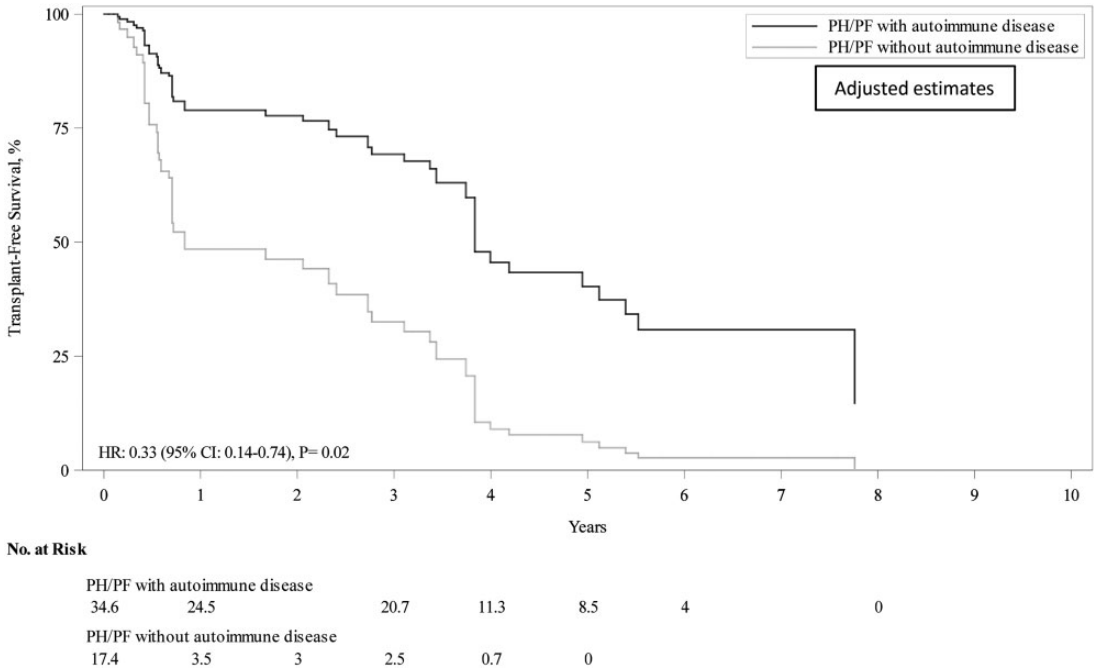

Fig. 3. Adjusted Kaplan–Meier estimates of survival (using weighted Cox proportional hazards modeling for age at PH diagnosis and gender) for pulmonary hypertension and pulmonary fibrosis (PH/PF) with autoimmune disease versus PH/PF without autoimmune disease.

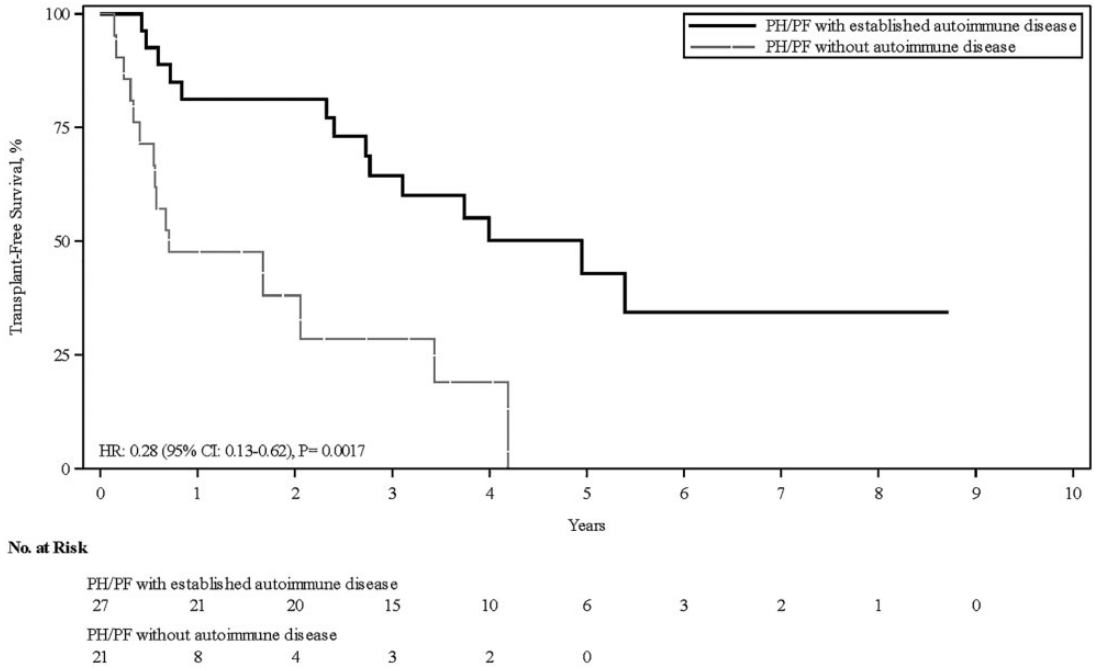

Fig. 4. Kaplan–Meier survival estimates comparing pulmonary hypertension and pulmonary fibrosis (PH/PF) due to *established* autoimmune disease to PH/PF without autoimmune disease. Established autoimmune disease excludes IPAF (interstitial pneumonia with autoimmune features[17]).

(CI 1.03–1.47); p = 0.017) and AI (HR 0.26 (CI 0.10–0.70); p = 0.008) (Table 4). When the multivariate regression was limited to the (+)AI subgroup only (Supplement Table 3), none of the variables were associated with transplant-free survival.

Discussion

The primary goal of this study was to determine if underlying AI was associated with survival in a cohort with severe PH associated with RV dysfunction and extensive PF. Central findings include the

Table 3. Hemodynamic parameters at enrollment and after repeat right heart catheterization in the pulmonary hypertension with pulmonary fibrosis with autoimmune disease ((+)AI) subgroup (Table 3A, n=34) and in the pulmonary hypertension with pulmonary fibrosis without autoimmune disease ((–)AI) subgroup (Table 3B, n=21).

Table 3A.

Variable	1st RHC (n = 34)	2nd RHC (n = 22)	Change from 1st RHC (n = 22)	p-Value
mAP (mmHg)	91.33 ± 17.91	81.53 ± 11.89	–7.38 ± 18.55	0.13
HR (beats/min)	84.52 ± 15.21	79.90 ± 11.29	–3.83 ± 17.26	0.35
SBP (mmHg)	120.66 ± 25.07	114.90 ± 20.75	–2.89 ± 29.07	0.66
DBP (mmHg)	71.91 ± 19.66	63.50 ± 8.77	–7.42 ± 22.61	0.17
mRAP (mmHg)	9.85 ± 5.14	6.14 ± 3.43	–4.55 ± 6.92	**<0.01**
sPAP (mmHg)	81.65 ± 19.23	62.91 ± 16.38	–17.64 ± 21.18	**<0.01**
dPAP (mmHg)	31.68 ± 7.19	25.18 ± 8.17	–5.55 ± 8.30	**<0.01**
mPAP (mmHg)	48.24 ± 9.52	38.50 ± 10.95	–8.91 ± 11.17	**<0.01**
PAWP (mmHg)	12.0 ± 3.45	11.23 ± 4.42	–0.82 ± 4.62	0.41
PA elastance (mmHg/mL)	1.11 ± 0.49	0.59 ± 0.30	–0.37 ± 0.45	**<0.01**
Cardiac output (L/min)	3.97 ± 1.11	5.71 ± 1.72	1.56 ± 1.98	**<0.01**
Cardiac index (L/m^2)	2.23 ± 0.53	3.32 ± 0.91	1.01 ± 0.98	**<0.01**
SVI (mL/m^2)	0.0274 ± 0.01	0.0421 ± 0.01	0.0119 ± 0.01	**<0.01**
Ea (mmHg/mL)	1817.9 ± 767.1	995.4 ± 487	–585.0 ± 794	**<0.01**
PVR (Wood units)	10.29 ± 4.82	5.33 ± 3.46	–4.03 ± 4.44	**<0.01**
PA saturation (%)	64.63 ± 10.29	70.81 ± 4.66	4.28 ± 10.71	0.14
Hemoglobin (gm/dL)	12.45 ± 2.13	12.41 ± 2.35	0.04 ± 1.56	0.94

Table 3B.

Variable	1st RHC (n =21)	2nd RHC (n = 9)	Change from 1st RHC (n=9)	p-Value
mAP (mmHg)	85.78 ± 17.30	84.83 ± 14.46	–4.00 ± 35.74	0.56
HR (beats/min)	79.53 ± 16.74	82.33 ± 12.79	7.00 ± 16.36	0.26
SBP (mmHg)	122.78 ± 22.91	117.44 ± 16.85	–0.75 ± 12.37	0.86
DBP (mmHg)	73.56 ± 12.25	67.67 ± 12.19	–3.63 ± 5.90	0.12
mRAP (mmHg)	10.05 ± 4.59	4.00 ± 2.45	–5.33 ± 5.48	**0.01**
sPAP (mmHg)	78.19 ± 14.34	64.67 ± 12.87	–12.56 ± 13.22	**0.02**
dPAP (mmHg)	33.10 ± 8.79	25.78 ± 7.01	–7.11 ± 4.96	**<0.01**
mPAP (mmHg)	47.76 ± 8.77	39.56 ± 9.11	–8.56 ± 8.57	**<0.01**
PAWP (mmHg)	11.81 ± 2.58	9.11 ± 3.95	–1.89 ± 3.14	0.10
PA elastance (mmHg/mL)	0.90 ± 0.44	0.65 ± 0.41	–0.32 ± 0.30	**0.01**
Cardiac output (L/min)	4.59 ± 1.47	5.58 ± 1.24	1.42 ± 1.01	**<0.01**
Cardiac index (L/m^2)	2.28 ± 0.67	2.93 ± 0.36	0.79 ± 0.55	**<0.01**
SVI (mL/m^2)	0.0283 ± 0.01	0.0366 ± 0.01	0.00836 ± 0.01	**<0.01**
Ea (mmHg/mL)	1625.7 ± 870.9	1101.1 ± 783.5	–621.0 ± 471.4	**<0.01**
PVR (Wood units)	9.26 ± 6.02	6.16 ± 4.34	–4.57 ± 3.78	**<0.01**
PA Saturation (%)	61.66 ± 8.68	71.76 ± 7.04	8.49 ± 6.51	**0.01**
Hemoglobin (gm/dL)	14.28 ± 2.38	14.29 ± 1.45	0.45 ± 1.57	0.60

Data are presented as mean ± SD; p-value calculated using Chi-square test and a two-tailed Student's t-test for categorical and continuous variables, respectively. mAP: mean systemic arterial pressure; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; mRAP: mean right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PA elastance: pulmonary artery elastance = [Pulmonary artery systolic pressure minus PA diastolic pressure]/SV; SVI: stroke volume index; Ea: arterial elastance = (sPAP/SV); PVR: pulmonary vascular resistance.

following: (a) PH/PF patients with AI had increased survival despite similar pulmonary hemodynamics compared to the (–)AI subgroup; (b) pulmonary hemodynamic improvements occurred in PH/PF patients treated with PAH-specific therapy regardless of AI status and without adverse effects on gas exchange; and (c) age at PH diagnosis and AI were both associated with transplant-free survival.

Table 4. Unadjusted (univariate) and adjusted (multivariate) analyses for mortality.

Baseline variables and mortality				
Variable	Unadjusted hazard ratio (95% CI)	p-Value*	Adjusted hazard ratio (95% CI)	p-Value*
Autoimmune disease	0.251 (0.117–0.539)	**0.0004**	0.261 (0.098–0.700)	**0.008**
Age at PH diagnosis (5 years)	1.225 (1.037–1.447)	**0.017**	1.231 (1.032–1.470)	**0.017**
Gender	2.054 (1.032–4.086)	**0.040**	1.226 (0.532–2.823)	0.633
D_LCO (% predicted)	0.969 (0.939–1.000)	**0.048**	0.984 (0.952–1.016)	0.313
PA elastance (mmHg/mL)	1.319 (0.622–2.800)	0.470		
Cardiac index (L/min)	0.988 (0.549–1.778)	0.969		
PVR (Wood units)	1.005 (0.944–1.071)	0.865		
Background oral PAH therapy	0.801 (0.368–1.745)	0.576		
Baseline oxygen Requirement (L/min)	1.023 (0.992–1.054)	0.142		
SVI (mL/m^2) unit = 0.01	0.866 (0.563–1.331)	0.512		
Ea (mmHg/mL) unit	1.000 (1.000–1.001)	0.455		

*p-Value of <0.05 considered significant in univariate and multivariate analyses.
FVC/D_LCO: forced vital capacity/diffusing capacity for carbon monoxide; PA elastance: pulmonary artery elastance = [PA systolic pressure minus PA diastolic pressure]/stroke volume; PVR: pulmonary vascular resistance; SVI: stroke volume index; Ea: arterial elastance = (sPAP/SV); sPAP: systolic pulmonary artery pressure; SV: stroke volume.

Based on recommendations from the 6th World Symposium on Pulmonary Hypertension (WSPH),[13] this study focused on the severe PH phenotype (mPAP≥35 mmHg) with pre-defined parameters of echocardiographic RV dysfunction,[24] and extensive PF confirmed by HRCT chest.[11] These inclusion criteria ensured the study of bonafide Group 3 PH/PF with pathophysiology similar to Group 1 PAH and the anticipated consequences of RV-PA (un)coupling.[25] As a result, the study cohort was enriched for the PH/PF profile most likely to benefit from PAH-specific therapy, a notion also suggested by a post hoc analysis of the STEP-IPF study.[26]

In contrast, the presence of mild PF has been consistently included in prior Group 1 PAH studies, although recent data suggests that even mild radiographic PF may negatively affect Group I PAH survival.[27] Importantly, the necessary distinction between Group I PAH with mild PF versus Group 3 PH/PF essentially hinges on the extent of radiographic PF, since the pulmonary hemodynamic profiles may be comparable. The definition of extensive PF chosen for this study was previously validated as a predictor of poor survival in the setting of PF and is objectively based on HRCT chest and pulmonary function test assessments.[11] While other reports have incorporated the same PF definition,[2,28] there continues to be heterogeneity and the absence of a consensus definition for PF across prior Group 3 PH registries.[1,29–31]

To date, prior PH/PF intervention studies have typically excluded AI, rather focusing on idiopathic interstitial pneumonias,[3–7] which are frequently associated with only modest degrees of PH (mPAP <35 mmHg) and relatively normal echocardiographic RV function. The phenotype of mild to moderate PH and normal/near normal RV function associated with PF in these prior reports may be one reason for the lack of response to PAH-specific therapy.[3–7]

In this study, the unadjusted three-year survival of the PH/PF subgroup with (+)AI was 71% which is increased compared to prior reports of a similar (+)AI phenotype (21–50% three-year survival).[1,2,28,31] One multi-institutional study from Japan reported a similar three-year survival of 68% for their (+)AI subgroup; however, this survival was in reference to the combined pulmonary fibrosis and emphysema subgroup and the definition of PF was not disclosed.[32] In contrast, the three-year survival of the (–)AI group in our study was 29% which is comparable to non-AI PH/PF historical controls (19–50% three-year survival).[29,30,33,34] In distinction to this study, the PAH-specific therapies offered in these prior PH/PF registries and reports were modest and limited to PDE five-inhibitors and/or endothelin receptor antagonists (ERAs), with notably minimal prostacyclin use.[1,2,28–31,33] Interestingly, the three-year survival of our (+)AI subgroup was similar to that of a contemporary Group 1 PAH cohort associated with AI (without extensive PF) from the REVEAL registry[35] (three-year survival of 61% in the SSc-PAH cohort), and increased when compared to a Group 1 PAH cohort with mild PF (three-year survival <30%).[27] While hypothesis-generating at best, these observations suggest that the severe PH/PF phenotype with (+) AI displays concurrent pulmonary manifestations (PH and PF) which are independently driven by the underlying AI, each with its own prognosis and potential for response to medical therapy.

There are several possible explanations for the disparity in survival between the subgroups with and without AI, despite similar baseline pulmonary hemodynamics and favorable response to PAH-specific therapy. Compared to

the (–)AI subgroup, the (+)AI subgroup revealed higher diffusing capacity which has been associated with improved survival in Group 3 PH[34] (inclusive of obstructive *and* restrictive lung disease); however, diffusing capacity has not been associated with survival in other reports dedicated to isolated Group 3 PH/PF,[30,33] which was also the finding in this study. In addition, male gender and older age at PH diagnosis were more prevalent in the (–)AI subgroup which may have contributed to its inferior survival, as both are recognized risk factors for poor survival in Group 1 PAH[29,36,37] and Group 4 PH.[38] A recent study evaluated RV function in Group 1 PAH based on the gold standard assessment of pressure–volume loop analysis and reported gender-based differences in RV contractile function and RV-PA coupling demonstrating superior RV adaptation in females.[39] To this point, in one Group 3 PH report focusing on RV function, male gender was the strongest predictor of reduced RV-FAC after adjusting for RV afterload,[40] although it should be noted that in contrast to Group 1 PAH,[39] gender differences using load-independent measures of RV function has yet to be demonstrated in Group 3 PH. While the differences in gender, age, and diffusing capacity between subgroups with and without AI are potentially confounding in the prediction of transplant-free survival, the statistical analyses (including the Kaplan-Meier (KM) survival analysis adjusted for age and gender) support the causal association of AI and transplant-free survival.

The pulmonary hemodynamics improved and gas exchange was no worse in both PH/PF subgroups after PAH-specific therapy; as such, either an unequal or a detrimental response to PAH-specific therapy does not appear to explain the disparate survival between subgroups with and without AI. In fact, the extent of the pulmonary hemodynamic response to PAH-specific therapy in this Group 3 PH/PF cohort is reminiscent of incident Group I PAH cohorts treated with upfront combination therapy.[41,42] Assuming the improvement in pulmonary hemodynamics after PAH-specific therapy was sustained in both subgroups, the inferior survival in the (–)AI subgroup could also be related to the natural history of the underlying PF. Compared to PF related to AI, the lower survival of PF without AI is well reported and has been attributed to prognostic differences in underlying PF pathology (usual interstitial pneumonia versus non-specific interstitial pneumonia, respectively).[43,44] In addition, idiopathic PF (representing ~40% of the (–)AI subgroup in this study), particularly when complicated by PH,[45] is more prone to acute PF exacerbations[46] when compared to either PF related to AI,[47] or IPAF.[48] Regardless of the PF type, acute exacerbations remain unpredictable and are associated with increased PF progression and short-term mortality.[46,49] While the exact reason for the divergent survival in PH/PF based on AI status remains unanswered in this study, we surmise that in addition to the possible progression of pulmonary vascular disease despite PAH-specific therapy, inherent differences in the non-AI subgroup with regard to the increased probability for PF progression *and* the heightened risk for acute exacerbation may also provide part of the explanation.

PH/PF studies and registries have historically reported an exceedingly low use of prostanoids (<10%), typically in the setting of "salvage" therapy and usually delivered via inhalation.[2,29,30,33] The negligible parenteral prostacyclin use in PH/PF is likely due to prior reports of worsening gas exchange in the setting of *acute* administration and *rapid* uptitration of parenteral prostacyclin.[50,51] In contrast, our group previously reported the successful *gradual* uptitration of parenteral prostacyclin in PH/PF *without* gas exchange abnormalities, and congruent improvements in quality of life, functional capacity, and pulmonary hemodynamics after chronic administration.[52,53] Similar to our prior experience,[52,53] the use of a parenteral prostacyclin (treprostinil) in this study was safe with regard to gas exchange and also resulted in pulmonary hemodynamic improvements regardless of AI status. The findings are also consistent with the lack of published evidence to support clinically relevant worsened gas exchange after studying the *chronic* administration of multiple non-prostanoid PAH-specific therapies in PH/PF.[3–7] Lastly, parenteral treprostinil has putative advantages related to pulmonary venodilation and anti-angiogenesis.[54] These properties may be of relevance since PH/PF lung pathology often exhibits venopathy and capillary proliferation,[55,56] in addition to the typical arteriopathy of Group I PAH.[57] Nevertheless, as this was not a prospective, controlled trial, the effects of parenteral prostacyclin in patients with PH/PF reported here do not prove efficacy of this agent, although recent data using inhaled prostacyclin appear promising in PH/PF and importantly, included an AI subgroup.[58]

AI and younger age at PH diagnosis were independently associated with improved transplant-free survival. While younger age also predicts better survival in Group I PAH,[59,60] AI associated with Group 1 PAH actually portends a poorer survival when compared to idiopathic PAH, despite similar hemodynamic responses to PAH-specific therapy.[35] Nevertheless, AI is a common risk factor for precapillary PH (regardless of WHO Group) which may respond favorably to PAH-specific therapy, irrespective of the presence or absence of extensive PF. One prior study reported findings restricted to a PH/PF (+)AI cohort and found that the only multivariate risk factor for survival was worsening oxygenation.[2] In our (+)AI subgroup, none of the baseline variables including oxygen requirements were associated with transplant-free survival. Future work should focus on prognostic variables at baseline *and* over time in Group 3 PH cohorts enriched for PH/PF and AI.

Study limitations

The limitations of this study include those intrinsic to the cohort study design and the relatively small number of

subjects at a single center. Either a randomized study or a validation cohort is required to confirm these observations. All efforts were made to account for each subject referred with PH/PF, and the smaller number of enrollees is the expected result of the enrichment strategy for severe PH and RV dysfunction. The reported transplant-free survival was compared to historical controls which inherently limits the strength of any conclusions from these analyses. While ~25% of the PH/PF cohort were *prevalent* cases, the date of PH diagnosis was appropriately based on the diagnostic RHC. A repeat RHC was not performed for ~50% of the cohort; however, all repeat RHC were done at the discretion of the treating physician and were uniformly performed for worsening cardiopulmonary status as opposed to surveillance. This study did not investigate respiratory hospitalizations or all-cause hospitalizations but these data should be investigated in future study to better understand the mechanisms of decreased survival of the PH/PF subgroup without AI. Within the limitations of the data set, the statistical approach was rigorous and attempted to minimize the influence of confounding variables in determining the association of AI and transplant-free survival. While the conclusions of this study cannot be extrapolated to all PH/PF, the study of severe PH and extensive PF is in accordance with suggestions made by the WSPH[13] and fosters a basis for further study.

Conclusions

This study demonstrates that in the setting of severe PH coupled with RV dysfunction and extensive PF and treated with PAH-specific therapy, both age at PH diagnosis and AI are independently associated with transplant-free survival. PH/PF associated with AI is a phenotype which should be included as part of an enrichment strategy in future clinical trials of PAH-specific therapy in Group 3 PH.

Authors' contributions

RS, RS: contributed to the conception, design and acquisition, analysis and interpretation of data for the work; drafting of the article and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PCG, RNC, CD, DJ: contributed to the analysis and interpretation of data for the work; drafting of the article and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MKM, LL, FS, JH, RNC, SSS, JPL, JAB, SSW, ALR, DJR, DMS, MYS, AD, AES: contributed to the acquisition of data for the work; drafting of the article and revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work, in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors agree to be accountable for all aspects of the publication.

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Conflict of interest

Rajan Saggar reports consulting fees and research funding fees from Actelion, United Therapeutics, LungRx, Acceleron, and Bellerophon. Chunquin Deng and Dana Johnson serve in the Department of Biostatistics, Statistical Programming and Data Management at United Therapeutics. Richard N. Channick has served as a consultant for and received research grants from Actelion, United Therapeutics, Bayer, Third Pole, and Gossamer Bio. He serves on the speaker bureau for Actelion and Bayer. Paresh C. Giri reports speaker bureau fees from United Therapeutics. Shelley S. Shapiro reports research funding fees from United Therapeutics, Lung Rx, PhaseBio, Bellerophon, and Liquidia. Other authors declare no conflict of interests.

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Supplemental material

Supplemental material for this article is available online.

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