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Progressive Interstitial Lung Disease in Relatives of Patients with Pulmonary Fibrosis

To the Editor:

First-degree relatives of patients with sporadic and familial pulmonary fibrosis have been demonstrated to have high rates of interstitial lung abnormalities (ILA) and interstitial lung disease (ILD) (1). However, less is known about the rates of progression in these relatives (2).

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Methods

Relatives enrolled as described previously in the CGS-PF (Clinical Genetics and Screening for Pulmonary Fibrosis) study (1) had baseline pulmonary function tests and chest computed tomography (CT) scans that were repeated 2 years after enrollment. Relatives underwent prone volumetric chest CT scans at full inspiration, and CTs were assessed for the presence of ILA defined by Fleischner Society recommendations (3) and subtyped as previously described (4, 5). All relatives with ILA on either baseline or 2-year CT had both sets of images simultaneously compared in order to determine imaging progression as previously defined (6). For comparison, relatives were divided into two groups: *1*) those with ILA at either baseline or 2-year follow-up; and *2*) those without ILA (no ILA or indeterminate) at both time points. Progression was assessed using thresholds of lung function decline alone (5% and 10%) or in combination with radiologic changes, including an adaptation of criteria used by the INBUILD trial of either an FVC loss of greater than 10% or 5–10% with progression on CT (7). Continuous variables were compared with Wilcoxon rank-sum and categorical variables with Fisher exact tests. Multivariable models were adjusted for age, sex, and history of ever smoking. Two-sided *P* values less than 0.05 were considered statistically significant. All analyses were performed using Statistical Analysis Software version 9.4 (SAS Institute).

Results

Of the 107 relatives in the original CGS-PF study, 73 had 2-year follow-up CTs, of which 20 had ILA at baseline and 53 did not. There were no statistically significant differences in baseline characteristics between relatives who did and did not participate in the 2-year follow-up. At 2 years, 21 had ILA, including 19 who had ILA at baseline and 2 additional cases with incident ILA, 51 relatives were without ILA at both baseline and 2-year follow-up, and 1 participant with ILA at baseline that was not present at the 2-year follow-up. Table 1 presents baseline characteristics for those with ILA at either time point and those without ILA at both time points. Compared with those without ILA, relatives with ILA were more likely to be male and, at baseline, had higher absolute monocyte counts and lower FEV_1/FVC ratio and percent predicted measures of FVC, TLC, and D_{LCO}.

At the 2-year follow-up, the majority (13 [65%]) of those with ILA at baseline had radiologic progression, and 2 (4%) of those without ILA at baseline developed ILA (examples shown in Figure 1). Of the 15 total relatives with radiologic progression, 4 (27%) were from families with familial pulmonary fibrosis; the remaining 11 (73%) had a single first-degree relative with IPF. Of the 20 relatives with baseline ILA, 6 (30%) had definite fibrosis, of which 5 (83%) had 2-year radiologic progression, whereas 8 of the 14 (57%) without baseline fibrosis progressed. At 2 years, FEV_1, FVC, and D_{LCO} remained reduced in those with ILA compared to without ILA. Although there were no statistically significant differences in the loss of FVC and D_{LCO} from baseline to 2 years between relatives with and without ILA, those with ILA had greater loss of FEV_1 in both unadjusted analyses (Table 1) and after adjusting for covariates (−145 ml; 95% confidence interval, −249 ml to −40 ml; $P = 0.007$) when compared with those without ILA. Almost half of the relatives with ILA (10 of the 22 [45%] with ILA at either time point; 9 of the 20 [45%] with ILA at

Table 1. Characteristics of Relatives with Interstitial Lung Abnormalities at Either Baseline or 2 Years versus without Interstitial Lung Abnormalities at Baseline and 2 Years

Variable	Without ILA at Baseline and 2 Years ($n = 51$ [70%])	ILA at Baseline or at 2 Years ($n = 22$ [30%])	Unadjusted *P* Value
Baseline			
Demographic characteristics			
Age (yr), median (IQR)	58.0 (53.0 to 63.0)	59.0 (56.0 to 65.0)	0.4
Gender (female), *n* (%)	35 (69)	9 (41)	0.04
BMI, median (IQR)	27.8 (24.9 to 32.8)	27.2 (22.2 to 31.2)	0.3
Ever-smoker, *n* (%)	20 (39)	12 (54)	0.3
Pack-years smoking, median (IQR)*	0 (0 to 2.3)	0.4 (0 to 23)	0.06
Comorbidities, *n* (%)			
Obstructive lung disease†	2 (4)	1 (5)	1.0
Cancer	6 (12)	1 (5)	0.7
Heart failure	0 (0)	0 (0)	—
Kidney disease	3 (5)	0 (0)	0.5
Liver disease	0 (0)	0 (0)	—
Relative with familial pulmonary fibrosis, *n* (%)	25 (49)	7 (32)	0.4
Baseline ILA status, *n* (%)	0 (0)	20 (91)	—
Lymphocyte telomere length <10th percentile for age, *n* (%)	14 (27)	10 (45)	0.2
MUC5B promoter variant, *n* (%)	21 (41)	14 (64)	0.1
Monocyte count (K/μl), median (IQR)‡	0.50 (0.42 to 0.60)	0.62 (0.48 to 0.69)	0.01
Pulmonary function			
FEV_1/FVC, median (IQR)	0.78 (0.75 to 0.80)	0.81 (0.78 to 0.83)	0.02
FEV_1% predicted, median (IQR)	111 (97 to 117)	103 (91 to 110)	0.07
FVC% predicted, median (IQR)	112 (98 to 123)	100 (89 to 108)	0.009
TLC% predicted, median (IQR)	104 (97 to 116)	96 (87 to 102)	0.004
D_{LCO}% predicted, median (IQR)	87 (79 to 99)	78 (63 to 88)	0.006
2-year follow-up			
CT change, *n* (%)			
Progression	—	15 (68)	—
Stable	—	7 (32)	—
FEV_1% predicted, median (IQR)§	107 (98 to 122)	99 (92 to 107)	0.049
FEV_1 change (ml), median (IQR)§	−75 (−135 to 40)	−130 (−260 to −80)	0.02
FEV_1 change (%), median (IQR)§	−2.4 (−4.9 to 1.2)	−4.7 (−7.6 to −2.7)	0.03
FVC% predicted, median (IQR)‖	107 (100 to 120)	92 (89 to 104)	0.01
FVC change (ml), median (IQR)‖	−90 (−240 to 0)	−175 (−330 to −30)	0.2
FVC change (%), median (IQR)‖	−3.1 (−6.3 to 0.0)	−4.4 (−9.0 to −0.7)	0.2
FVC change (≥10% loss), *n* (%)‖	6 (12)	5 (22)	0.1
FVC change (≥5% loss), *n* (%)‖	17 (35)	10 (45)	0.4
D_{LCO}% predicted, median (IQR)‖	83 (77 to 99)	76 (62 to 84)	0.007
D_{LCO} change (ml/min/mm Hg), median (IQR)‖	−1.1 (−2.1 to 0.0)	−0.6 (−1.3 to 0.2)	0.3
D_{LCO} change (%), median (IQR)‖	−6.3 (−9.2 to 0.1)	−3.1 (−10.9 to −1.2)	0.4
D_{LCO} change (≥10% loss), *n* (%)‖	12 (24)	6 (27)	0.8
D_{LCO} change (≥5% loss), *n* (%)‖	27 (55)	8 (36)	0.2

Definition of abbreviations: BMI = body mass index; CT = computed tomography; ILA = interstitial lung abnormality; IQR = interquartile range. For unadjusted analyses, a comparison of categorical variables was made using Fisher exact tests and continuous variables with Wilcoxon rank-sum.

*Missing pack-year smoking history data for nine relatives (two with ILA and seven without ILA).

†Obstructive lung disease, defined as $FEV_1/FVC < 70\%$.

‡Missing monocyte count data for six relatives (three with ILA and three without ILA).

§Missing 2-year FEV_1 for three relatives (one with ILA and two without ILA); change values are compared with baseline.

‖Missing 2-year FVC and D_{LCO} data for two relatives (two without ILA); change values are compared with baseline.

enrollment) demonstrated adapted INBUILD trial criteria for progression (Table 1).

Discussion

In this 2-year follow-up study, disease progression, whether defined by imaging alone or in combination with loss of lung function, is common among first-degree relatives of patients with pulmonary fibrosis. Imaging progression was observed in 65% of relatives with ILA, and those with ILA were more likely to be male, had higher circulating monocyte counts, and had significantly greater loss of their FEV_1 at 2 years compared with those without ILA.

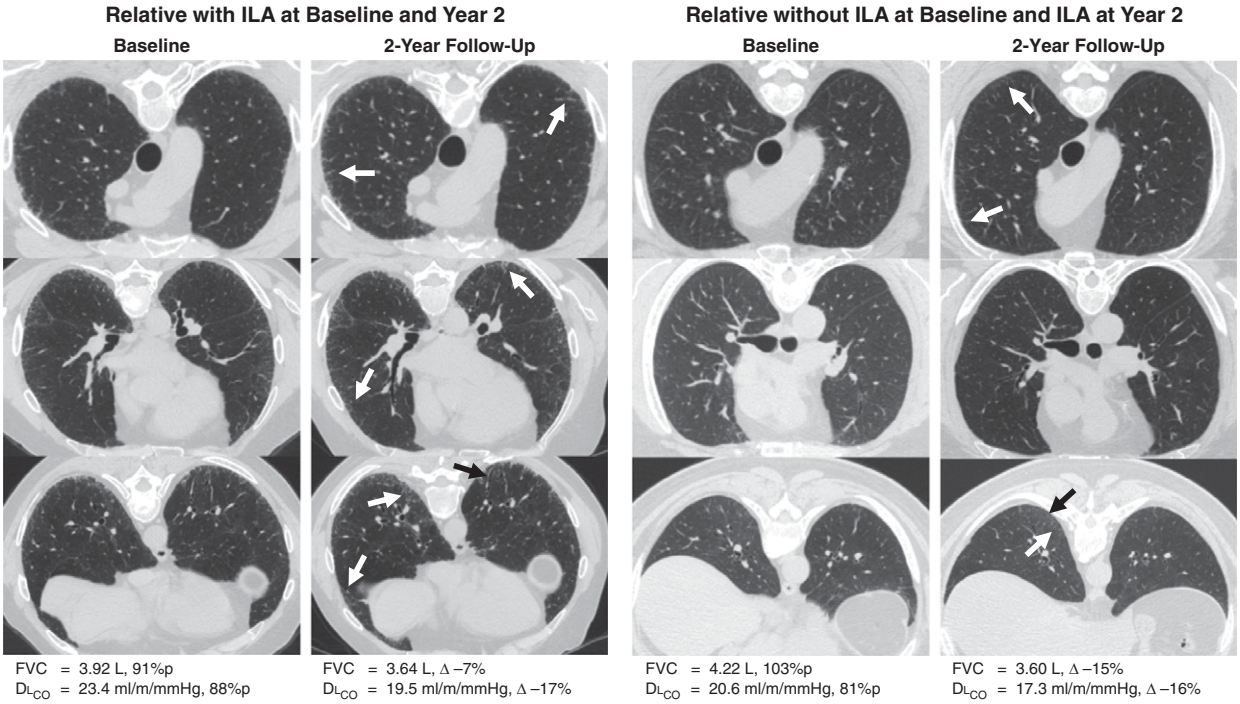

Figure 1. Computed tomography scans of the chest from two relatives with interstitial lung abnormalities (ILA) and progression at the 2-year follow-up. The first participant with ILA at baseline and 2-year follow-up had radiologic progression, including worsening reticulations throughout the lungs (white arrows) and increased basilar traction bronchiolectasis (black arrow). At the 2-year follow-up, FVC had decreased by 7% and D_{LCO} by 17%. The second participant was indeterminate for ILA at baseline but had ILA at the 2-year follow-up and radiologic progression, including new and increased areas of upper lobe and basilar reticulation (white arrows) as well as new basilar traction bronchiolectasis (black arrow). At the 2-year follow-up, FVC had decreased by 15% and D_{LCO} by 16%.

The rates of imaging progression among relatives with ILA at 2 years (65%) is high and greater than that reported in other cohorts over this time interval (e.g., the National Lung Cancer Screening Study) (8), possibly because of the unique risk of this population. Although the INBUILD study helped to define criteria for progression on the basis of patients with known pulmonary fibrosis (7), when these criteria are extrapolated to relatives with ILA at enrollment, 9 of the 20 (45%) had either a loss of FVC of $\geq$10% or FVC loss of 5–10% plus imaging progression. Among all relatives, 21% had imaging progression, and 14% made a modified INBUILD criteria for progressive ILD overall.

Our findings are consistent with the conclusions of studies in the general population (not selected on the basis of family history of fibrosis) that ILA is associated with an accelerated loss of lung volume over time (6). In addition, lung function loss in relatives without ILA is somewhat higher than expected in the general population, which may be cohort-specific or because of other factors such as obstructive lung disease (given the lower FEV_1/FVC ratio in those without ILA). Further longitudinal follow-up is necessary to understand if the rate of lung function loss in relatives is greater than that of other groups, if the rate of loss accelerates over time, and if lung function loss correlates with other adverse clinical outcomes.

There are several limitations to this work. Most notably, our small sample size may have limited statistical power to detect differences between those with and without ILA. This study is now actively recruiting additional relatives, which may help to address issues with power in future analyses. In addition, whereas the rates of progression at 2-year follow-up are quite high, longer follow-up will be needed to provide a more complete picture of the rates of progression and the risk of ILA and ILD in this population.

Conclusions

This study demonstrates that radiologic progression is common in relatives of patients with pulmonary fibrosis that have ILA during 2 years of follow-up and may be associated with accelerated loss of lung function. Future work will be needed to identify risk factors for progression, assess various criteria used to define progression, and evaluate clinical outcomes. The findings of this study add more weight to the argument for screening relatives of patients with pulmonary fibrosis and suggest that future studies to assess therapeutic interventions may be warranted. ■

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Jonathan A. Rose, M.D., M.S.
Maria A. Planchart Ferretto, M.D.
Anthony H. Maeda, M.D.
Pulmonary and Critical Care Division
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Maria F. Perez Garcia, M.D.
Pulmonary Critical Care and Sleep Medicine
Baylor College of Medicine
Houston, Texas

Nikkola E. Carmichael, M.S., Ph.D.
Division of Pulmonary Medicine
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Swati Gulati, M.S.
Pulmonary and Critical Care Division
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Mary B. Rice, M.D., M.P.H.
Pulmonary, Critical Care & Sleep Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

Hilary J. Goldberg, M.D.
Rachel K. Putman, M.D., M.P.H.
Pulmonary and Critical Care Division
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Hiroto Hatabu, M.D., Ph.D.
Department of Radiology
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Benjamin A. Raby, M.D., M.P.H.
Division of Pulmonary Medicine
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Ivan O. Rosas, M.D.
Pulmonary Critical Care and Sleep Medicine
Baylor College of Medicine
Houston, Texas

Gary M. Hunninghake, M.D., M.P.H.*
Pulmonary and Critical Care Division
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

ORCID IDs: 0000-0003-3024-8309 (J.A.R.); 0000-0003-2538-391X (M.B.R.).

*Corresponding author (e-mail: ghunninghake@bwh.harvard.edu).

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Differences in Patient Outcomes across the Pulmonary Fibrosis Foundation Care Center Network

To the Editor:

Interstitial lung disease (ILD) is a clinical classifier that encompasses numerous specific conditions, some of which can result in scarring of the lungs or pulmonary fibrosis (1, 2). The care and management of patients with ILD are challenging because of its heterogeneous etiology (and therefore treatment and prognosis), but also because of care delivery-related factors, including delays in accurate diagnosis and treatment and poor access to symptom management and supplemental oxygen (3–7).

The PFF-CNN (Pulmonary Fibrosis Foundation-Care Center Network) was established to improve the lives of those living with ILD by providing education and access to high-quality care through CCN sites. However, there are varying infrastructure, personnel, and resources across the network sites (8). It is unknown if these differences impact clinically important outcomes.

The primary aim of this study was to determine if there was significant site-level variation in key clinical outcomes among the PFF-CCN sites. Some results have been reported in the form of an abstract (9).

Methods

The design of the PFF-CCN and PFF Patient Registry has been previously published (10). Data was collected from PFF Care Center sites between March 2016 and February 2020. Subjects were required to have either 12 months of follow-up or death or transplant within 12 months of enrollment to be included. Sites with

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