CHEST

Original Research

DIFFUSE LUNG DISEASE

Predicting Pulmonary Fibrosis Disease Course From Past Trends in Pulmonary Function

Shelley L. Schmidt, MD; Nabihah Tayob, MS; Meilan K. Han, MD; Christopher Zappala, MD; Dolly Kervitsky, CRT; Susan Murray, ScD; Athol U. Wells, MD; Kevin K. Brown, MD, FCCP; Fernando J. Martinez, MD; and Kevin R. Flaherty, MD, FCCP

Background: **The clinical course of idiopathic pulmonary fibrosis (IPF) is characterized by progressive decline in lung function and eventual mortality. We sought to determine if future declines in pulmonary function, mortality, or both can be predicted from prior trends in pulmonary function tests (PFTs).**

Methods: **Data from 1981 to 2008 on 4,431 PFTs and mortality were analyzed from 734 subjects with IPF. The Kaplan-Meier method was used for mortality analyses. Mixed models were used to describe longitudinal pulmonary function dynamics, since PFTs were observed at varying time points from baseline.**

Results: **During the first year of follow-up, 135 subjects (73%) had stable FVC while 50 subjects (37%) showed a decline in FVC. During months 12 to 24 (1-2 years after diagnosis), a stable FVC occurred with the same frequency among both subjects whose FVC had declined during year 1 and whose FVC had remained stable (84.0% and 80.7%, respectively; *P* = .59). Among subjects alive at the end of year 1, those with a stable FVC were more likely to be alive at the end of year 2 than those whose FVC declined (hazard ratio [HR], 0.91 [95% CI, 0.87-0.94] and HR, 0.71 [95% CI, 0.62-0.78], respectively).**

Conclusions: **PFT decline predicts early mortality, but not future declines in physiology, regardless of time since diagnosis.** ***CHEST 2014; 145(3):579–585***

Abbreviations: DLCO = diffusion capacity of the lung for carbon monoxide; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic, diffuse parenchymal lung disease. Although the median survival is often described as 2 to 3 years, the more recent IPF consensus statement highlighted that the disease course of an individual patient is variable, with some patients surviving for many years, others progressing more rapidly, and still others having acute exacerbations.[1] This heterogeneity complicates the ability to provide clear prognostic information to patients and complicates the design of therapeutic clinical trials. With no cure, IPF has been the focus of multiple therapeutic studies over the last decade.[2-12] Unfortunately, effective treatments have been elusive. While there are many considerations as to why any given trial may not show

Manuscript received April 8, 2013; revision accepted September 9, 2013.

Affiliations: From the University of Michigan Health System (Drs Schmidt, Han, Martinez, and Flaherty), Ann Arbor, MI; University of Michigan Department of Biostatistics (Ms Tayob and Dr Murray), Ann Arbor, MI; Royal Brompton and Harefield National Health Service Foundation Trust (Drs Zappala and Wells), London, England; and National Jewish Health (Ms Kervitsky and Dr Brown), Denver, CO.

Part of this article was presented at the American Thoracic Society International Conference, May 13-18, 2011, Denver, CO, and in abstract form (Schmidt SL, Han MK, Tayob N, et al. *Am J Respir Crit Care Med.* 2011;183:A5299).

Funding/Support: This study was supported by National Institutes of Health [Grant HL093351 to Dr Han and Grants K24HL11316, R01HL19743 and HL007749 to Dr Flaherty].

Correspondence to: Kevin R. Flaherty, MD, FCCP, 3916 Taubman Center, 1500 E Medical Center Dr, SPC 5360, Ann Arbor, MI 48109-5360; e-mail: Flaherty@med.umich.edu

DOI: 10.1378/chest.13-0844

significance, one is that the natural history of the disease has not been defined well enough to allow for the creation of inclusion criteria that result in an adequate number of clinical end points over the duration of the trial.

Several characteristics of patients with IPF are associated with increased mortality, including older age, male sex, increased severity of dyspnea, worse pulmonary function, decreased exercise capacity, and radiographic findings such as increased fibrosis.[13-17] Six- and 12-month longitudinal declines in pulmonary function and exercise tests have also been reported to predict mortality.[18-23] Unfortunately, there are no clear variables that allow for the prediction of how these characteristics will change for individual patients or for populations of patients enrolled in clinical trials. To both provide better prognostic information to patients with IPF and understand implications for future clinical trials, we wanted to determine if an individual's prior trend in pulmonary function predicts future trends, 1-year mortality, and progression-free survival.

Materials and Methods

We identified pulmonary function tests (PFTs) for patients with IPF through interstitial lung disease databases from the Royal Brompton and Harefield National Health Service Foundation Trust, National Jewish Health, and the University of Michigan Health System from 1981 through 2008. Patients were diagnosed with IPF either through surgical lung biopsy or characteristic chest CT scan.[1,24] For each patient, sex, age, and every PFT they had performed at their home center were captured for analysis. Percent predicted values of FVC and diffusion capacity of the lung for carbon monoxide (Dlco) were analyzed. Mortality data were confirmed through the Social Security Death Registry Index or the UK National Health Service censured by 3 months to account for reporting lag. The study was approved by the University of Michigan institutional review board (study HUM00018279), the ethics committee at the Royal Brompton (study 01-246), and the National Jewish institutional review board (Study HS-1603).

The PFTs were grouped into baseline and follow-up categories of first year, second year, third year, and fourth year. To be included in an interval, the PFT had to be dated within 3 months prior to or 3 months after the interval. Patient-specific regression lines were generated from baseline to 1 year, 1 year to 2 years, 2 years to 3 years, and 3 years to 4 years. All PFTs within a given interval were included to build the regression lines. A patient had to be alive with data at the start and finish of an interval to be included in it. Predicted PFT values were then obtained from the regressions to standardize across patients at exactly 1, 2, 3, or 4 years. Mean change was defined as (% predicted PFT at end of interval − % predicted PFT at start of interval)/(% predicted PFT at start of interval). The actual PFT value was used for the start of each interval, while the 12-month value was estimated from an individual regression line for each patient. The Kaplan-Meier method was used to analyze if a prior year's mean change in PFT predicted mortality in the next year. Mixed models were used to describe longitudinal pulmonary function dynamics, since PFTs were observed at varying time points from baseline. All statistics were performed with SAS, version 9.2 (SAS Institute Inc).

Results

Patient Population

A total of 4,431 PFTs were analyzed from 734 patients (characteristics are in Table 1). Fewer patients had baseline Dlco measurement performed than FVC: 657 vs 730, respectively. If a patient had subsequent Dlco measured, their data would return to the analysis for later years. An aggregate mean FVC and Dlco were recorded for each year of the analysis and were remarkably consistent between the years: within 5% predicted for FVC and 4% predicted for Dlco.

Due to losses to follow-up, we compared the baseline demographics depending on the patients' eventual outcome during year 1 (Table 2). There were 109 deaths (14.9%) within the first year of follow-up. There were more male patients in the declined/dead group (77.2%) vs the stable/lost-to-follow-up group (65.5%, χ^2 $P = .001$), although survival at 1 year was similar for male patients and female patients (log-rank test $P = .1643$). One-year survival in male patients was 0.84 and in female patients was 0.88. In general, the baseline pulmonary function of the patients lost to follow-up approximated that of those who declined during the year and was better than those who ultimately died. The lost-to-follow-up group was older with a higher proportion of women than any of the other groups.

Predicting Future Trends in Pulmonary Function

Among the 85% of subjects who survived year 1, FVC remained stable in the majority of patients over the subsequent year, regardless of the prior year's trend in pulmonary function (Tables 3, 4). Whether the FVC was stable or declined during year 1, 80.7% and 84.0%, respectively, were stable over year 2 ($P = .60$). Three-quarters of the patients with a stable FVC between years 1 and 2 would continue to be stable between years 2 to 3. The prior year's trend in pulmonary function did not differentiate between those whose pulmonary function would decline the following year and those whose pulmonary function would remain stable.

To further clarify pulmonary function dynamics over time, Figure 1 shows the trends in pulmonary function trajectory by mixed model analysis grouped by prior year stability or decline. In Figure 1, the graph of patients with a stable FVC baseline to year 1 demonstrates a greater decline (solid line with greater downward slope) in FVC over time compared with those who had declined in year 1 (line with tick marks) ($P < .0001$). After year 1, the rate of decline (slope of curves) in FVC is similar, regardless of the stability or decline of the prior year ($P = .78$) (Fig 1).