Pirfenidone treatment in individuals with idiopathic pulmonary fibrosis: Impact of timing of treatment initiation

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a debilitating, progressive, fatal, fibrosing lung disease (1, 2). Pirfenidone and nintedanib are oral antifibrotics with demonstrated efficacy in reducing lung function decline in individuals with IPF, independent of baseline lung function (3–7). Intervention with an antifibrotic as early as possible in the disease course might be the most appropriate strategy to preserve lung capacity (5). However, many physicians are reluctant to initiate antifibrotics at diagnosis, and delay treatment until disease progression is observed (8). Furthermore, certain countries do not reimburse antifibrotic treatment for individuals with preserved lung function (% predicted forced vital capacity [FVC] > 80%) (8). These post hoc analyses aimed to assess: 1) FVC decline during long-term pirfenidone treatment in RECAP in individuals with IPF categorized by baseline % predicted FVC and 2) the impact of deferring pirfenidone treatment on annual FVC decline in individuals with IPF during CAPACITY (3) and RECAP (9).

Methods

RECAP (NCT00662038) was an open-label extension study, including individuals who had completed the double-blind, placebo-controlled trials of pirfenidone in individuals with IPF (ASCEND [Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis] [NCT01366209]; CAPACITY [Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes] [NCT00287716/NCT00287729]); the methods and primary outcomes of RECAP have been described previously (9). Individuals who previously received pirfenidone or placebo treatment for 72–120 weeks in CAPACITY and received 2,403 mg/d pirfenidone during RECAP were included in the analyses. Individuals from ASCEND were not included due to lack of FVC follow-up data.

Association of baseline FVC (at entry into RECAP) with rate of FVC decline during RECAP (first aim) was assessed over 180 weeks using change from baseline in % predicted FVC, categorized by baseline % predicted FVC (<50%, ≥50% to <60%, ≥60% to <70%, ≥70% to <80%, ≥80% to <90%, and ≥90%).

Association of timing of pirfenidone initiation with annual FVC decline (ml/yr) during CAPACITY and RECAP (second aim) was assessed over 220 weeks by categorizing individuals who completed CAPACITY and enrolled in RECAP by CAPACITY treatment group (2,403 mg/d pirfenidone or placebo; the 1,197 mg/d pirfenidone group was not included). Annual FVC decline was calculated for Weeks 0–120 (CAPACITY), Weeks 72–120 (the transition period), and Week 120 onward (RECAP), as described in Figure 1. This analysis was also stratified based on CAPACITY study of origin (004 or 006).

Results

FVC decline by baseline lung function. Overall, 584 individuals who entered RECAP with baseline FVC values were included in this analysis (median age, 69.0 years; male, 71.9%; white, 97.8%; median body mass index [BMI], 28.9 kg/m²). At baseline, 28.6%, 52.2%, and 19.2% of individuals had a gender, age, and physiology (GAP) index of I, II, and III, respectively. Mean % predicted FVC and hemoglobin-corrected diffusing capacity of the lung for carbon monoxide (DLCO) at baseline in individuals with available data were 70.9% and 41.1%, respectively (baseline FVC: <50%, n = 54; ≥50% to <60%, n = 113; ≥60% to <70%, n = 136; ≥70% to <80%, n = 123; ≥80% to <90%, n = 84; ≥90%, n = 74).

For all baseline FVC subgroups, mean declines in % predicted FVC over 180 weeks (2.5–4.3%) and annual rates of FVC decline (101.1–181.0 ml) during RECAP were similar (Figure 2).

FVC decline and timing of pirfenidone initiation. Overall, 485 CAPACITY participants (n = 236, 2,403 mg/d pirfenidone; n = 249, placebo) were enrolled in RECAP and had FVC value(s) recorded in the transition period. Demographics were similar between treatment groups (CAPACITY) and previous treatment groups (RECAP) (median age, 67.0–69.0 yr; male, 69.9–73.5%; white, 97.5–97.7%; median BMI, 29.0–30.0 kg/m²). Median % predicted FVC and DLCO at baseline were similar between pirfenidone and placebo groups in CAPACITY (FVC: 73.7% and 72.1%, respectively; DLCO: 45.6% and 45.4%, respectively), and previous pirfenidone and placebo groups in RECAP (FVC: 69.8% and 69.4%, respectively; DLCO: 40.4% and 40.1%, respectively).

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During CAPACITY, annual rate of FVC decline was 142.0 ml and 182.3 ml (–40.3 ml difference) in pirfenidone and placebo groups, respectively (Figure 3). During RECAP, annual rate of FVC decline for previous pirfenidone and placebo groups, respectively, was 155.2 and 151.9 ml (3.3 ml difference) in the transition period and 145.3 and 140.9 ml (4.4 ml difference) after Week 120.

FVC decline in the placebo group in CAPACITY Study 006 was attenuated (3); therefore, this analysis was stratified based on CAPACITY study of origin. The difference between annual rate of FVC decline in the pirfenidone and placebo groups was larger during Study 004 (155.8 vs. 212.1 ml) than Study 006 (128.6 vs. 151.8 ml). Corresponding rates after CAPACITY were 123.2 versus 123.6 ml (previous Study 004) and 187.1 versus 184.7 ml (previous CAPACITY).

**Figure 1.** Treatment periods for calculating annual forced vital capacity (FVC) decline during CAPACITY and RECAP to assess the association of FVC decline and timing of pirfenidone initiation (aim 2). *Pirfenidone was titrated from 801 mg/d over the first 15 days in RECAP up to the maintenance dose (or maximum tolerated dose if this was lower). CAPACITY = Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes.

**Figure 2.** Rate of lung function decline over 180 weeks by baseline % predicted forced vital capacity (FVC) category in RECAP.
Study 006) during the transition period, and 138.5 versus 137.7 ml (previous Study 004) and 152.3 versus 144.4 ml (previous Study 006) after Week 120.

**Discussion**

These *post hoc* analyses of CAPACITY and RECAP found that long-term pirfenidone treatment had similar efficacy regardless of baseline FVC, and there was no effect of prior treatment on FVC change during RECAP. Importantly, loss of lung function that occurred before pirfenidone initiation was not recovered after initiation in RECAP, confirming that delaying antifibrotic treatment results in increased irreversible FVC loss. The efficacy of pirfenidone in reducing FVC decline was maintained for over 4 years, with little change in annual rate of FVC decline after more than 1 year of treatment in individuals who received pirfenidone during CAPACITY. These results are in line with previous analyses indicating that pirfenidone treatment is beneficial in individuals with IPF, regardless of stage of lung function or time since diagnosis at initiation (5, 10, 11).

These findings are limited by the fact that they represent *post hoc* exploratory analyses, and that RECAP was an open-label extension study with no placebo group. Long-term follow-up might have introduced selection bias toward individuals with more preserved lung function over time, because they were less likely to discontinue treatment during CAPACITY or RECAP. In addition, individuals enrolled in CAPACITY had fewer comorbidities than are observed in unselected populations (3); thus, the benefits of initiating pirfenidone in individuals with more comorbidities could not be determined.

Overall, these results add weight to evidence supporting pirfenidone initiation at diagnosis in individuals with IPF to prevent irreversible loss of lung function.

**Figure 3.** Annual rate of lung function decline in CAPACITY and RECAP by treatment group during CAPACITY. *Annual rates of forced vital capacity (FVC) decline during RECAP were calculated on the basis of all available RECAP FVC values, but only presented up to Week 220. CAPACITY = Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes. Adapted by permission from Reference 12.

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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Using Syndromic Surveillance to Evaluate the Respiratory Effects of Fine Particulate Matter

To the Editor:

Particulate air pollution is a prevalent exposure in urban areas and has been linked to mortality and adverse respiratory conditions, including asthma, chronic obstructive pulmonary disease, lower respiratory infection, and lung cancer (1–3). Studies of daily changes in fine particulate matter (aerodynamic diameter <2.5 μm [PM_{2.5}]) and acute respiratory effects often use data from the healthcare system, typically acute care events, such as emergency department visits, hospital admissions, and to a lesser extent provider visits (4–6). However, this approach may overlook some events, because patients presenting with subacute complaints may not initially seek care in these ways due to access (e.g., travel time), insurance coverage (e.g., copayments), or other factors such as presence of comorbidities (e.g., ability to travel). In addition, some subacute symptoms may not warrant emergency care but instead can be addressed through a primary care physician visit or contact with a nurse via phone or email.

We adopted a syndromic surveillance framework to examine the relationship between ambient PM_{2.5} concentrations and respiratory symptoms in a large health maintenance organization–based healthcare system in the Mid-Atlantic region of the United States. Syndromic surveillance identifies changes in disease activity using either clinical features detected before diagnosis is confirmed or activities prompted by the onset of symptoms (7). We hypothesized that calls and e-mails related to respiratory symptoms would represent an association with PM_{2.5} similar to the associations observed with emergency department and urgent care visits.

**Methods**

We constructed an innovative database of information collected during routine provision of medical care by Kaiser Permanente Mid-Atlantic States (KPMAS), which serves approximately 700,000 residents of the northern Virginia, District of Columbia, Maryland, and Baltimore areas. This study was approved by institutional review boards at KPMAS and Georgia State University.

Healthcare utilization data were collected from the comprehensive electronic health databases of KPMAS. We identified four types of utilization events for 2013 and 2014: 1) any phone contact or e-mail message (member or provider initiated); 2)...

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**References**


