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Pirfenidone Treatment in Individuals with Idiopathic Pulmonary Fibrosis: Impact of Timing of Treatment Initiation

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Running Head: Impact of timing of pirfenidone initiation [42/50 characters]

Key Words: Idiopathic pulmonary fibrosis, antifibrotic, pirfenidone, early intervention, preserved lung function

Word Count: 1000

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 (percent 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 percent 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 [NCT01366209]; CAPACITY [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 pirfenidone 2403 mg/day 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 percent predicted FVC, categorized by baseline percent 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/year) 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 (pirfenidone 2403 mg/day or placebo; the pirfenidone 1197 mg/day group was not included). Annual FVC decline was calculated for Weeks 0–120 (CAPACITY), Weeks 72–120 (the transition period), and Week 120 onwards (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, Physiology Index of I, II, and III, respectively. Mean percent predicted FVC and hemoglobin-corrected carbon monoxide diffusing capacity (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 percent 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, pirfenidone 2403 mg/day; 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 years; male, 69.9–73.5%; white, 97.5–97.7%; median BMI, 29.0–30.0 kg/m². Median percent predicted FVC and DLco at baseline were similar between pirfenidone and placebo groups in CAPACITY (FVC: 73.7% and 72.1%; DLco: 45.6% and 45.4%, respectively), and previous pirfenidone and placebo groups in RECAP (FVC: 69.8% and 69.4%; DLco: 40.4% and 40.1%, respectively).

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 vs 123.6 mL (previous Study 004) and 187.1 vs 184.7 mL (previous Study 006) during the

transition period and 138.5 vs 137.7 mL (previous Study 004) and 152.3 vs 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 >4 years, with little change in annual rate of FVC decline after >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 towards individuals with more preserved lung function over time, since they were less likely to discontinue treatment during CAPACITY or RECAP. Additionally, 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.

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Data sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Figure Legends

Figure 1. Treatment periods for calculating annual 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/day over the first 15 days in RECAP up to the maintenance dose (or maximum tolerated dose if this was lower). FVC, forced vital capacity

Figure 2. Rate of lung function decline over 180 weeks by baseline percent predicted FVC category in RECAP. FVC, forced vital capacity; SD, standard deviation

Figure 3. Annual rate of lung function decline in CAPACITY and RECAP by treatment group during CAPACITY. *Annual rates of FVC decline during RECAP were calculated on the basis of all available RECAP FVC values, but only presented up to Week 220. FVC, forced vital capacity; SE, standard error

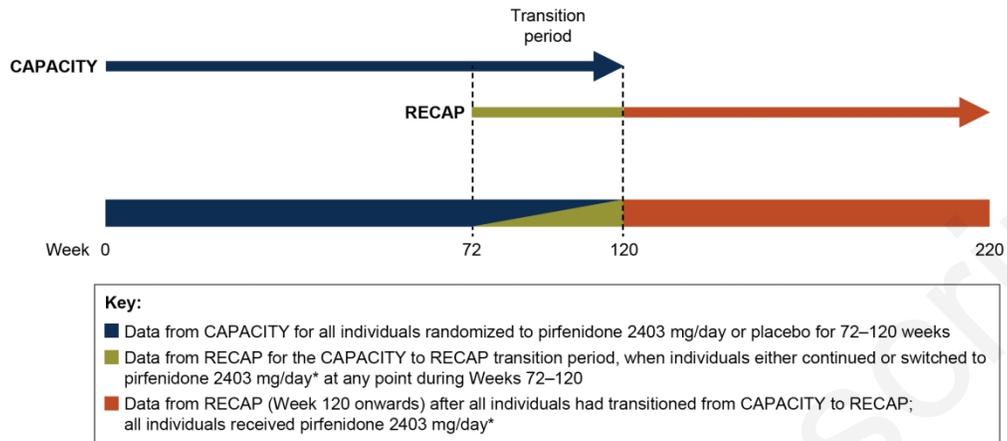


Figure 1

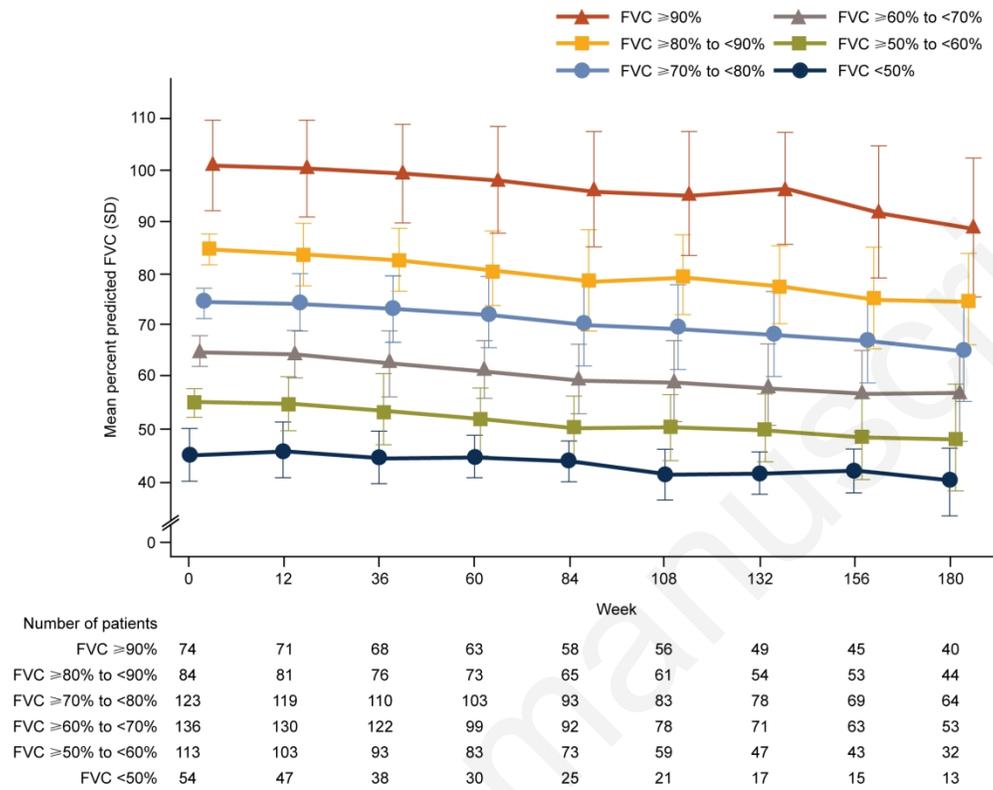


Figure 2

