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ORIGINAL ARTICLE

Pirfenidone Reduces Respiratory-related Hospitalizations in Idiopathic Pulmonary Fibrosis

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Abstract

Rationale: Respiratory-related hospitalizations of patients with idiopathic pulmonary fibrosis (IPF) are more frequent than those for acute IPF exacerbations and are associated with poor outcomes.

Objectives: To compare the risk of nonelective hospitalization by type (all-cause, respiratory related, and non–respiratory related) and death after hospitalization with use of pirfenidone versus placebo over 52 weeks using data derived from three phase III IPF clinical trials.

Methods: Individual patient data was pooled from three phase III randomized, placebo-controlled studies of pirfenidone for IPF (the two CAPACITY [Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes] trials and the ASCEND [Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis] trial), including all patients randomized to pirfenidone 2,403 mg/d (n = 623) or placebo (n = 624). The risk of hospitalization over 52 weeks was compared using standard time-to-event methods. Among those hospitalized, the risk of death after hospitalization was compared with adjustment for treatment group propensity.

Measurements and Main Results: A total of 1,247 patients (692 from the CAPACITY trials and 555 from the ASCEND trial) were included in the pooled analysis. Pirfenidone was associated with lower risk of respiratory-related hospitalization than placebo (7% vs. 12%; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.36–0.77; $P = 0.001$), but all-cause (HR, 0.91; 95% CI, 0.70–1.19;

$P = 0.528$) or non–respiratory-related hospitalization (HR, 1.32; 95% CI, 0.92–1.88; $P = 0.145$) was not. Among those hospitalized for any reason, treatment with pirfenidone was associated with lower risk of death after hospitalization up to 52 weeks after randomization, but this association was no longer significant with longer follow-up.

Conclusions: In a pooled analysis of three phase III IPF clinical trials, patients receiving pirfenidone had a lower risk of nonelective respiratory-related hospitalization over the course of 1 year. The effect of pirfenidone on death after hospitalization is uncertain.

Keywords: idiopathic pulmonary fibrosis; pirfenidone; hospitalization; mortality

At a Glance Summary

Scientific Knowledge on the Subject: Nonelective hospitalizations, especially those for respiratory reasons, are associated with increased mortality and health care costs in idiopathic pulmonary fibrosis (IPF). Pirfenidone is proven to reduce the decline in FVC in IPF, but the impact of pirfenidone on hospitalizations is unknown.

What This Study Adds to the Field: Analysis of pooled individual patient data from three phase III IPF trials demonstrated that pirfenidone treatment is associated with a reduced risk of respiratory-related hospitalization and possibly death after hospitalization of any type among patients with IPF.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease occurring primarily in older adults, with a median survival of 3–5 years from diagnosis (1). During their disease course, most patients with IPF will be hospitalized several times, for both respiratory and non–respiratory-related reasons (2–5). Respiratory-related hospitalizations are particularly important clinical events in IPF because of the associated morbidity, cost, and short-term mortality risk (2, 3, 5–12). Respiratory-related hospitalizations are more easily identified than acute IPF exacerbations and are directly relevant to how patients feel, function, and survive (13–16). Therefore, treatments that reduce the risk and/or morbidity of respiratory-related hospitalizations could have a major impact in the field.

Pirfenidone is a U.S. Food and Drug Administration–approved treatment for IPF that is proven to slow disease progression as defined by 1-year decline in FVC (17–19). Pirfenidone has also been shown to reduce decline in exercise capacity as defined by 6-minute-walk distance (6MWD) and progression-free survival over the course of 1 year as defined by decline in FVC, decline in 6MWD, or death (18). Pooled analysis of three phase III clinical trials in IPF has also suggested a significant reduction in 1-year mortality (18, 20, 21). However, the impact of pirfenidone on the risk of respiratory hospitalization and subsequent mortality remains unknown.

The objective of this study was to evaluate the 1-year risk of nonelective hospitalization (including all-cause, respiratory related, and non–respiratory related) and death after hospital admission among patients randomized to pirfenidone versus placebo, using data derived from three large phase III clinical trials of pirfenidone in IPF.

Methods

Study Population
The study population included all patients randomized to pirfenidone 2,403 mg daily or placebo in three completed phase III trials: the two CAPACITY (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) trials (004 and 006) (17) and the ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic

Pulmonary Fibrosis) trial (18). The enrollment criteria for CAPACITY and ASCEND are described in more detail elsewhere (17, 18). All patients were required to have a diagnosis of IPF (confident diagnosis by the local investigator for CAPACITY and centrally confirmed diagnosis according to international criteria [1] for ASCEND), an FVC percent predicted of at least 50%, and a 6MWD of at least 150 m. Key differences were in the diffusing capacity of the lung for carbon monoxide ($D_{L_{CO}}$) percent predicted cutoff ($\geqslant$35% for CAPACITY vs. $\geqslant$30% for ASCEND), post-bronchodilator FEV_1/FVC ratio ($\geqslant$70% for CAPACITY vs. $\geqslant$80% for ASCEND), and upper limits allowed for FVC and $D_{L_{CO}}$ percent predicted (either required to be $\leqslant$90% for CAPACITY vs. both required to be $\leqslant$90% for ASCEND).

Study Design
Patients were followed for 72–120 weeks and 52 weeks from the time of randomization in the CAPACITY and ASCEND trials, respectively. Clinical assessments, including pulmonary function testing, were performed at randomization and every 12 weeks in the CAPACITY trials and every 13 weeks in the ASCEND trial for the duration of the trials. The primary endpoint for both CAPACITY and ASCEND was change in FVC percent predicted from randomization to the end of the trial (72 weeks in CAPACITY vs. 52 weeks in ASCEND). CAPACITY 004 and ASCEND were positive studies, whereas CAPACITY trial 006 failed to meet its primary endpoint (16). In CAPACITY,

hospitalization was a prespecified secondary endpoint, and the local site investigator selected the primary reason for hospitalization from among acute respiratory decompensation; IPF exacerbation; pneumonia; respiratory related, other; or non–respiratory related. For this analysis, all but non–respiratory related were considered respiratory-related hospitalizations. In ASCEND, hospitalizations were recorded as serious adverse events. For the purposes of this study, all hospitalizations in ASCEND were retrospectively reviewed independently by two experienced pulmonologists blinded to treatment group and categorized as either respiratory related or non–respiratory related. Discordance (n = 1) was independently adjudicated by a third experienced pulmonologist blinded to treatment group.

Statistical Analysis
Individual patient data from all randomized patients were pooled and analyzed according to treatment assignment at randomization (i.e., based on intention to treat). Follow-up was censored at the time of loss to follow-up, death, or administratively at 52 weeks. Deaths after admission to the first hospitalization were recorded. Elective hospitalizations for lung transplant were excluded.

Cox proportional hazards models stratified by trial, Kaplan-Meier curves, and the log-rank test were used to compare time to first nonelective hospitalization (including all-cause, non–respiratory related, and respiratory related) in pirfenidone-treated versus placebo-treated patients. Sensitivity analyses were performed, including (1) a repeated failure

Table 1. Characteristics of Patients Pooled from Three Phase III Trials of Pirfenidone versus Placebo in Idiopathic Pulmonary Fibrosis

Characteristic	Pirfenidone (n = 623)	Placebo (n = 624)
Age, yr, mean (SD)	67.2 (7.6)	67.1 (7.5)
Male sex, n (%)	463 (74.3)	465 (74.5)
White race, n (%)	592 (95.0)	590 (94.6)
FVC, % predicted, mean (SD)	71.6 (13.2)	72.0 (13.6)
$D_{L_{CO}}$, % predicted, mean (SD)	45.6 (10.2)	45.6 (11.1)
FEV_1/FVC ratio, mean (SD)	0.84 (0.04)	0.83 (0.05)
6MWD, m, mean (SD)	403.8 (93.7)	411.8 (94.2)
UCSD SOBQ, mean (SD)	34.2 (21.4)	34.9 (21.6)
Supplemental oxygen, n (%)	155 (24.9)	150 (24.0)
HRCT-based definite UIP, n (%)	574 (92.3)	584 (93.6)
Time since diagnosis, yr, median (range)	1.1 (>0–5)	1.1 (>0–4)

Definition of abbreviations: 6MWD = 6-minute-walk distance; $D_{L_{CO}}$ = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution computed tomography; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire; UIP = usual interstitial pneumonia.

Table 2. Nonelective Hospitalization Events by Type (All-Cause, Respiratory Related, and Non–Respiratory Related) and by Treatment Group

	All-Cause Hospitalizations		Respiratory Hospitalizations		Nonrespiratory Hospitalizations	
	Pirfenidone (*n* = 623)	Placebo (*n* = 624)	Pirfenidone (*n* = 623)	Placebo (*n* = 624)	Pirfenidone (*n* = 623)	Placebo (*n* = 624)
Total events, n	139	151	54	87	85	64
Patients with at least one event, n (%)	106 (17)	115 (18)	41 (7)	74 (12)	70 (11)	54 (9)
Events per 100 person-years	23.1	25.3	9.0	14.6	14.1	10.7

analysis for hospitalizations (i.e., not restricted to time to first hospitalization), (*2*) including trial as a covariate in Cox models with testing for trial-by-treatment interactions, and (*3*) extending follow-up time to 72 weeks for the CAPACITY trials.

To evaluate the risk of death after admission for the first nonelective hospitalization, we compared the time to death after hospital admission by treatment group among those patients hospitalized. Because this subgroup of patients was selected by a postrandomization factor (hospitalization), we performed a propensity score–adjusted analysis to account for potential confounding between treatment assignment and postadmission death. The propensity score model was constructed using a multivariable logistic regression model for treatment assignment (pirfenidone vs. placebo) among those hospitalized with inclusion of all demographic and baseline characteristics that had a *P* value less than 0.25 in univariate analysis for each hospitalization type. A Cox proportional hazards model was then used for time to death after hospital admission, including treatment assignment (pirfenidone vs. placebo) and adjustment for the propensity score. The primary analysis was again restricted to 52 weeks after randomization to align trials, and a sensitivity analysis was performed using up to 72 weeks of follow-up in the CAPACITY trials.

Results

Cohort Characteristics and Hospitalizations

A total of 1,247 patients were enrolled (CAPACITY, n = 692; ASCEND, n = 555). Of these, 623 were randomized to treatment with pirfenidone 2,403 mg daily, and 624 were randomized to placebo. Baseline characteristics of the pooled cohort

are shown in Table 1 and are well matched, as expected for randomized trials. There were a total of 139 nonelective hospitalizations (54 respiratory related and 85 non–respiratory related) in pirfenidone-treated patients and 151 nonelective hospitalizations (87 respiratory related and 64 non–respiratory related) in placebo-treated patients (Table 2). Hospitalization rates were similar for centers in the United States (18.4% [165 of 897] of patients had one or more all-cause hospitalizations and 8.7% [78 of 897] had one or more respiratory-related hospitalizations) and non-U.S. centers (16.0% [56 of 350] of patients had one or more all-cause hospitalizations and 10.6% [37 of 350] had one or more respiratory-related hospitalizations).
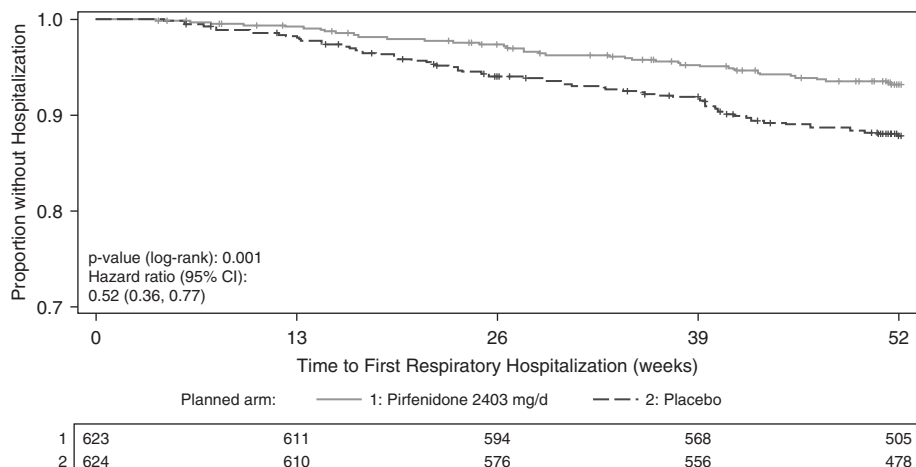
Risk of Hospitalization

In pirfenidone-treated patients, 17% (106 of 623) experienced at least one nonelective hospitalization, 7% (41 of 623) experienced at least one respiratory-related hospitalization, and 11% (70 of 623) experienced at least one non–respiratory-related hospitalization (Table 2). In

placebo-treated patients, 18% (115 of 624) experienced at least one nonelective hospitalization, 12% (74 of 624) experienced at least one respiratory-related hospitalization, and 9% (54 of 624) experienced at least one non–respiratory-related hospitalization. Pirfenidone-treated patients were less likely than placebo-treated patients to experience respiratory-related hospitalization (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.36–077; $P = 0.001$ by log-rank test) (Figures 1 and 2). There were no significant differences in risk of all-cause hospitalization (HR, 0.91; 95% CI, 0.70–1.19; $P = 0.528$ by log-rank test) or non–respiratory-related hospitalizations (HR, 1.32; 95% CI, 0.92–1.88; $P = 0.145$ by log-rank test) (Figure 1). The results were similar when we used a repeated-failures analysis for all hospitalizations (*see* Table E1 in the online supplement) and after extending follow-up time in CAPACITY to 72 weeks (Table E2). We did not find evidence for significant treatment-by-trial interactions on risk of hospitalization of any type (Table E3).

HR (95% CI) of Hospitalizations—Pirfenidone vs. Placebo
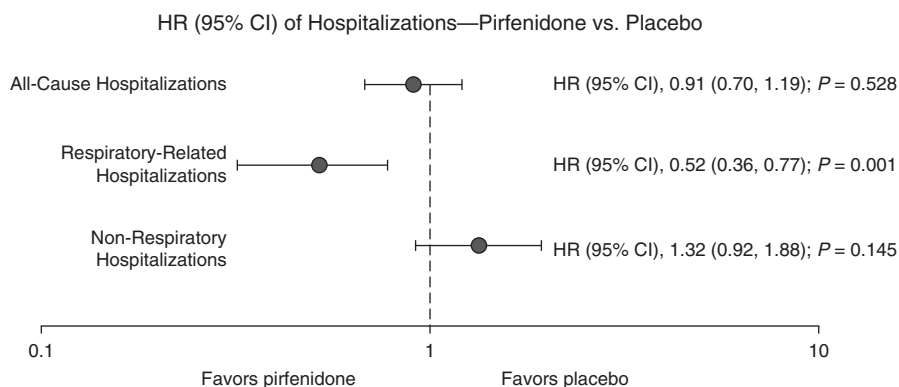
Figure 1. Forest plot demonstrating risk of first nonelective hospitalization by type (all-cause, respiratory related, and non–respiratory related) in pirfenidone-treated patients compared with placebo-treated patients. CI = confidence interval; HR = hazard ratio.

Figure 2. Kaplan-Meier plot for time to first nonelective respiratory-related hospitalization in pirfenidone-treated patients compared with placebo-treated patients. CI = confidence interval.

Death after Hospitalization

Among those with at least one nonelective hospitalization, 18 of 106 (17%) died in the pirfenidone group and 37 of 115 (32%) died in the placebo group (Table 3), which was consistent with an association between allocation to the pirfenidone arm and lower risk of death in unadjusted (HR, 0.49; 95% CI, 0.28–0.86; $P = 0.013$) and propensity score–adjusted (HR, 0.56; 95% CI, 0.32–0.99; $P = 0.047$) analyses (Table 4). This difference appeared to be driven largely by reduced risk of death among those hospitalized for respiratory-related reasons (Tables 3 and 4). However, this association was no longer significant when we considered follow-up to 72 weeks in the CAPACITY trials (Table E4).

Discussion

On the basis of pooled individual patient data from three phase III clinical trials of pirfenidone in IPF, this study demonstrates that treatment of IPF with pirfenidone is associated with a significant reduction in the risk of hospitalization for respiratory reasons over the course of 1 year of therapy. It also suggests a reduced risk of death after any hospital admission (respiratory related or not) over the course of 1 year for those taking pirfenidone compared with placebo. To our knowledge, this is the first study reporting a beneficial effect of any treatment on respiratory hospitalizations in IPF. Respiratory hospitalizations are clinically relevant events for patients with IPF with a high risk of short-term mortality as well as excessive morbidity and additional health care costs; therefore, prevention of respiratory hospitalizations should be regarded as an important goal of therapy.

How pirfenidone results in reduced risk of respiratory hospitalization is unclear, considering the multiple reasons that a patient with IPF may be hospitalized with worsening respiratory symptoms (2). One plausible explanation is that pirfenidone, by preserving lung function (physiological reserve) (17, 18), reduces the relative risk of acute IPF exacerbation. Unfortunately, we were unable to examine this hypothesis directly, because acute exacerbations were not systematically collected and adjudicated in the source trials. Another possibility is that pirfenidone reduces disease activity, thereby limiting the collateral damage resulting from respiratory stressors such as infection that may drive admissions. Regardless of the reason, the effect of pirfenidone on reducing nonelective hospitalizations seems to be specific to those resulting from worsening respiratory symptoms and not other nonpulmonary acute events that result in hospitalization in the older IPF population. Although not statistically significant, a numerical increase in nonrespiratory hospitalizations in pirfenidone compared with placebo-treated patients was observed that is of unclear clinical significance. It is reassuring that despite this, the risk of death after nonrespiratory hospitalization was not increased in pirfenidone-treated patients, and in contrast to respiratory hospitalizations, nonrespiratory reasons for hospitalization in patients with IPF do not appear to be associated with increased risk of subsequent mortality (6). We also did not observe an increase in any specific reason for nonrespiratory hospitalization in pirfenidone-treated versus placebo-treated patients, but our study lacked statistical power for definitive conclusions to be drawn.

Although decline in FVC has served as an important surrogate endpoint in IPF trials, there is a strong desire to identify clinically meaningful endpoints more directly (14–16, 22). This study lends further support for respiratory hospitalization as a modifiable and clinically meaningful endpoint in IPF trials (6, 12). Respiratory hospitalizations can be enriched by including patients with greater physiological impairment, an important aspect of efficient clinical trial design lacking for FVC decline (23). Concerns regarding varying rationales for hospitalization across countries are not supported by our data, which show

Table 3. Deaths Occurring after Nonelective Admission to the Hospital, by Hospitalization Type (All-Cause, Respiratory Related, and Non–Respiratory Related) and by Treatment Group

	All-Cause Hospitalizations		Respiratory Hospitalizations		Nonrespiratory Hospitalizations	
	Pirfenidone (n = 106)	Placebo (n = 115)	Pirfenidone (n = 41)	Placebo (n = 74)	Pirfenidone (n = 70)	Placebo (n = 54)
Deaths, n (%)	18 (17)	37 (32)	11 (27)	34 (46)	8 (11)	9 (17)

The n values given in column heads are the number of patients with at least one hospitalization.

Table 4. Risk of Death after Nonelective Hospitalization, by Type (All-Cause, Respiratory Related, and Non–Respiratory Related) in Pirfenidone-treated Patients versus Placebo-treated Patients, Unadjusted and Adjusted for Treatment Propensity

	Hazard Ratio	95% Confidence Interval	P Value
All-cause hospitalization (n = 221*)			
Unadjusted	0.49	0.28–0.86	0.013
Adjusted for propensity score[†]	0.56	0.32–0.99	0.047
Respiratory-related hospitalization (n = 115*)			
Unadjusted	0.55	0.28–1.08	0.082
Adjusted for propensity score[†]	0.50	0.25–1.03	0.061
Non–respiratory-related hospitalization (n = 124*)			
Unadjusted	0.67	0.26–1.74	0.412
Adjusted for propensity score[†]	0.73	0.27–1.97	0.537

Definition of abbreviations: D_{LCO}% = diffusing capacity of the lung for carbon monoxide percent predicted; GAP = Gender-Age-Physiology Index.
*Number of patients experiencing at least one event.
[†]Propensity score models were constructed using multivariable logistic regression for treatment assignment (pirfenidone vs. placebo) among those hospitalized with inclusion of demographic and baseline characteristics that had a *P* value less than 0.25 in univariate analysis for each hospitalization type. For all-cause hospitalization, the propensity score included GAP stage, baseline oxygen use, years since idiopathic pulmonary fibrosis diagnosis, and baseline D_{LCO}%. For respiratory-related hospitalization, the propensity score included study, GAP stage, racial group, baseline D_{LCO}%, baseline 6-minute-walk distance, and baseline University of California, San Diego Shortness of Breath Questionnaire score. For nonrespiratory hospitalization, the propensity score included GAP stage, age, baseline body mass index, years since idiopathic pulmonary fibrosis diagnosis, baseline D_{LCO}%, and baseline 6-minute-walk distance.

consistent rates of respiratory hospitalization, regardless of region.

There are important limitations to this study. First, it is a *post hoc* analysis of pooled data. However, this is a large dataset of well-characterized patients with IPF and high-quality prospective data collection, and in our study we analyzed individual patient–level data, allowing for more flexible accounting for confounding factors (e.g., propensity scores) than is possible in conventional meta-analyses. Also, the observed reduction in respiratory hospitalizations with pirfenidone versus placebo is consistent with the positive findings for other disease progression events, such as decline in FVC, observed in these trials. Second, the methods of collection and adjudication of hospitalization events differed between the source studies, which may have affected the accuracy of hospitalization classification. We believe this to be unlikely, considering the near-complete agreement between independent adjudicators for the ASCEND study. Although misclassification of hospitalization type could reduce the observed effect size, investigative sites (CAPACITY) and adjudicators (ASCEND) were blinded to treatment assignment, and thus their classification of hospital type should not have biased our results. Importantly, we found no significant effect of trial or trial-by-treatment interaction in the analyses. Third, in the analysis of death after hospitalization, we selected patients on a postrandomization factor (hospitalization), thus introducing the possibility of unmeasured confounders. Our use of a propensity score helps limit, but does not eliminate, the possibility of confounding in this analysis. We acknowledge that it is also difficult to explain how pirfenidone might reduce the risk of death after hospitalization of any type, especially in light of the fact that we observed a nonsignificant increase in rates of nonrespiratory hospitalization in the pirfenidone group. Although not statistically significant in isolation, this association appears to be driven primarily by lower risk of death after respiratory hospitalizations. These results should be interpreted with caution because the association is no longer significant with longer-term follow-up. Finally, the small number of respiratory hospitalization events and the retrospective data review limit our ability to decipher which types of respiratory events were and were not impacted by pirfenidone therapy.

In conclusion, pooled data from three phase III clinical trials in IPF indicate that pirfenidone reduces the risk of hospitalization for respiratory reasons. Future studies are needed to examine the long-term effects of pirfenidone on hospitalization rates, outcomes of hospitalization, and health care costs in IPF. We believe that reducing the risk of respiratory hospitalization is an important goal of therapy, and it should be included as a key endpoint in future IPF trials. ■

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