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Antacid Therapy and Disease Progression in Patients with Idiopathic Pulmonary Fibrosis Who Received Pirfenidone

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Keywords

Antacid therapy · Gastroesophageal reflux disease · Idiopathic pulmonary fibrosis · Pirfenidone · Progression-free survival

Abstract

Background: Gastroesophageal reflux disease is a potential risk factor for idiopathic pulmonary fibrosis (IPF) progression; however, the impact of antacid therapy (AAT) is under debate. ***Objective:*** To evaluate the effect of AAT on IPF progression in pirfenidone-treated patients. ***Methods:*** This post hoc analysis included patients with IPF who received pirfenidone in 3 trials (CAPACITY [PIPF-004/PIPF-006] and ASCEND [PIPF-016]). Pulmonary function, exercise tolerance, survival, hospitalizations, and adverse events (AEs) over 52 weeks were analyzed by baseline AAT use. Disease progression was defined as a decrease in forced vital capacity (FVC) of ≥10%, a decrease in 6-min walking distance of ≥50 m, or death over 1 year. ***Results:*** Of 623 patients, 44% received AAT. No significant differences were found at 52 weeks (AAT versus non-AAT, respectively) in disease progression (24.9 vs. 30.6%; $p = 0.12$), all-cause mortality rate (2.9 vs. 4.0%; $p = 0.47$), IPF-related mortality rate (1.1 vs. 2.0%; $p = 0.37$), all-cause hospitalization rate (16.1 vs. 18.3%; $p = 0.48$), or mean change in percent FVC (–2.7 vs. –3.1%; $p = 0.44$). A relative, but not absolute, FVC decline of ≥10% favored AAT (15 vs. 22%; $p = 0.03$). Severe gastrointestinal AEs (3.7 vs. 0.9%; $p = 0.015$) and severe pulmonary infections (3.7 vs. 1.1%; $p = 0.035$) were more frequent with AAT. ***Conclusions:*** AAT and pirfenidone had outcomes comparable to those of pirfenidone alone in patients with IPF, underscoring the need for prospective trials to elucidate the role of AAT with or without antifibrotic drugs as a treatment for IPF.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a debilitating, progressive, unpredictable, and ultimately fatal fibrosing lung disease characterized by a relentless decline in lung function, worsening dyspnea, and diminished exercise tolerance. The rate of IPF progression can vary from person to person, and the median survival time from diagnosis is 2–3 years [1]. Pirfenidone and nintedanib have demonstrated significant slowing of disease progression in clinical trials compared with placebo and are approved for the treatment of IPF [2–4].

The clinical efficacy and safety of pirfenidone were demonstrated in 4 randomized controlled phase 3 trials [3–6]. Efficacy data from these trials, and a pooled analysis, confirmed a clinically meaningful benefit of pirfenidone compared with placebo in multiple measures of disease status, including 6-min walking distance (6MWD), forced vital capacity (FVC), and progression-free survival (PFS).

Comorbidities – such as cardiovascular disease, lung cancer, and gastroesophageal reflux disease (GERD) – significantly affect the symptoms and survival associated with IPF [7]. GERD is characterized by heartburn, dyspepsia, regurgitation, and chest pain [8]. The incidence of GERD is higher in patients with IPF (8–87%) compared with the general population (10–38%) [9–13]. This may be due to shared risk factors, including age and smoking [14]. GERD may also be induced by lung fibrosis, but the causal relationship is unclear [15–18]. The treatment of GERD includes lifestyle interventions, antacid therapy (AAT) with histamine H_2 receptor antagonists (H_2 blockers) or proton pump inhibitors (PPIs), and fundoplication [8]. PPIs (not H_2 blockers) may have antifibrotic properties that act independently of gastric acid neutralization [19]. Current treatment guidelines give a conditional recommendation for AAT in patients with IPF, albeit with very low confidence in estimates of effect [20]. Although some studies have demonstrated that AAT is associated with longer survival time and slower disease progression, recent post hoc analyses do not support a protective effect of AAT on disease progression in patients with IPF [21, 22], which led to some discussion on the role of AAT in IPF [23–25]. The impact of AAT on disease progression in patients with IPF who receive pirfenidone is unknown.

The objective of this study was to compare the incidence of the composite endpoint of disease progression as well as other clinical outcomes – including mortality, change in FVC, change in 6MWD, and hospitalization rate – between patients with IPF randomized to pirfenidone in 3 large phase 3 trials stratified by AAT at baseline.

Subjects and Methods

Study Population

The study population included all patients with IPF randomized to 2,403 mg/day pirfenidone in 3 trials (CAPACITY [PIPF-004], NCT00287716; CAPACITY [PIPF-006], NCT00287729; and ASCEND [PIPF-016], NCT01366209); patients randomized to a lower dose were excluded. Patients were stratified into 2 subgroups on the basis of AAT use (i.e., yes versus no; either H_2 blockers and/or PPIs) at trial baseline. The eligibility criteria for the trials were previously described [3, 4]. All trial participants provided written informed consent, and the ethics committee or institutional review board at each participating institution approved the protocol for each trial.

Data Collection

Data collected included patient demographic and clinical characteristics, pulmonary function (e.g., FVC and hemoglobin-corrected predicted diffusing capacity of the lung for carbon monoxide [DL_{CO}]), exercise tolerance (6MWD), dyspnea (University of California at San Diego Shortness of Breath Questionnaire [UCSD-SOBQ] score), medication use (e.g., H_2 blockers and PPIs), indication for use, adverse events (AEs), hospitalization rate, and vital status. FVC, 6MWD, and UCSD-SOBQ score were measured at trial baseline and periodically during the trial; DL_{CO} was assessed after baseline only in the CAPACITY trials. PFS was defined as the time to the first occurrence of a confirmed decrease in predicted FVC of ≥10%, a confirmed decrease in 6MWD of ≥50 m, or death. The primary cause of any death and its relation to IPF were assessed in a blinded fashion by an independent mortality assessment committee in the ASCEND trial [3] and by the site investigators in the CAPACITY trials [4]. For this study, all safety events through 52 weeks were considered. Severe gastrointestinal (GI)-related side effects and severe pulmonary infections were defined as grade 3 or 4 (grade 3 is severe and grade 4 is life-threatening).

Post hoc Analysis of Study Outcomes

The primary study outcome of disease progression was defined as a decrease in FVC of ≥10%, a decrease in 6MWD of ≥50 m, or death (whichever occurred first) over 1 year from baseline. Functional worsening (FVC decrease of ≥10% and/or 6MWD decrease of ≥50 m) was considered only when observed on 2 consecutive occasions ≥6 weeks apart. Secondary outcomes included all-cause and IPF-related mortality, decreases in FVC (absolute and relative decreases of ≥5 and ≥10%, respectively), all-cause and IPF-related hospitalization rates, and potentially important AEs (GI-related AEs, infections, and severe pulmonary infections). Outcomes were additionally analyzed based on patient FVC baseline of greater lung function loss (FVC <70%) and less lung function loss (FVC ≥70%). A baseline FVC of 70% was chosen because it was the mean FVC of the patient population.

Statistical Analyses

The demographic and clinical characteristics of the study population were evaluated separately by trial, collectively and stratified by use of AAT at baseline. Unadjusted risks of binary study outcomes as well as changes from baseline in FVC and 6MWD among baseline users of AAT versus baseline nonusers were compared using an independent-sample *t* test for continuous variables and χ^2 test for categorical variables. AAT use was examined against binary study outcomes using a shared frailty model (an extension of the

Table 1. Baseline demographics and clinical characteristics by antacid therapy use

	AAT (n = 273)	No AAT (n = 350)	p value
Age, years			
Mean ± SD	67.9±7.8	66.7±7.3	0.0499
Median (IQR)	69 (62–74)	67 (62–72)	–
Male	195 (71.4%)	268 (76.6%)	0.1449
Physiological (mean ± SD)			
FVC, % predicted	71.6±13.4	71.6±13.1	0.9909
DL_{CO}, % predicted	45.7±10.0	45.5±10.3	0.7878
6MWD	396.8±90.2	409.3±96.1	0.1013
Dyspnea (mean ± SD)			
UCSD-SOBQ	34.7±21.5	33.8±21.3	0.6299
Medical history			
Comorbidities			
CVD	79 (28.9%)	90 (25.7%)	0.3693
CRF	6 (2.2%)	6 (1.7%)	0.6631
COPD	14 (5.1%)	8 (2.3%)	0.0565
Pulmonary embolism	4 (1.5%)	5 (1.4%)	0.9697
Pulmonary hypertension	7 (2.6%)	7 (2.0%)	0.6374
Atrial fibrillation	14 (5.1%)	17 (4.9%)	0.8773
Sleep apnea	45 (16.5%)	46 (13.1%)	0.2414
Gastrointestinal comorbidities			
GERD	236 (86.4%)	84 (24.0%)	<0.001
Hiatal hernia	35 (12.8%)	19 (5.4%)	0.0011
Barrett esophagus	14 (5.1%)	2 (0.6%)	<0.001
HP-positive gastritis	1 (0.4%)	1 (0.3%)	0.8600
Cardiovascular risk factors			
Hypertension	142 (52.0%)	168 (48.0%)	0.3200
Smoker (current/former)	180 (65.9%)	226 (64.6%)	0.7232
Diabetes	63 (23.1%)	87 (24.9%)	0.6061
Hypercholesterolemia	149 (54.6%)	161 (46.0%)	0.0336
Obesity (BMI >30)	128 (46.9%)	156 (44.6%)	0.5649
PPI use only	245 (89.74%)	–	–
H_2 use only	17 (6.23%)	–	–
PPI + H_2 use	11 (4.03%)	–	–

Values are presented as n (%) unless indicated otherwise. 6MWD, 6-min walking distance; AAT, antacid therapy; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRF, chronic respiratory failure; CVD, cardiovascular disease; DL_{CO}, hemoglobin-corrected predicted diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; H_2, histamine H_2 receptor antagonist; HP, *Helicobacter pylori*; IQR, interquartile range; PPI, proton pump inhibitor; SD, standard deviation; UCSD-SOBQ, University of California at San Diego Shortness of Breath Questionnaire.

Cox proportional hazards model that adjusts for intracluster [i.e., intratrial] correlation), without and with adjustment for age, sex, smoking status, lung function, and comorbidity profile. Survival curves were estimated based on the corresponding multivariate models and using the mean of covariates method; comparisons were based on the likelihood ratio test. Only observed data were used. Individuals were censored at the time of loss to follow-up, at the time of lung transplant, or at the end of the 1-year follow-up period, whichever occurred first. The presence of multicollinearity, hazards assumptions, and treating death as a competing risk (when appropriate) were evaluated using published methods [26, 27].

Results

A total of 623 patients were included in the study, of whom 273 (43.8%) received AAT (89.74% PPIs, 6.23% H_2 blockers, and 4.03% PPIs and H_2 blockers; Table 1) and 350 (56.2%) received no AAT. The baseline demographic and clinical characteristics of patients by trial are presented in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000468546).

Table 2. Indications for antacid therapy use by trial

Indication	CAPACITY PIPF-004 (n = 74)	CAPACITY PIPF-006 (n = 77)	ASCEND PIPF-016 (n = 122)	Pooled (n = 273)
GERD	58 (78.4%)	65 (84.4%)	100 (82.0%)	223 (81.7%)
Dyspepsia	0	5 (6.5%)	6 (4.9%)	11 (4.0%)
Gastritis	3 (4.1%)	0	5 (4.1%)	8 (2.9%)
Prophylaxis	2 (2.7%)	1 (1.3%)	4 (3.3%)	7 (2.6%)
Hiatal hernia	4 (5.4%)	0	2 (1.6%)	6 (2.2%)
Other	4 (5.4%)	2 (2.6%)	0	6 (2.2%)
Nonspecific GI disease	2 (2.7%)	2 (2.6%)	1 (0.8%)	5 (1.8%)
Ulcer	0	2 (2.6%)	1 (0.8%)	3 (1.1%)
Barrett esophagus	1 (1.4%)	0	1 (0.8%)	2 (0.7%)
Cough	0	0	2 (1.6%)	2 (0.7%)

Values are presented as n (%). Antacid therapy consisted of proton pump inhibitors, histamine H_2 receptor antagonists, or both. GERD, gastroesophageal reflux disease; GI, gastrointestinal.

Table 3. Unadjusted 1-year study outcomes by antacid therapy use

	AAT[a] (n = 273)	No AAT[a] (n = 350)	p value
Disease progression[b, c]	68 (24.9%)	107 (30.6%)	0.1187
All-cause mortality	8 (2.9%)	13 (3.7%)	0.5906
Absolute FVC decrease ≥10%[d]	14 (5.1%)	27 (7.7%)	0.1965
6MWD decrease ≥50 m	48 (17.6%)	72 (20.6%)	0.3479
Mortality			
All-cause	8 (2.9%)	14 (4.0%)	0.4730
IPF-related	3 (1.1%)	7 (2.0%)	0.3746
FVC change			
Absolute decrease ≥10%	17 (6.2%)	35 (10.0%)	0.0912
Relative decrease ≥10%	41 (15.0%)	77 (22.0%)	0.0273
Absolute decrease ≥5%	69 (25.3%)	113 (32.3%)	0.0562
Relative decrease ≥5%	99 (36.3%)	145 (41.4%)	0.1901
FVC change			
Observed, % predicted (mean ± SD)	−2.7±5.7	−3.1±6.4	0.4375
Imputed, % predicted (mean ± SD)	−4.6±11.3	−5.9±14.5	0.2091
Observed, L (mean ± SD)	−0.11±0.23	−0.12±0.26	0.5162
Other outcomes			
6MWD decrease ≥50 m	49 (17.9%)	75 (21.4%)	0.2804
All-cause hospitalization	44 (16.1%)	64 (18.3%)	0.4781
Side effects			
GI side effects[e]	10 (3.7%)	3 (0.9%)	0.0151
Infections	184 (67.4%)	237 (67.7%)	0.9336
Severe pulmonary infections[e]	10 (3.7%)	4 (1.1%)	0.0352
Duration of follow-up, days (mean ± SD)	350.2±56.7	349.7±53.3	0.9181

Values are presented as n (%) unless indicated otherwise. [a] All patients were considered in the analyses unless noted otherwise. [b] FVC decrease of ≥10%, 6MWD decrease of ≥50 m, or death, whichever came first. [c] Only the first event was considered in the analysis. Events that occurred on the same day were counted in each subcategory, but contributed only a single event to the composite measure. [d] Includes only confirmed cases, defined as those for whom follow-up assessment was repeated ≥6 weeks following initial assessment and in whom criteria for outcome were met. [e] An adverse event of grade 3 or 4; grade 3 is severe and grade 4 is life-threatening. 6MWD, 6-min walking distance; AAT, antacid therapy; FVC, forced vital capacity; GI, gastrointestinal; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.

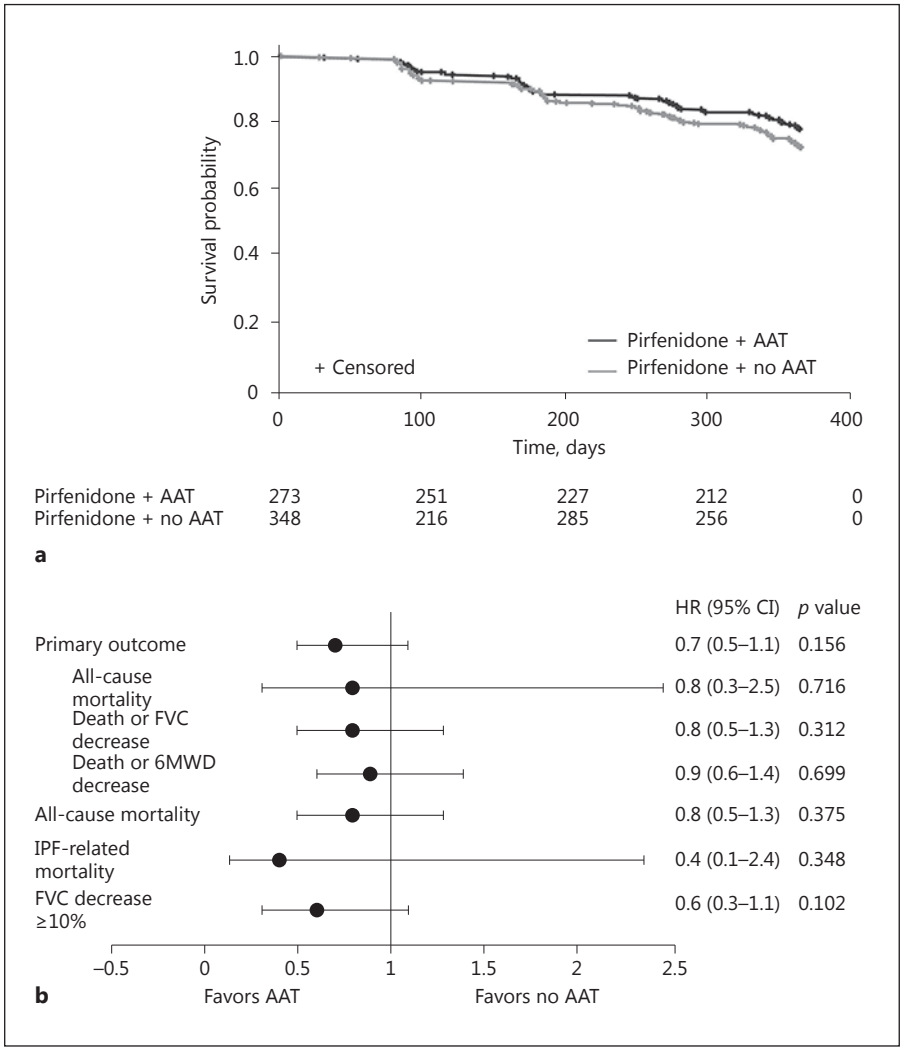

Fig. 1. Adjusted 1-year risk of progression-free survival (**a**) and study outcomes (**b**). Progression-free survival was defined as the time to the first occurrence of a confirmed decrease of ≥10% in predicted forced vital capacity (FVC), a confirmed decrease of ≥50 m in the 6-min walking distance (6MWD) test, or death. The primary outcomes were an FVC decrease of ≥10%, a 6MWD decrease of ≥50 m, or death. Adjusted analyses included age, sex, smoking status, lung function, and comorbidity profile. AAT, antacid therapy; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis.

The baseline demographic and comorbidity profiles were similar between the AAT and the non-AAT group, with the exception of a significantly higher proportion of AAT users having GERD (AAT, 86.4%; non-AAT, 24.0%; $p < 0.001$), hiatal hernia (AAT, 12.8%; non-AAT, 5.4%; $p = 0.001$), Barrett esophagus (AAT, 5.1%; non-AAT, 0.6%; $p < 0.001$), and hypercholesterolemia (AAT, 54.6%; non-AAT, 46.0%; $p = 0.0336$) (Table 1). The most common indications for AAT use were GERD (81.7%), dyspepsia (4.0%), and gastritis (2.9%) (Table 2); most patients received omeprazole (45.8%).

The mean follow-up time of the AAT and the non-AAT group was similar (350.2 vs. 349.7 days; $p = 0.918$) (Table 3). The proportion of patients in the AAT and the non-AAT group was similar for each component of the disease progression composite endpoint, which included the first events of all-cause mortality (2.9 vs. 3.7%; $p = 0.591$), absolute decrease in FVC of ≥10% (5.1 vs. 7.7%; $p = 0.197$), or decrease in 6MWD of ≥50 m (17.6 vs. 20.6%; $p = 0.348$). When the analyses were adjusted for confounders, disease progression was similar between AAT and non-AAT users at 1 year (hazard ratio [HR], 0.7; 95% CI, 0.5–1.1; $p = 0.156$) (online suppl. Table 2; Fig. 1). These results were similar to those from unadjusted analyses (Table 3). Also, when adjusted for confounders, the risk of all-cause or IPF-related death was not significantly reduced in the AAT group compared with the non-AAT group (all-cause mortality: HR, 0.8; 95% CI, 0.3–2.5; $p = 0.716$; IPF-related mortality: HR, 0.4; 95% CI, 0.1–2.4; $p = 0.348$) (online suppl. Table 2; Fig. 1b). These results were similar to those from unadjusted analyses (Table 3).

Table 4. Unadjusted 1-year risk of study outcomes by antacid therapy use and baseline forced vital capacity (% predicted; <70% vs. ≥70%)

	FVC <70%			FVC ≥70%		
	AAT[a] (*n* = 126)	no AAT[a] (*n* = 165)	*p* value	AAT[a] (*n* = 147)	no AAT[a] (*n* = 169)	*p* value
Disease progression[b, c]	42 (33.3%)	58 (35.2%)	0.7462	26 (17.7%)	49 (26.5%)	0.0569
All-cause mortality	7 (5.6%)	9 (5.5%)	0.9701	1 (0.7%)	4 (2.2%)	0.2708
Absolute FVC decrease ≥10%[d]	6 (4.8%)	7 (4.2%)	0.8317	8 (5.4%)	20 (10.8%)	0.0804
6MWD decrease ≥50 m	31 (24.6%)	45 (27.3%)	0.6075	17 (11.6%)	27 (14.6%)	0.4186
Mortality						
All-cause	7 (5.6%)	9 (5.5%)	0.9701	1 (0.7%)	5 (2.7%)	0.1694
IPF-related	3 (2.4%)	3 (1.8%)	0.7378	0 (0.0%)	4 (2.2%)	0.0729
FVC change						
Absolute decrease ≥10%	9 (7.1%)	13 (7.9%)	0.8140	8 (5.4%)	22 (11.9%)	0.0417
Relative decrease ≥10%	26 (20.6%)	47 (28.5%)	0.1259	15 (10.2%)	30 (16.2%)	0.1119
Absolute decrease ≥5%	34 (27.0%)	53 (32.1%)	0.3429	35 (23.8%)	60 (32.4%)	0.0842
Relative decrease ≥5%	51 (40.5%)	73 (44.2%)	0.5197	48 (32.7%)	72 (38.9%)	0.2378
FVC change (mean ± SD)						
Number	107	143		141	168	
FVC change (observed), % predicted	−3.1±5.8	−3.1±5.5	0.9124	−2.4±5.7	−3.2±7.1	0.2843
FVC change (imputed), % predicted	−6.5±13.8	−6.3±13.4	0.8775	−3.0±8.4	−5.6±15.4	0.0505
FVC change (observed), L	−0.12±0.23	−0.12±0.23	0.9397	−0.10±0.23	−0.12±0.28	0.3739
Other outcomes						
6MWD decrease ≥50 m	32 (25.4%)	45 (27.3%)	0.7193	17 (11.6%)	30 (16.2%)	0.2272
All-cause hospitalization	27 (21.4%)	31 (18.8%)	0.5763	17 (11.6%)	29 (15.7%)	0.2815
Side effects						
GI side effects[e]	5 (4.0%)	1 (0.6%)	0.0455	5 (3.4%)	2 (1.1%)	0.1438
Infections	90 (71.4%)	122 (73.9%)	0.6332	94 (63.9%)	115 (62.2%)	0.7382
Severe pulmonary infections[e]	8 (6.3%)	3 (1.8%)	0.0446	2 (1.4%)	1 (0.5%)	0.4329
Duration of follow-up, days (mean ± SD)	338.3±77.0	341.4±68.2	0.7198	360.3±26.3	357.2±33.3	0.3387

Values are presented as *n* (%) unless indicated otherwise. [a] All patients were considered in the analyses unless noted otherwise. [b] FVC decrease of ≥10%, 6MWD decrease of ≥50 m, or death, whichever came first. [c] Only the first event was considered in the analyses. [d] Includes only confirmed cases, defined as those for whom follow-up assessment was repeated ≥6 weeks following initial assessment and in whom criteria for outcome were met. [e] An adverse event of grade 3 or 4; grade 3 is severe and grade 4 is life-threatening. 6MWD, 6-min walking distance; AAT, antacid therapy; FVC, forced vital capacity; GI, gastrointestinal; IPF, idiopathic pulmonary fibrosis; SD, standard deviation.

AAT users had similar mean changes in FVC from baseline to week 52 compared with non-AAT users (Table 3). With the exception of a relative FVC decline of ≥10%, absolute and relative declines in FVC, a decrease in 6MWD of ≥50 m, and hospitalization rates after 52 weeks were similar between the AAT and the non-AAT patient group. The results were largely unchanged when patients who received only PPIs and not H_2 blockers were considered (data not shown).

The pirfenidone dose intensity of 90% was not significantly different between the AAT and the non-AAT group (68.9 vs. 67.4%; $p = 0.730$).

When patients were stratified by mean baseline FVC (≥70% or <70%), no significant differences were observed in either stratified group in disease progression or mortality between the AAT and the non-AAT group (Table 4). The unadjusted disease progression rates of patients with a percent predicted FVC of <70% (AAT, 42 [33.3%]; non-AAT, 58 [35.2%]; $p = 0.746$) and of patients with a percent predicted FVC of ≥70% (AAT, 26 [17.1%]; non-AAT, 49 [26.5%]; $p = 0.057$) were similar. Furthermore, no significant differences were observed in 6MWD decrease of ≥50 m and all-cause hospitalization rate between the AAT and the non-AAT groups when stratified by percent predicted FVC.

Patients who received AAT had significantly more severe GI-related AEs than those who did not (3.7 vs. 0.9%; $p = 0.015$) (Table 3). Overall, the incidence of infections was similar between the AAT and the non-AAT group (67.4 vs. 67.7%; $p = 0.934$). More severe pulmonary infec-

tions were observed in the AAT group than in the non-AAT group (3.7 vs. 1.1%; $p = 0.035$). Patients with a percent predicted FVC of <70% who received AAT had significantly more GI-related AEs and severe pulmonary infections than those who did not receive AAT.

Discussion

In this post hoc analysis, both AAT and non-AAT users at baseline had similar clinical outcomes at 52 weeks. No association between AAT use and disease progression or mortality was observed in patients who received AAT in combination with pirfenidone.

The 2015 treatment guidelines for IPF make a conditional recommendation for the use of AAT based on results from retrospective studies suggesting that patients with IPF who received AAT had slower disease progression and improved survival compared with patients who did not receive AAT [28, 29]. In a prespecified post hoc analysis of 3 IPFnet-sponsored trials, data were collected prospectively at baseline and longitudinally during follow-up. In those IPFnet-sponsored studies, patients with IPF who received AAT for various indications, but not as a designated treatment for IPF, had significantly less deterioration of pulmonary function than those not receiving AAT; however, no between-group differences in all-cause mortality or all-cause hospital admission rates were observed [29, 30]. Other reports suggested that AAT may help stabilize IPF and result in fewer acute exacerbations [31]. The results of our post hoc analysis do not support a clinically meaningful beneficial effect of AAT in patients with IPF receiving pirfenidone. This observation is in agreement with a previously published post hoc analysis comparing AAT use and non-AAT use in patients randomized to placebo in the same clinical trials [21]. Indeed, we observed no clear benefit of AAT use for the composite outcome of PFS or all-cause and IPF-related mortality rates.

Possible causes for discrepancies between this and previous studies may relate to differences in the patient population. Although differences between trials cannot be excluded, the clustering model adjusted for between-group differences. The CAPACITY and ASCEND studies excluded patients awaiting lung transplantation. In comparison with the IPFnet-sponsored trials, with the exception of PANTHER, the pooled CAPACITY and ASCEND studies showed higher mean baseline percentages of predicted FVC (≈70%) compared with ≈59% in the STEP-IPF study, ≈58.5% in the ACE-IPF study, and ≈71% in the PANTHER study [3, 4, 6, 29]. AAT may also benefit patients awaiting lung transplantation [32]. As such, it is possible that those who had more severe GERD and/or higher GERD activity responded more effectively to AAT. In this study, 70% FVC stratification was performed to understand if more advanced disease had different outcomes. Patients with an FVC of <70% who received AAT had PFS and mortality rates similar to those who did not receive AAT.

A potential benefit of AAT in patients receiving pirfenidone cannot be ruled out completely. The estimated HRs suggest a trend favoring AAT, as does the observation that a lower proportion of AAT users experienced a relative, but not absolute, FVC decline of ≥10%. This may represent a false-positive finding, owing to the limitations inherent in post hoc analyses. Our analysis may not have been adequately powered to detect further significant differences. Moreover, it cannot be excluded that drug interactions between PPI and pirfenidone may have altered outcomes in either way. Another possibility is that a between-group imbalance in dose intensity due to different AEs may have influenced the results; however, in our analyses, there was no significant difference in pirfenidone dose intensities between the AAT and the non-AAT group. These inconsistencies underscore the need for prospective randomized, double-blind, placebo-controlled studies assessing the role of AAT in IPF.

AAT may also be associated with more frequent and severe AEs. An association between AAT use and more frequent GI side effects was observed. Moreover, severe pulmonary infections occurred at a significantly higher rate in patients who received AAT. Previous studies have reported similar results, with AAT use resulting in increased rates of ventilator-associated and community-acquired pneumonia compared with non-AAT use [33, 34]. This is further supported by a recent systematic review in which the most frequently reported AE was community-acquired pulmonary infection [35].

This study had limitations. This was a post hoc analysis and therefore the findings are to be interpreted with caution. The study population was not randomized for AAT or stratified for imbalances in comorbidities. Patients at baseline who received AAT may have had more GI comorbidities, which is potentially a confounding issue. Although the analyses were adjusted – based on observed factors – to address potential confounders, the results may be biased due to differences in unobserved factors. The population was grouped by baseline exposure to AAT. The analysis did not account for AAT use that oc-

curred after baseline in the non-AAT group, nor the duration of AAT exposure prior to baseline. Time-dependent covariate analysis was not possible given the limitations of the data. Because of the relatively small sample size, these analyses were probably underpowered to detect meaningful differences; however, a formal power analysis was not performed. Patients with advanced disease, such as those awaiting lung transplantation or those with an FVC of <50%, were not included in the trials. Finally, a longer trial time of >52 weeks, and consequently a longer duration of AAT, may have a positive effect on disease progression.

Conclusions

This study does not suggest that AAT might be beneficial as a treatment for IPF in combination with pirfenidone. The data suggest that patients with IPF receiving pirfenidone treatment who are receiving AAT might be at a higher risk of severe pulmonary infection than those not receiving AAT, and may have more GI side effects. Therefore, we believe that the role of AAT in IPF, either alone or in combination with antifibrotic drugs, should be prospectively assessed in a randomized, double-blind, placebo-controlled trial before being considered a specific treatment for IPF. Until these trials are completed, neither the effectiveness nor the safety of AAT as a treatment of IPF can be supposed.

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