Efficacy of pirfenidone for idiopathic pulmonary fibrosis: An Italian real life study

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Efficacy of pirfenidone for idiopathic pulmonary fibrosis: an Italian real life study.

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LATE-BREAKING ABSTRACT: Efficacy of Pirfenidone for Idiopathic Pulmonary Fibrosis (IPF): an Italian real life study

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Abstract

Background

In this retrospective Italian study, which involved all major national interstitial lung diseases centers, we evaluated the effect of pirfenidone on disease progression in patients with IPF.

Methods

We retrospectively studied 128 patients diagnosed with mild, moderate or severe IPF, and the decline in lung function monitored during the one-year treatment with pirfenidone was compared with the decline measured during the one-year pre-treatment period.

Results

At baseline (first pirfenidone prescription), the mean percentage forced vital capacity (FVC) was 75% (35-143%) of predicted, and the mean percentage diffuse lung capacity (DLCO) was 47% (17-120%) of predicted. Forty-eight patients (37.5%) had mild disease (GAP index stage I), 64 patients (50%) had moderate IPF (stage II), and 8 patients (6.3%) had severe disease (stage III).

In the whole population, pirfenidone attenuated the decline in FVC (p=0.065), but did not influence the decline in DLCO (p=0.355) in comparison to the pre-treatment period.

Stratification of patients into mild and severe disease groups based on %FVC level at baseline (>75% and ≤75%) revealed that attenuation of decline in FVC (p=0.002) was more pronounced in second group of patients. Stratification of patients according to GAP index at baseline (stage I vs. II/III) also revealed that attenuation of decline in lung function was more pronounced in patients with more severe disease.

Conclusions

In this national experience, pirfenidone reduced the rate of annual FVC decline (p = 0.065). Since pirfenidone provided significant treatment benefit

for patients with moderate-severe disease, our results suggest that the drug may also be effective in patients with more advanced disease.

Keywords: IPF, pirfenidone, therapy

Abbreviations list

AE= Acute Exacerbation;
ATS= American Thoracic Society;
EMA= European Medicine Agency;
ERS= European Respiratory Society;
DLCO= carbon monoxide diffusing capacity;
FVC= Forced Vital Capacity;
IPF= Idiopathic pulmonary fibrosis;
NAC= N-acetylcysteine;
NPP= Named Patient Access Program;
NSIP= non-specific interstitial pneumonia;
PIRF= Pirfenidone;
UIP= Usual interstitial pneumonia;
6MWT= 6 minute walk test;

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and devastating pulmonary disease that leads to respiratory failure and death within few years of diagnosis.[1] Since 2001, the search for effective treatment has involved a large number of clinical trials. Although most of the investigational agents failed to provide significant success, some trials led to significant developments in the treatment of the disease. In 2011, pirfenidone, a novel antifibrotic agent, was the first drug to be approved for the treatment of IPF in Europe. Pirfenidone has been available in Japan since 2008.[2,3] The approval by the European Medicine Agency (EMA) was based on key clinical studies supporting the efficacy of pirfenidone in reducing lung function deterioration in IPF patients.[4] Results from the ASCEND study[5] confirmed that pirfenidone reduced disease progression in patients with IPF, as reflected by lung function, exercise tolerance, and progression-free survival; the treatment was associated with an acceptable side-effect profile and fewer deaths.

Recently, both pirfenidone and the kinase inhibitor nintedanib received approval from the U.S. Food and Drug Administration for the treatment of IPF.[5,6]

Pirfenidone has been evaluated in several randomized multicenter trials.[2-5] However, clinical trials are often conducted on IPF patient populations that are not truly representative of those seen in daily clinical practice: therefore, the efficacy of pirfenidone in a general population of patients with IPF has not yet been fully investigated.

The aim of this study was to investigate the effect of pirfenidone in the treatment of IPF in real-life clinical practice.

For this reason, we analyzed the data on the use of pirfenidone that have been accumulated by the major referral centers for interstitial lung disease in

Italy that participated to the European Named Patient Access Program (NPP). This program, which was supported by the company (InterMune inc.) responsible for the development and commercialization of pirfenidone in Europe, allowed qualified physicians to make the newly approved pirfenidone available (free of charge) to their IPF patients, provided that pre-specified medical criteria and conditions were met, before it was commercially available within a given European country.

Material and Methods

Population and study design

This was an observational, retrospective, multicenter, unsponsored study, which involved 12 Italian interstitial lung disease centers distributed across the country.

For our study, we evaluated the data obtained from the 12 centers that enrolled at least 3 patients in the NPP program.

We reviewed clinical records of those IPF patients whose functional evaluation was documented for at least one year before and one year after initiation of pirfenidone therapy. Patients who received steroids, azathioprine, or N-acetylcysteine (NAC) before the initiation of pirfenidone therapy were not excluded from the analysis. Patients who were previously enrolled in the CAPACITY trials and subsequently entered the NPP program were also included in the analysis. In order to evaluate the effect of pirfenidone on the progression of IPF, we analyzed the variation of various pulmonary function parameters (%FVC, DLCO, %DLCO and the distance walked at 6MWT) during the one-year period before (the pretreatment period) and the one-year period after initiation of the treatment with pirfenidone (the follow-up period). In each patient, the decline in lung function experienced over the follow-up period was compared to the one monitored over the pretreatment period,

irrespective of any use of steroids, azathioprine, or NAC. Our analysis was based on the assumption that, other than pirfenidone, there was no effective treatment for IPF and, therefore, the use of any of the above-mentioned drugs during the pretreatment period would not have influenced the course of disease in a clinically meaningful way.[7,8]

Moreover, in order to investigate whether the response to treatment could vary depending upon disease severity, the effect of pirfenidone was evaluated in patients stratified into mild and severe disease groups based on their percent predicted FVC values (%FVC) and GAP stage[9] at treatment initiation (the baseline).

This study was approved by the San Giuseppe Hospital Ethical Committee (protocol number 27/13).

Statistical analysis

Due to the retrospective nature of this study, the lung function parameters were not collected using the same time schedule among all patients and centers.

Therefore, the number of assessments performed during the pretreatment and the follow-up periods varied among patients, ranging from a minimum of three assessments (1 performed one year before initiation of pirfenidone therapy, 1 performed at therapy initiation, and 1 performed one year after treatment initiation) in 17 patients, to more than six assessments in 20 patients. In order to efficiently use all data, we opted to include in the statistical analysis all lung function measurements (when available) collected during the 2-year time frame, using a regression approach.

Mixed linear models for unbalanced repeated measures were used to assess the trends of spirometry parameters and the 6MWT distance before and after pirfenidone therapy. For these models, we used lung function parameters measured during the one-year period before starting treatment with pirfenidone (the pretreatment period), at treatment initiation (the baseline),

and during the one-year period after the initiation of pirfenidone therapy (the follow-up period).

Two trend terms were estimated: β_1, related to the trend over the pretreatment period, and β_2, related to the follow-up period. The predicted values at one year before and one year after treatment entry were estimated from the models, and changes in percent predicted values during the two one-year periods were calculated.

The null hypothesis that there was no difference in the two one-year trends (i.e. $\beta_1=\beta_2$) or, equivalently, that changes in percent predicted values during the pretreatment period were equal to changes in percent predicted values during the follow-up period was tested.

To evaluate the effect of the administration of lower than standard doses of pirfenidone (2403 mg) on the outcomes, we introduced in the models an interaction term between dose reduction (dichotomized as indicated at a given visit or absent) and the trend over the year following pirfenidone initiation.

Similarly, the %FVC values measured at baseline (stratified by > 75% and ≤ 75% of predicted) and the GAP score at baseline (stratified by stage I and stage II/III) were introduced in the models as binary covariates, and their interaction terms with trends were evaluated in order to test the homogeneity of difference in percent changes among strata.

Statistical analyses were performed with SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

A total of 128 consecutive patients who were enrolled from 12 centers were evaluated in our analysis. Patients' characteristics are reported in Table 1.

Most of the patients were men (75%), ex smokers (75.8%), with a clinical-radiological diagnosis of IPF (75%), and aged more than 65 years (71.1%). Many of these patients had received corticosteroids (58%), NAC (41%), or azathioprine (24%), sometimes in combination, during the pretreatment period. The mean period elapsed between the diagnosis of IPF and the initiation of pirfenidone therapy was 2.0 years (SD: 1.8 years): in particular, the time lapse was less than one year for 43 patients, it ranged between 1-2 years for 40 patients, and it was greater than 2 years for the remaining 45 patients.

The pulmonary function profiles of our patient population at baseline are illustrated in Table 2. The mean FVC was 75% (SD ± 18) of predicted value, the mean DLCO was 47% (SD ± 15) of predicted, and the average distance walked during the 6MWT in patients not requiring supplemental oxygen was 442 meters (SD ± 101).

Stratification of the population based on gender, age, %FVC, %DLCO and GAP severity index at baseline is reported in Table 3.

Effects of pirfenidone therapy are described in Table 4. Over the one-year pretreatment period, patients experienced a mean decrement of 6.3% in percent predicted FVC: the average FVC dropped from 80% (95% IC: 77-84) to 75% (95% IC: 72-79) of predicted. Over the follow-up period, a reduction in the mean decline in FVC was observed, with a mean decrement of only 1.3% in the percent predicted FVC: the average FVC decreased from 75% (95% IC: 72-79) to 74% (95% CI: 70-77) of predicted (see also Figure 1). The difference in percent changes between the pretreatment and the follow-up period was 4.9% (p-value = 0.065; see Table 1).

There was no significant difference in %DLCO and in the distance walked during the 6MWT before and after treatment with pirfenidone.

Only 22 patients out of 128 (17,1%) were treated with lower than the standard dose of pirfenidone (2403 mg/day); however, such dose reduction did not influence the outcomes observed during the one-year follow-up period.

The effects of pirfenidone therapy in subgroups of patients stratified by disease severity at baseline are illustrated in Table 5.

The attenuation in the rate of FVC decline was more pronounced in the group of patients with more severe disease (FVC ≤ 75% of predicted) at baseline (p-value for homogeneity of difference between strata = 0.002). In patients with FVC > 75% of predicted, the pirfenidone therapy did not influence the decline in FVC: the mean decrement of 1.1% monitored over the pretreatment period did not statistically differ from the 3.3% decrement experienced over the follow-up period (p = 0.332). On the contrary, in patients with FVC ≤ 75% of predicted, the pirfenidone therapy completely prevented further decline in FVC: in fact, these patients experienced a mean decrement of 12.7% in percent predicted FVC over the pretreatment period, while they experienced no decrement (mean change = 0%) over the follow-up period (p = 0.006).

No differences were observed between these two subgroups of IPF patients in terms of DLCO, %DLCO, and distance walked during the 6MWT before and after treatment with pirfenidone.

Stratification of patients using GAP index at baseline (stage I vs. II/III) also revealed that, compared to patients with less advanced disease (GAP stage I), those with more advanced disease (GAP stages II and III) could benefit the most by the administration of pirfenidone in terms of reduction of decline in FVC (p-value for homogeneity of difference between strata = 0.041). Moreover, a benefit in terms of 6MWT distance was observed in those patients with stage II/III IPF who received supplemental oxygen during the test. For more details, see Table 6.

It is worth to note that in 16 out of 128 patients (12.5%), the pirfenidone therapy was associated with an improvement in FVC of more than 10% (data not shown). Interestingly, 3 of these patients had a histological diagnosis of IPF: findings obtained from these patients certainly deserve further investigation.

Discussion

In this study, the effect of pirfenidone on annual rate of decline in %FVC has been retrospectively analyzed in 128 Italian patients with IPF: our results indicated that pirfenidone reduced the decline in %FVC, and this effect was more pronounced in patients with moderate to severe disease (%FVC ≤75%). No consistent changes in DLCO have been observed.

Several multicenter randomized trials have investigated the efficacy of pirfenidone.[2-5] However, limited data are available on the use of this drug in daily clinical practice. A real-life experience with pirfenidone in Japanese patients with IPF has been described by Okuda et al.[10] Oltmanns et al.[11] reported their findings from an observational cohort study conducted on a German tertiary referral center for interstitial lung disease. Chauduri et al.[12] described their results on pirfenidone tolerability and its effects on the decline of %FVC and %DLCO in UK patients involved in the NPP program. However, all these retrospective trials were conducted in a single center and on small patient populations. In our study, we reviewed data obtained from a national multicenter Italian experience, which involved all major interstitial lung disease centers and was conducted on a large cohort of IPF patients who received long-term treatment with pirfenidone.

In our patient population, the use of corticosteroids, azathioprine, or NAC was rather common during the pretreatment period; however, since it has been largely demonstrated that these drugs are ineffective in IPF,[7,8,13,14] we assumed that the use of these medications had no influence on the course of disease.

The results obtained from our study indicated that pirfenidone attenuated the decline in FVC in IPF patients; compared to the decline observed during the pretreatment period, the attenuation of decline in %FVC almost reached statistical significance ($p = 0,06$).

Stratification of patients into mild and severe disease groups based on %FVC level at baseline (≤ 75%, n = 69 patients, or > 75%, n = 59) revealed that patients with advanced IPF could benefit the most from pirfenidone therapy: in fact, in these patients the treatment completely prevented further decline of %FVC. FVC is the most commonly employed and accepted endpoint in clinical trial for the evaluation of disease progression.[15-19]

The study of Okuda et al.[10] showed that patients who had experienced the most severe decline in FVC during the 6-month period prior to the therapy initiation were those who could benefit the most from the treatment. The more recent study of Loeh et al,[20] which was also conducted in a real-life setting, confirmed that patients with a clear progression of disease before pirfenidone therapy showed an even more favorable course under pirfenidone treatment. In our experience, a different influence of pirfenidone treatment based on disease progression before initiation of therapy was not observed (data not shown).

Last but not least, our data suggest that pirfenidone might be useful also in more severe stages of IPF.

Stratification of patients into mild and severe disease groups based on GAP staging system gave similar results, thus confirming that patients with more severe IPF at baseline (stages GAP II and III) would benefit the most from pirfenidone treatment.

To our knowledge, this is the first study describing the experience with pirfenidone, the first antifibrotic therapy approved for the treatment of IPF, in a large multicenter study conducted in a real-life setting. Loeh et al[20] conducted a retrospective analysis in two large independent IPF cohorts in Germany and Italy but ours is the first national study really multicenter, including the 12 major interstitial lung disease centers in Italy.

The results from this experience outlined a clinical profile of Italian patients with IPF similar to that described in the international guidelines and in clinical trials.[1,5] In this study, patients who received pirfenidone did not necessarily

presented with specific medical conditions and criteria required for the enrollment in randomized trial. However, the physiological and epidemiological profiles of our IPF patients were similar to those of patients enrolled in the ASCEND trial.[5] Compared to that trial, our study was conducted on a smaller study population; moreover, the study design was different. Nevertheless, our results are in agreement with the findings of the ASCEND study, and support the efficacy of pirfenidone in reducing the decline in FVC in patients with IPF.

In addition, our study provides new and important results on the efficacy of pirfenidone in IPF patients with more severe impairments of lung function (as defined based on the %FVC and GAP stage at baseline): to our knowledge, this evaluation has never been performed before. Interestingly, 12.5% of patients experienced an improvement in predicted percent FVC greater than 10%. So far, improvements of pulmonary function following pirfenidone treatment have been observed in a few cases; in our study, such improvement was observed in a quite large number of patients. Thus, the question arises on whether this may reflect the presence of an alternative diagnosis or indicate that pirfenidone therapy may be more effective in some subpopulations of IPF patients; however, this issue will be addressed in further investigations.

The main strength of our observational study is that we investigated the effect of pirfenidone therapy in a large multicenter national cohort of patients with IPF in real-world settings.

Our study has several limitations. First of all, it is a retrospective study, and therefore it has the typical disadvantages of this kind of medical investigations. Second, there was no control over the procedures adopted by physicians of the centers participating to the NPP program to document medical records and select diagnostic modalities (as a matter of fact, 75% of our patient population had a clinical/radiological diagnosis).

It cannot be ruled out that some patients with a diagnosis of non-specific interstitial pneumonia (NSIP) or fibrotic NSIP were also enrolled in the program. Nevertheless, this is not necessary a disadvantage, and outlines the efficacy of pirfenidone; as a matter of fact, fibrotic NSIP is probably often managed as usual interstitial pneumonia (UIP) in daily practice. Another limitation of this study is the lack of data on adverse events, toxicities and mortality that, however, were not the objective of our study. Some negative effects of therapies received during the pretreatment period, including the combination of steroids, azathioprine, or N-acetylcysteine - which is known to be associated with an increased risk of major adverse events[7,14] - cannot be excluded. However, only 21% of patients had been treated with a combination of these three medications: thus, it seems unlikely that this therapy had significant impact on safety outcomes.

Conclusions

In conclusion, the results of this retrospective Italian multicenter experience conducted on IPF patients in a real-life setting confirm that pirfenidone reduces the decline in FVC, a surrogate marker of mortality,[16,17] and suggest that the drug may be also effective in patients with more advanced disease.

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Tables

Table 1. Patients' characteristics (N=128)

Variable	Levels	N (%)
Center	Catania	14 (10.9)
	Forlì	13 (10.2)
	Milano	12 (9.4)
	Modena	9 (7.0)
	Monza	9 (7.0)
	Napoli	2 (1.6)
	Padova	7 (5.5)
	Roma 1	8 (6.3)
	Roma 2	5 (3.9)
	Siena	6 (4.7)
	Torino	18 (14.1)
	Trieste	25 (19.5)
Gender	Female	32 (25.0)
	Male	96 (75.0)
Age at baseline (years)*	<=60	17 (13.3)
	61-65	20 (15.6)
	65+	91 (71.1)
Smoking status	Ex-smoker	97 (75.8)
	Non smoker	27 (21.1)
	Smoker	4 (3.1)
Histological diagnosis	No	96 (75.0)
	Yes	32 (25.0)
Cortisone	No	53 (41.4)
	Yes	75 (58.6)
Azathioprine	No	97 (75.8)
	Yes	31 (24.2)
N-Acetylcysteine	No	75 (58.6)
	Yes	53 (41.4)
Time from diagnosis of IPF to initiation of pirfenidone therapy (years) **	< 1	43 (33.6)
	1-2	40 (31.2)
	>2	45 (35.2)

* Mean age: 69 years (SD: 7 years)

** Mean time from diagnosis of pulmonary fibrosis to initiation of treatment with pirfenidone: 2.0 years (SD: 1.8 years)

Table 2. Spirometry parameters and 6MWT distance at the time of initiation of therapy with pirfenidone (baseline)

	N	Mean (SD)	Min-Max
% FVC	128	75 (18)	35-143
DLCO	120	11.27 (4.02)	1.52-26.40
% DLCO	120	47 (15)	17-120
Distance (m) (without suppl. O_2)*	63	442 (101)	250-750
Distance (m) (with suppl. O_2)**	25	360 (86)	150-490
FEV1/FVC (Tiffenau Index)	119	83 (9)	55-120

* Five patients did not complete the 6MWT (not included in the analyses)

** Three patients did not complete the 6MWT (not included in the analyses)

Table 3. GAP index and stage of patients at the time of initiation of therapy with pirfenidone (baseline)

	Predictor	N (%)	Median, (Min-Max)
G - Gender	Female	32 (25.0)	
	Male	96 (75.0)	
A - Age class	<=60	17 (13.3)	
	61-65	20 (15.6)	
	65+	91 (71.1)	
P - Physiology	% FVC		
	>=75	59 (46.1)	
	50-75	67 (52.3)	
	<50	2 (1.6)	
	% DLCO		
	>55	26 (20.3)	
	36-55	75 (58.6)	
	<=35	19 (14.8)	
	N/A	8 (6.3)	
GAP index		-	4 (1-6)
Stage	I (GAP index 0-3)	48 (37.5)	
	II (GAP index 4-5)	64 (50.0)	
	III (GAP index 6-8)	8 (6.3)	
	N/A*	8 (6.3)	

* N/A: not available

Table 4. Spirometric parameters and 6MWT distance measured one year before pirfenidone therapy initiation (1-yr before), at the time of treatment entry (baseline), and one year after therapy initiation (1-yr after).

Parameter	Time	Mean* (95% CI)	Change (%)	Difference in changes (%)	p-value[§]
% FVC	1-yr before	80 (77, 84)	-	-	
	Baseline	75 (72, 79)	-6.3**	-	
	1-yr after	74 (70, 77)	-1.3***	4.9	0.065
DLCO	1-yr before	12.28 (11.45, 13.11)	-	-	
	Baseline	11.27 (10.60, 11.95)	-8.2**	-	
	1-yr after	9.78 (8.90, 10.66)	-13.2***	-5.0	0.355
% DLCO	1-yr before	51 (48, 55)	-	-	
	Baseline	47 (44, 49)	-7.8**	-	
	1-yr after	40 (37, 43)	-14.9***	-7.1	0.249
6MWT distance (without suppl.O_2)	1-yr before	452 (423, 481)	-	-	
	Baseline	433 (411, 454)	-4.4**	-	
	1-yr after	421 (393, 450)	-2.6***	1.8	0.661
6MWT distance (with suppl. O_2)	1-yr before	403 (340, 466)	-	-	
	Baseline	358 (331, 386)	-11.1**	-	
	1-yr after	362 (330, 394)	1.0***	12.1	0.280

*Based on predicted values at 1-yr before, at baseline and at 1-yr after therapy initiation, as estimated from a linear mixed model

** % change during pre-treatment period: (baseline - 1yr before)/(1yr before)

*** % change during follow-up period: (1yr after -baseline)/(baseline)

[§]Based on the null hypothesis that % change over pre-treatment period = % change over follow-up period

Table 5. Spirometric parameters and 6MWT distance measured one year before pirfenidone therapy initiation (1-yr before), at the time of treatment entry (baseline), and one year after therapy initiation (1-yr after) in patients stratified by percent predicted FVC (≤75% and >75%) at baseline.

		FVC at baseline >75 % of predicted				FVC at baseline ≤ 75% of predicted			
Parameter	**Time**	**Mean* (95% CI)**	**Change (%)**	**Difference in change (%)**	**p-value§**	**Mean* (95% CI)**	**Change (%)**	**Difference in change (%)**	**p-value§**
FVC (% of predicted)	1-yr before	92 (88, 95)	-	-		71 (67, 74)	-	-	
	baseline	91 (88, 94)	-1.1**	-		62 (59, 65)	-12.7**	-	
	1-yr after	88 (84, 92)	-3.3***	-2.2	0.332	62 (58, 65)	0.0***	12.7	0.006
	p-value for homogeneity of difference in % changes between strata:				*0.002*				
DLCO	1-yr before	13.22 (12.05, 14.39)	-	-		11.46 (10.33, 12.58)	-	-	
	baseline	12.33 (11.38,13.29)	-6.7**	-		10.34 (9.44, 11.24)	-9.8**	-	
	1-yr after	11.24 (9.98, 12.50)	-8.8***	-2.1	0.792	8.49 (7.31, 9.67)	-17.9***	-8.1	0.317
	p-value for homogeneity of difference in % changes between strata:				*0.618*				
DLCO (% of predicted)	1-yr before	55 (50, 60)	-	-		48 (43, 52)	-	-	
	baseline	51 (47, 55)	-7.3**	-		43 (39, 46)	-10.4**	-	
	1-yr after	45 (41, 50)	-11.8***	-4.5	0.605	35 (30, 39)	-18.6***	-8.2	0.279
	p-value for homogeneity of difference in % changes between strata:				*0.707*				
Distance (without suppl. O_2)	1-yr before	479 (438, 520)	-	-		427 (385, 468)	-	-	
	baseline	448 (418, 478)	-6.5**	-		417 (387, 448)	-2.2**	-	
	1-yr after	457 (420, 495)	2.1***	8.5	0.134	381 (340, 422)	-8.8***	-6.6	0.339
	p-value for homogeneity of difference in % changes between strata:				*0.084*				
Distance (with suppl. O_2)	1-yr before	414 (301, 526)	-	-		401 (324, 478)	-	-	
	baseline	342 (296, 387)	-17.4**	-		368 (333, 403)	-8.3**	-	
	1-yr after	367 (309, 425)	7.3***	24.7	0.248	360 (321, 399)	-2.0***	6.3	0.611
	p-value for homogeneity of difference in % changes between strata:				*0.453*				

*Based on predicted values at 1-yr before, at baseline and at 1-yr after therapy initiation, as estimated from a linear mixed model

** % change during pre-treatment period: (baseline - 1yr before)/(1yr before)

*** % change during follow-up period: (1yr after -baseline)/(baseline)

§Based on the null hypothesis that % change over pre-treatment period = % change over follow-up period

Table 6. Spirometric parameters and 6MWT distance measured one year before pirfenidone therapy initiation (1-yr before), at the time of treatment entry (baseline), and one year after therapy initiation (1-yr after) in patients stratified by GAP stage (I and II/III) at baseline.

		STAGE I at baseline				STAGE II/III at baseline			
Parameter	**Time**	**Mean* (95% CI)**	**Change (%)**	**Difference in change (%)**	**p-value[§]**	**Mean* (95% CI)**	**Change (%)**	**Difference in change (%)**	**p-value[§]**
FVC (% of predicted)	1-yr before	87 (82, 93)	-	-		77 (72, 81)	-	-	
	Baseline	85 (80, 89)	-2.3**	-		70 (66, 74)	-9.1**	-	
	1-yr after	81 (75, 86)	-4.7***	-2.4	0.713	69 (64, 73)	-1.4***	7.7	0.007
	p-value for homogeneity of difference in % changes between strata:				*0.041*				
DLCO	1-yr before	13.96 (12.74, 15.17)	-	-		11.21 (10.17, 12.24)	-	-	
	Baseline	13.00 (12.01, 13.99)	-6.9**	-		10.11 (9.30, 10.92)	-9.8**	-	
	1-yr after	11.20 (9.83, 12.56)	-13.8***	-7.0	0.305	8.79 (7.67, 9.90)	-13.1***	-3.2	0.739
	p-value for homogeneity of difference in % changes between strata:				*0.570*				
DLCO (% of predicted)	1-yr before	58 (53, 63)	-	-		47 (43, 51)	-	-	
	Baseline	54 (51, 58)	-6.9**	-		41 (38, 44)	-12.8**	-	
	1-yr after	46 (41, 50)	-14.8***	-7.9	0.113	35 (31, 39)	-14.6***	-1.9	0.897
	p-value for homogeneity of difference in % changes between strata:				*0.259*				
Distance (without suppl. O_2)	1-yr before	456 (413, 498)	-	-		447 (406, 487)	-	-	
	Baseline	437 (404, 470)	-4.1**	-		430 (400, 459)	-3.8**	-	
	1-yr after	438 (393, 482)	0.1***	4.2	0.513	405 (365, 444)	-5.8***	-2.0	0.771
	p-value for homogeneity of difference in % changes between strata:				*0.497*				
Distance (with suppl. O_2)	1-yr before	357 (270, 445)	-	-		464 (363, 566)	-	-	
	Baseline	389 (333, 444)	8.8**	-		341 (307, 374)	-26.7**	-	
	1-yr after	329 (262, 397)	-15.3***	-24.1	0.207	367 (329, 406)	7.9***	34.5	0.021
	p-value for homogeneity of difference in % changes between strata:				*0.013*				

*Based on predicted values at 1-yr before, at baseline and at 1-yr after therapy initiation, as estimated from a linear mixed model

** % change during pre-treatment period: (baseline - 1yr before)/(1yr before)

*** % change during follow-up period: (1yr after -baseline)/(baseline)

[§]Based on the null hypothesis that % change over pre-treatment period = % change over follow-up period

Figure Legend

Figure 1. Mean FVC percentage (and 95% CI) at 1-yr before, at baseline and at 1-yr after pirfenidone initiation, estimated from the linear mixed model.