Original Article

Analysis of treatment efficacy, tolerability, and survival of patients receiving antifibrotic therapy for progressive nonidiopathic pulmonary fibrosis

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ABSTRACT

BACKGROUND: There are still disagreements about diagnostic criteria and treatment of progressive pulmonary fibrosis (PPF). Real-life data and survival analyses have a guiding role in clarifying this issue.

METHODS: In this multicenter retrospective cohort study, real-life data of adult patients diagnosed with PPF and treated with antifibrotics for at least 6 months were examined.

RESULTS: Of the 222 patients, 161 were treated with Nintedanib (N) and 61 with Pirfenidone (P). The most common PPF subtype was connective tissue disease-related interstitial lung disease (CTD-ILD) (53.2%). The progression rate was significantly higher in patients with usual interstitial pneumonia (UIP) (P = 0.003). A −3.1% (−49.2 ml) decrease was detected in forced vital capacity (FVC) in the 6th month. The 6th month and overall progression-free survival (PFS) rates were 83.3% and 51.8%. The 6th month and overall clinical event-free survival (CEFS) rates were 89.6% and 53.6%. The survival rates for 6th, 12th, and entire follow-up periods were found to be 98.2%, 89.2%, and 77.5%. CT-ILD had the longest survival time (166.5 ± 9.2 months) and fibrotic hypersensitivity pneumonia had the shortest survival time (87.6 ± 9.2 months) (P = 0.011). N was advantageous in patients with UIP in terms of FVC loss and estimated survival. While PFS during the entire follow-up period was in favor of N, CEFS had no significant difference between drugs.

CONCLUSION: PPF subtypes have significant differences in terms of prognosis and survival. The effect of AF drugs on progression varies, especially among radiological patterns. An individualized approach is required in the diagnosis, follow-up, and treatment of patients with PPF.

KEYWORDS

Antifibrotic, idiopathic pulmonary fibrosis, nintedanib, pirfenidone, pulmonary fibrosis, survival

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Background

Progressive pulmonary fibrosis (PPF) was defined with the guide published in 2022.[1] Since the results of

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the clinical studies that led to the definition of PPF were shared, the use of antifibrotics (AFs) in this heterogeneous patient group has already come to the fore.

Nintedanib (N) and Pirfenidone (P) are two AF drugs that have been approved and are currently used in the treatment of idiopathic pulmonary fibrosis (IPF).[2] Considering the mechanisms of action of these drugs, it seems reasonable that they may be effective not only in IPF but also in non-IPF interstitial lung disease (ILD), where fibrosis progresses despite inflammation regressing. Based on this, studies were conducted on non-IPF fibrosing ILDs such as fibrotic hypersensitivity pneumonia (fHP), fibrotic nonspecific interstitial pneumonia (fNSIP), and connective tissue disease-related ILD (CT-ILD).[3-6] As a result of these studies, it was revealed that AFs were promising in PPF patients. On the other hand, some confusions still continue; PPF subgroup analyses yielded variable findings, progression criteria are still not completely clear, patients included in the clinical studies represent a more refined group. Hence, questions persist about the validation of a single common approach in such a heterogeneous group.[7] At this point, the guidance of real-life data became very important.

Progression-free survival (PFS), clinical event-free survival (CEFS), and overall survival (OS), which are frequently used in oncology studies, are increasingly important in the follow-up of chronic diseases.[8] The treatment and follow-up principles of patients with PPF can be considered similar to those of cancer patients in many aspects. In this regard, PFS, CEFS, and OS examinations have started to come to the fore in PPF.[8,9] However, large PPF registry studies that include this information are still needed. With this multicenter, registry-based cohort study, we aimed to reveal the characteristics of PPF patients, the efficacy and tolerability of AFs, and their effects on prognosis assessed by survival analyses.

Methods

Study design

In this multicenter retrospective cohort study, real-life data of patients diagnosed with PPF and treated with AF therapy for at least 6 months before the date December 31, 2023 were examined. The screening was conducted until early September 2019, when an AF drug was first FDA approved for SSc-ILD. Only centers run by ILD specialists who have been monitoring IPF and PPF for at least 10 years and have significant experience in AF treatments were invited to this registry. Seven experienced ILD centers in six major cities of our country participated in the study. The study was granted ethical approval.

Patients

Patients who met the following inclusion criteria were included: being 18 years of age or older, being diagnosed according to the criteria determined for PPF, having received AF medication for at least 6 months and having the data recorded reliably. Patients with insufficient data and those who were lost to follow-up were excluded from the study. The presence of one of the INBUILD criteria was taken as the basis of the diagnosis of PPF.[3]

Collection and analysis of data

The data collected from all centers were subjected to central revision and their suitability was confirmed. Baseline demographic data of the patients, PPF subtype, radiological pattern (usual interstitial pneumonia [UIP] or Non-UIP), pulmonary function test (PFT) results, adverse event (AE), patient's compliance to AF medication, PFS, CEFS, OS, duration of AF medication and survival time with the disease were recorded. For the definition of "Progression," the presence of one of the following was considered decisive: the presence of physiological progression (either a decrease in forced vital capacity [FVC] >10%, a decrease in diffusing capacity of the lung for carbon monoxide [DLCO] >15%, a decrease in 6-min walking distance >50 m compared with baseline), and/or radiological progression.[10] The presence of Grade 3–5 AEs, hospitalization due to respiratory deterioration, and all-cause death were assessed as "Clinical event."[10,11]

Statistical methods

All data were analyzed using IBM SPSS Statistics Version 25th (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp). For descriptive data analysis, continuous variables were expressed as mean ± standard deviation, and the categorical variables were expressed as number (*n*) and percentage (%). The compliance of continuous variables with normal distribution was evaluated with the Kolmogrov–Smirnov test. Mann–Whitney *U* test or Student-*t* tests were used depending on whether the groups were normally distributed or not. The parametric distribution of the values was investigated by Q-Q plot analysis. Independent samples *t*-test and ANOVA were used to compare the other two group analyses, mainly survival and drug comparison. Tukey and Games–Howell *post hoc* analysis was the preferred *post hoc* method depending on the distribution of parameters. The Chi-squared test was used for the comparison of categorical variables. Kaplan–Meier survival analysis, with log-rank for pairwise comparison, was performed on parameters affecting survival. Logistic regression analysis was used to determine which parameters could potentially affect survival. Binominal logistic regression analysis, with the overall mortality being the dependent

parameter, was done to evaluate if any parameters observed as statistically significant with correlation analysis could be defined as independent factors in their role of mortality risk assessment.

Results

Baseline characteristics of the patients

A total of 222 patients were included in the study [Table 1]. More than half of the patients (53.2%) had been diagnosed with a CT-ILD. The fHP and fNSIP were the second and third most common reported PPF subtypes (20.7% and 12.2%, respectively). The dominant radiological pattern in all variants was UIP, with a frequency of 59.9%.

Antifibrotic treatment process

Situations experienced during the AF medication were evaluated in terms of treatment compliance, AE, progression, clinical events, and mortality [Table 1]. AF was permanently discontinued in 11.7% by physician and/or patient decision. Mortality rates for 6 months, 1 year, and the entire follow-up period were 1.8%, 10.8%, and 22.5%, respectively.

Radiological patterns

The rate of preference for N over P was higher in the UIP group (P = 0.005). While the persistence of AF medication was more common in the UIP group, the frequency of hospitalization and death was higher in the Non-UIP group, but the differences were not statistically significant (P > 0.05 in all). The two radiological patterns did not have a significant difference in terms of hospitalization frequency and mortality rate (P = 0.210 and P = 0.198, respectively).

Progressive pulmonary fibrosis subtypes

Subgroup analysis according to the PPF subtypes was then performed, with five main groups being utilized: fNSIP, fHP, CT-ILD, unclassified ILD (uILD), and the other PPFs (group consisting of subtypes with fewer than five patients each) [Table 1]. There were significant differences among PPF subtypes in terms of the radiological pattern, selected AF medications, duration of therapy before AF, and persistence in AF medication (P = 0.001, 0.001, 0.008, and 0.014, respectively) [Table 2]. In the *post hoc* analysis, the difference in the radiological pattern was present, especially between fNSIP and CT-ILD (P = 0.001, a mean difference of 0.531) and between fHP and CT-ILD (P = 0.001, a mean difference of 0.388). The UIP pattern was significantly more frequent in CTD-ILD and uILD, while the Non-UIP pattern was more frequent in fHP and fNSIP (P = 0.001). The difference between fHP and CT-ILD was significant and the preference rates of N over P were higher in the CT-ILD group (P = 0.001, a mean difference of 0.374). The frequency of P was highest

Table 1: Baseline characteristics of the patients and clinical events experienced during antifibrotic medication

Demographics	*n* (%)
Age, mean±SD	64.7±10.3
Gender	
Female	112 (50.5)
Male	110 (49.6)
BMI, mean±SD	26.7±4.9
Smoking status	
Nonsmoker	110 (49.6)
Former/current smoker	112 (50.4)
Tobacco burden packet/year, mean±SD	28.5±15.0
Occupational/environmental exposure	38 (17.1)
Presence of comorbidity	169 (76.1)
Comorbidity type	
HT	99 (44.6)
CAD	63 (28.4)
DM	56 (25.2)
PH	29 (13.1)
Others	85 (38.3)
PPF subtype	
CT-ILD	118 (55.9)
fHP	46 (20.7)
fNSIP	27 (12.2)
uILD	18 (8.1)
Other PPFs	
Drug induced pulmonary fibrosis	4 (1.8)
Sarcoidosis	1 (0.5)
Asbestosis	2 (0.9)
Radiation pneumonitis	2 (0.9)
Post-COVID 19 fibrosis	4 (1.8)
Connective tissue disease type (in itself)	
SSc	55 (46.6)
RA	39 (33.1)
SJ	20 (16.1)
MCTD	4 (3.4)
Vasculitis	4 (3.4)
Myositis	2 (1.7)
Radiological pattern	
UIP	133 (59.9)
Non-UIP	89 (40.1)
PPF diagnostic criteria	
FVC decline >10%	107 (48.2)
FVC decline between 5% and 10% + clinical or radiological worsening	46 (20.7)
Clinical and radiological worsening	69 (31.1)
Treatment (s) used before AF	
None	41 (18.5)
CS	101 (45.5)
MTX	33 (14.9)
AZT	40 (18.0)
Cyclophosphamide	41 (18.5)
MMF	56 (25.2)
Cyclosporine	3 (1.4)
Biological agent	29 (13.1)
AF	

Contd...

Table 1: Contd...

Demographics	*n* (%)
Pirfenidone	61 (27.5)
Nintedanib	161 (72.5)
Concomitant treatment (s) with AFs	
None	91 (41.0)
CS	90 (40.5)
MTX	5 (2.3)
AZT	18 (8.1)
Cyclophosphamide	8 (3.0)
MMF	57 (25.7)
Cyclosporine	2 (0.9)
Biological agent	22 (9.9)
Presence of AE	126 (56.8)
Side effect type	
Nausea	74 (33.3)
Diarrhea	68 (30.6)
Anorexia	52 (23.4)
Weight loss	35 (15.8)
Liver enzyme elevation	21 (9.5)
Skin rash	17 (7.7)
Photosensitivity	6 (2.7)
Distribution of AE severity (in itself)	
Grades 1and 2 (mild/moderate)	92 (73.0)
Grade 3 (severe)	27 (21.4)
Grades 4 and 5 (life-threatening/death)	7 (5.6)
Compliance with AF treatment	
Persistent in treatment	151 (68.0)
Treatment interruption	31 (14.0)
Switch	14 (6.3)
Treatment discontinuation	26 (11.7)
Hospitalization	
Hospitalization occurred	99 (44.6)
Number of hospitalizations, mean±SD	1.5±0.6
Death	50 (22.5)
Cause of death	
Severe respiratory failure due to PPF	25 (50.0)
Pulmonary infections	12 (24.0)
Diseases of other systems	13 (26.0)

SD=Standard deviation, BMI=Body mass index, HT=Hypertension, CAD=Coronary artery disease, DM=Diabetes mellitus, PH=Pulmonary hypertension, CT-ILD=Connective tissue disease related interstitial lung disease, fHP=Fibrotic hypersensitivity pneumonia, fNSIP=Fibrotic nonspecific interstitial pneumonia, uILD=Unclassified interstitial lung disease, PPF=Progressive pulmonary fibrosis, RA=Rheumatoid arthritis, SSc=Systemic sclerosis, SJ=Sjogren's syndrome, MCTD=Mixed connective tissue disease, UIP=Usual interstitial pneumonia, FVC=Forced vital capacity, AF=Antifibrotic, CS=Corticosteroid, MTX=Methotrexate, AZT=Azathioprine, MMF=Mycophenolate mofetil, AE=Adverse event.

in fHP (47.8% of all fHPs). In terms of pre-AF therapy and AF medication persistence times, similar statistical differences were observed between the fHP and CT-ILD groups in *post hoc* analysis ($P = 0.001$, a mean difference of 17.768, and $P = 0.001$, a mean difference of 9.549) [Table 2].

Medication

N was used in 161 (72.5%) patients and P was used in 61 patients (27.5%). The relationship between radiological patterns and AF drugs was statistically significant [Table 3]. The rate of UIP in those who received N therapy was significantly higher ($P = 0.031$). The frequency of concomitant anti-inflammatory treatment after the onset of AF was significantly higher in the N group ($P = 0.001$). There was no significant difference between the two drugs in terms of treatment compliance and AEs. The overall persistence time in AF medication was longer in the P group ($P = 0.001$). The frequency of hospitalization, the number of hospitalizations per patient, and the mortality rate were significantly higher in the P group ($P = 0.053$, 0.037, and 0.047, respectively).

Progression

The progression rate in the first 6 months was significantly higher in UIP patients ($P = 0.003$) [Table 4]. However, when sub-breakdowns of the definition of progression were examined, it was seen that this difference was due to PFT results, while radiological progression did not differ significantly between the two radiological patterns ($P = 0.376$).

The PFT changes detected in the 6th and 12th months were examined. In all cases, a −3.1% (−49.2 ml) decrease was detected in FVC at the 6th month. These changes were measured as −5.5% (−87.8 ml) in those who completed the 12th month. In DLCO, a −2.2% decrease was recorded in the 6th month and a −5.6% decrease was recorded in the 12th month compared to the baseline. In cases with UIP, FVC decreases were significantly lower in 6th and 12th months. In the comparison between AF drugs, the results were found in favor of N [Table 5].

Survival analysis

Progression-free survival

Progression was observed in 48.2% ($n = 107$) of all patients during the entire follow-up period, and in 34.6% of them, progression occurred within the first 6 months [Table 4].

Clinical event-free survival

During the entire follow-up period, 46.4% of patients had any clinical event. Of these, 48.5% were determined as death and 51.5% were other clinical events [Table 4].

Overall survival

Considering the follow-up periods, 6-month, 12-month, and OS rates were found to be 98.2%, 89.2%, and 77.5%, respectively. The 8% of deaths occurred in the first 6 months, and 48% died in the first 12 months; the remaining deaths occurred after the 1st year. Across all patients, the median follow-up time with PPF was found to be 67.2 ± 38.1 months. This period was 60.2 ± 32.1 months in the mortality group and 69.2 ± 39.4 months in the survival group ($P = 0.125$).

Table 2: Analysis of data according to progressive pulmonary fibrosis subtypes

	CT-ILD (*n*=118)	fHP (*n*=46)	fNSIP (*n*=27)	uILD (*n*=18)	Other PPFs (*n*=13)	*P*
Radiological pattern (among the PPF subtypes), *n* (%)						
UIP	93 (78.8)	16 (34.8)	5 (18.5)	12 (66.7)	7 (53.9)	0.001
Non-UIP	25 (21.2)	30 (65.2)	22 (81.5)	6 (33.3)	6 (46.2)	
AF (among the PPF subtypes), *n* (%)						
Pirfenidone	16 (15.6)	22 (47.8)	7 (25.9)	7 (38.9)	9 (69.2)	0.001
Nintedanib	102 (86.4)	24 (52.2)	20 (74.1)	11 (61.1)	4 (30.8)	
Concomitant treatment (among the PPF subtypes)	81 (68.6)	28 (60.9)	11 (40.7)	6 (33.3)	6 (46.2)	0.288
Pre-AF therapy duration (months) (25^{th}–75^{th})	36 (24–76)	25 (24–84)	45 (24–67)	26 (24–39.8)	36 (24–69)	0.008
Persistent in AF medication (months) (25^{th}–75^{th})	12 (9–20)	20 (12–28.5)	13 (10–23.5)	19.5 (12–25)	18 (9–26.5)	0.014
Overall survival with PPF (months) (25^{th}–75^{th})	52 (37–90.5)	52 (43.8–84)	47.5 (36–86)	53 (44–82)	56 (45–99)	0.583

CT-ILD=Connective tissue disease-related interstitial lung disease, fHP=Fibrotic hypersensitivity pneumonia, fNSIP=Fibrotic nonspecific interstitial pneumonia, uILD=Unclassified interstitial lung disease, UIP=Usual interstitial pneumonia, AF=Antifibrotic, PPF=Progressive pulmonary fibrosis.

Table 3: Comparison of findings in terms of antifibrotic medication

	Nintedanib (*n*=161), *n* (%)	Pirfenidone (*n*=61), *n* (%)	*P*
Radiological pattern			
UIP	106 (65.8)	27 (44.3)	0.031
Non-UIP	55 (34.2)	34 (55.7)	
Presence of comorbidity	115 (71.4)	49 (80.3)	0.291
Comorbidity type			
HT	71 (44.1)	25 (41.0)	0.548
CAD	45 (27.9)	16 (26.2)	0.702
DM	35 (21.7)	17 (27.8)	0.402
PH	23 (14.3)	6 (9.8)	0.342
Others	59 (36.7)	22 (36.1)	0.811
Concomitant treatment	105 (67.2)	26 (42.6)	0.001
Presence of AE	85 (52.8)	38 (62.3)	0.295
Side effect type			
Nausea	52 (32.3)	20 (32.8)	0.939
Diarrhea	46 (28.6)	21 (34.4)	0.481
Liver enzyme elevation	18 (11.2)	3 (4.9)	0.139
Weight loss	27 (16.8)	6 (9.8)	0.170
Skin rash	13 (8.1)	3 (4.9)	0.389
Photosensitivity	5 (3.1)	1 (1.6)	0.529
Anorexia	34 (21.1)	16 (26.2)	0.488
Severity of AE			
Grades 1 and 2 (mild/moderate)	63 (39.1)	29 (47.5)	0.819
Grade 3 (severe)	19 (11.8)	8 (13.1)	
Grades 4 and 5 (life-threatening/death)	5 (3.1)	2 (3.3)	
Compliance with treatment			
Treatment withdrawal	20 (12.4)	6 (9.8)	0.545
Treatment interruption	20 (12.4)	10 (16.4)	0.495
Switch	9 (5.6)	5 (8.2)	0.515
Clinical events			
Hospitalization	63 (39.1)	33 (54.1)	0.053
Number of hospitalization, mean±SD	1.45±0.6	1.59±0.6	0.037
Mortality	24 (14.9)	26 (42.6)	0.047
AF duration after PPF diagnosis (months)	16.6	26.1	0.001

UIP=Usual interstitial pneumonia, HT=Hypertension, CAD=Coronary artery disease, DM=Diabetes mellitus, PH=Pulmonary hypertension, AE=Adverse event, SD=Standard deviation, PPF=Progressive pulmonary fibrosis, AF=Antifibrotic.

After the onset of AF medication, the median follow-up time was found to be 19.4 ± 14.3 months. This period was 20.6 ± 15.9 months in the mortality group and 19.1 ± 13.8 months in the survival group ($P = 0.550$).

The mean survival time estimated by Kaplan–Meier survival analysis was 147.8 ± 8.1 months. fHP had the lowest survival time, notably [Figure 1]. Regarding the radiological patterns, 1-year and OS times did not

Table 4: Examination of progression status in terms of progressive pulmonary fibrosis type, radiological pattern and antifibrotic medication

	Progression in the first 6 months			Progression over the entire follow-up period			Clinical event in the first 6 months			Clinical event over the entire follow-up period		
	Progression free (*n*=185)	Progression occurred (*n*=37)	*P*	Progression free (*n*=115)	Progression occurred (*n*=107)	*P*	Clinical event free (*n*=199)	Clinical event occurred (*n*=23)	*P*	Clinical event free (*n*=119)	Clinical event occurred (*n*=103)	*P*
PPF subtype, *n* (%)												
CT-ILD	95 (80.5)	23 (19.5)	0.041	55 (46.6)	63 (53.4)	0.067	104 (88.1)	14 (11.9)	0.035	74 (62.7)	44 (37.3)	0.015
fHP	40 (87.0)	6 (13.0)		28 (60.9)	18 (39.1)		41 (89.1)	5 (10.9)		14 (30.4)	32 (69.6)	
fNSIP	23 (85.2)	4 (14.8)		14 (51.9)	13 (48.2)		24 (88.9)	3 (11.1)		9 (33.3)	18 (66.7)	
uILD	16 (88.9)	2 (11.1)		10 (55.6)	8 (44.4)		18 (100.0)	0		14 (77.8)	4 (22.2)	
Other	11 (84.6)	2 (15.4)		8 (61.5)	5 (38.5)		12 (92.3)	1 (7.7)		9 (69.2)	5 (38.5)	
Radiological pattern, *n* (%)												
UIP	103 (77.4)	30 (22.6)	0.003	69 (51.9)	64 (48.1)	0.510	121 (91.0)	12 (9.0)	0.453	77 (57.9)	56 (42.1)	0.646
Non-UIP	82 (92.1)	7 (7.8)		46 (51.7)	43 (48.3)		78 (87.6)	11 (12.4)		42 (47.2)	47 (52.8)	
AF, *n* (%)												
Pirfenidone	49 (80.3)	12 (19.7)	0.250	27 (44.3)	34 (55.7)	0.870	57 (93.4)	4 (4.4)	0.066	21 (34.4)	40 (65.6)	0.025
Nintedanib	136 (84.5)	25 (15.5)		81 (50.3)	80 (49.7)		142 (88.2)	19 (11.8)		98 (60.9)	63 (39.1)	

CT-ILD=Connective tissue disease related interstitial lung disease, fHP=Fibrotic hypersensitivity pneumonia, fNSIP=Fibrotic nonspecific interstitial pneumonia, uILD=Unclassified interstitial lung disease, UIP=Usual interstitial pneumonia, AF=Antifibrotic.

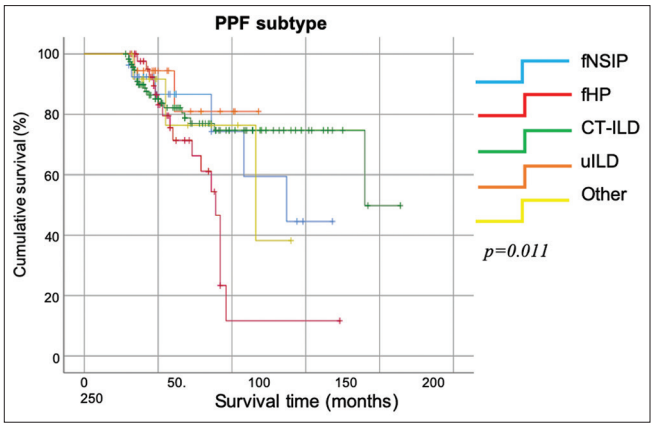

Figure 1: Kaplan–Meier survival estimates based on PPF subtypes. The estimated survival times for progressive pulmonary fibrosis types were made by pairwise analysis. Note that the difference between connective tissue disease-related interstitial lung disease (166.5 ± 9.2 months) and fibrotic hypersensitivity pneumonia (87.6 ± 9.2 months) is significant (Log-rank Chi-square 6.478, *P* = 0.011). PPF: Progressive pulmonary fibrosis, fHP: Fibrotic hypersensitivity pneumonia, fNSIP: Fibrotic non-specific interstitial pneumonia, CT-ILD: Connective tissue disease related interstitial lung disease, uILD: unclassified interstitial lung disease.

vary within groups (154.5 ± 9.2 months in UIP versus 114.3 ± 9.2 months in non-UIP, log-rank Chi-square 0.881, *P* = 0.348). Patients who received N had a more prolonged overall survival. The survival benefit of N over P was prominent only in CT-ILD (176.5 ± 9.3 months versus 85.8 ± 13.5 months, Log-rank Chi-square 0.017, *P* = 0.017). When survival times were evaluated together in terms of radiological patterns and the AF drugs, the survival advantage of N was present only in patients with UIP patterns. The addition of anti-inflammatory therapy to AFs did not affect overall estimated survival times (192.5 ± 6.5 months in the anti-inflammatory and AF combined group to 147.9 ± 7.2 months in the AF alone group, log-rank Chi-square 1.212, *P* = 0.271). "P and anti-inflammatory combination" had a lower survival time [Figure 2]. No significant difference was found between the 6th- and 12th-month progression status and survival times. Only radiological progression in the 12th month had a significant survival relationship [Figure 3].

Discussion

Real-life data on the follow-up and treatment of PPF subtypes provide varying results.[12-16] Our results also demonstrate this variability. The earliest transition to AF therapy with a diagnosis of PPF was seen in patients with fHP. We interpreted that if progression is detected in fHP, the lack of an alternative treatment approach and the fact that HP probably progresses to fibrosis faster than other groups may have shortened this period. This result was considered compatible with the information presented by Hambly *et al*., who stated that the progression rate of fHP is similar to that of IPF.[12] Based on this, it can be

Table 5: Evaluation of the differences in pulmonary function tests at 6th and 12th months compared to baseline in terms of radiological patterns and anifibrotic drugs

	UIP	Non-UIP	*P*	Nintedanib	Pirfenidone	*P*
Difference in FVC (%)						
6th month	−1.6	−5.3	0.001	−2.8	−3.8	0.025
12th month	−4.4	−7.1	0.015	−4.8	−7.2	0.011
Difference in FVC (mL)						
6th month	−36.7	−67.9	0.018	−33.1	−91.6	0.003
12th month	−73.1	−109.7	0.005	−77.7	−114.4	0.005
Difference in DLCO (%)						
6th month	−2.1	−2.3	0.602	−1.9	−2.9	0.046
12th month	−5.1	−6.4	0.063	−5.4	−6.1	0.062

FVC=Forced vital capacity, DLCO=Diffusing capacity of the lung for carbon monoxide, UIP=Usual interstitial pneumonia, AF=Antifibrotic.

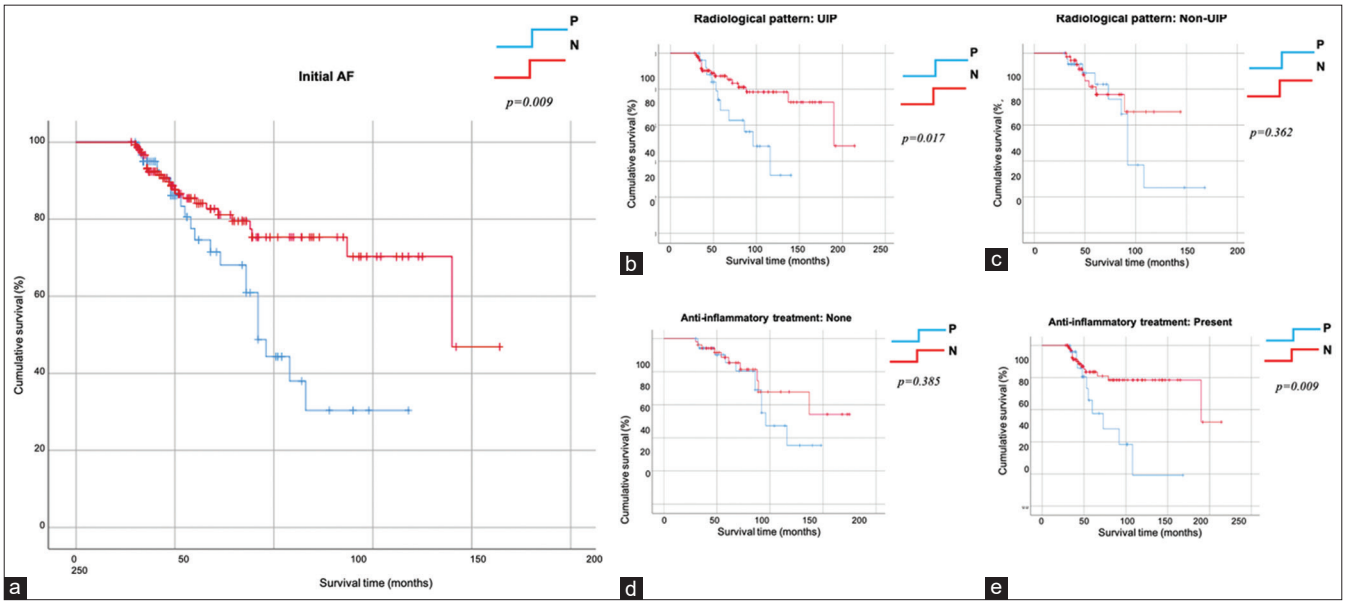

Figure 2: Kaplan–Meier survival estimates based on antifibrotic medication due to radiological patterns and additional anti-inflammatory therapies. Patients who received N treatment had a more prolonged overall survival (OS) time compared to those treated with pirfenidone (165.5 ± 8.8 months to 105.1 ± 8.9 months, Log-rank Chi-square: 0.680, *P* = 0.009) (a). Note that the survival advantage of nintedanib was present in patients with usual interstitial pneumonia (UIP) pattern (170.1 ± 9.7 months to 96.1 ± 9.1 months, Log-rank Chi-square 5.694, *P* = 0.017) (b), but did not show a significant difference in those with non-UIP pattern (116.8 ± 8.2 months to 103.3 ± 11.9 months, Log-rank Chi-square 0.831, *P* = 0.362) (c). In patients with no additional anti-inflammatory therapy, there was no difference between P and N (106.3 ± 8.7 months vs. 135.1 ± 10.8 months, Log-rank Chi-square 0.754, *P* = 0.385) (d). However, the difference was significant with a lower OS present in "*P* and anti-inflammatory combination" (89.9 ± 13.7 months vs. 172.1 ± 9.6 months, Log-rank Chi-square 6.884, *P* = 0.009) (e). AF: Antifibrotic, P: Pirfenidone, N: Nintedanib, UIP: Usual interstitial pneumonia).

considered reasonable that close follow-up is required in fHP and that perhaps, with studies to be conducted in the future, upfront AF medication may be recommended in fHP, as in IPF. 56.8% of patients experienced at least one AE. This is slightly lower than the frequencies stated in the literature.[13-16]

Real-world data obtained from this study validate the PFT reduction rates reported in the INBUILD study. The annual FVC loss was found to be −87.8 ml, which is quite close to the −80.8 ml reported in the INBUILD study. On the other hand, if we consider that only N was used in the study group of the INBUILD study, it seems more reasonable to compare the results of patients treated only with N. The mean annual FVC loss of 161 patients who received N was −77.7 ml. Another point consistent with the INBUILD study is that the advantage in annual FVC loss with AF is more evident in patients with UIP. This can be interpreted as patients with secondary UIP have a higher potential to benefit from AFs. This supports some ideas about evaluating UIP as a separate entity within PPF and considering upfront AF treatment.[17,18]

In the current literature, very few survival data have been reported after AFs were included in the treatment algorithm in PPF.[13] PFS, CEFS, and OS definitions, which are frequently used in the follow-up and treatment of cancer patients, also have a guiding potential in the follow-up of chronic and progressive diseases such as PPF.[8,19,20] While there are some reports dealing with this concept in IPF, we come across a much more limited number of analyses in PPF.[21-23] We observed no significant relationship between mortality

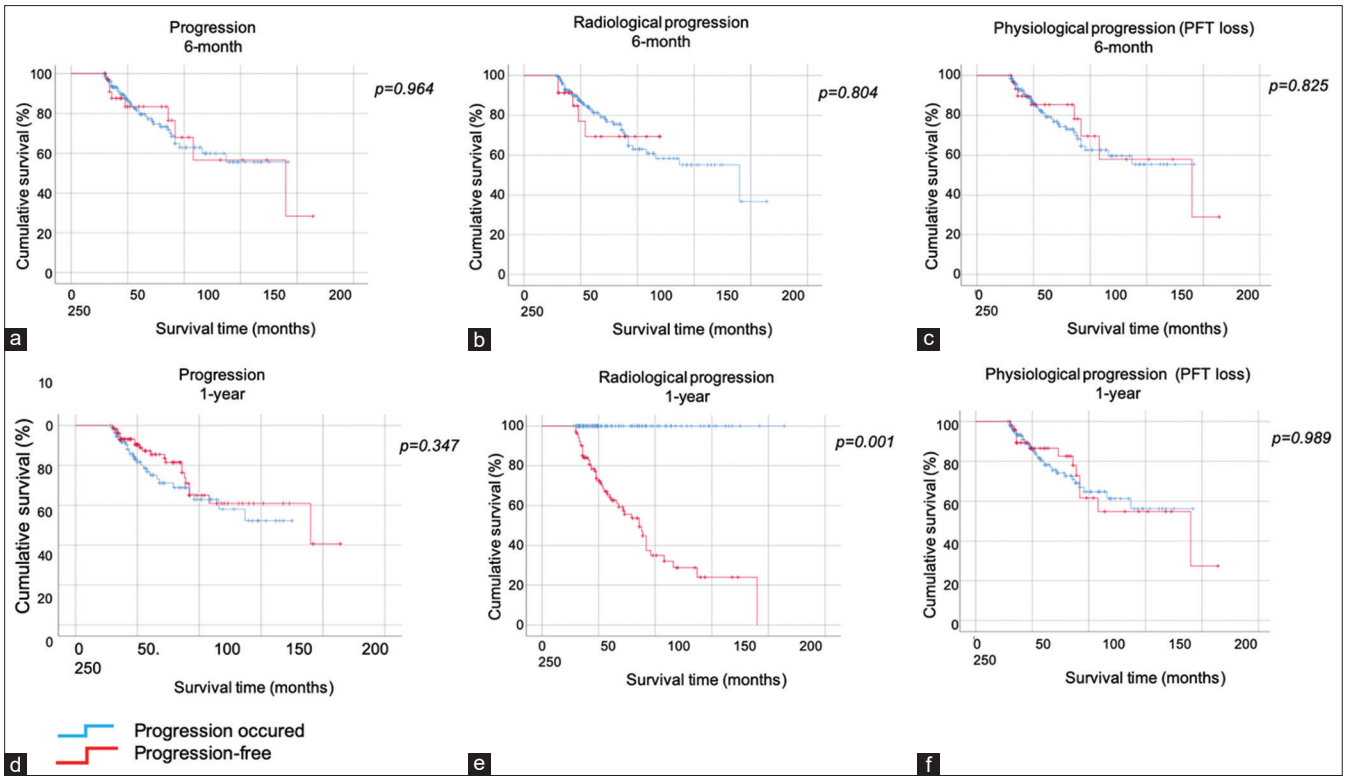

Figure 3: Kaplan–Meier survival estimates according to the presence of progression. Relationships between progression status and survival at 6th (a-c) and 12th months (d-f) were assessed. Progression presence within the first 6 months did not affect the estimated median survival (139.3 ± 6.9 months for patients with progression vs. 146.6 ± 17.1 months for progression-free patients, log-rank Chi-square 0.002, *P* = 0.96) (a). The difference was not statistically significant for radiological progression (96.5 ± 9.0 months in patients with radiological progression vs. 147.1 ± 8.2 months in patients with no radiological progression, log-rank Chi-square 0.061, *P* = 0.804) (b). The difference in terms of PFT loss was also not significant (149.3 ± 17.3 months in patients with stable PFT vs. 138.8 ± 6.9 months those with pulmonary function test (PFT) loss, log-rank Chi-square 0.490, *P* = 0.825) (c). Progression presence within 1 year did also not affect the estimated median survival (for 6-month: 4; for 1-year: 126.1 ± 7.7 months in patients with progression vs. 153.9 ± 10.5 months in progression-free patients, log-rank Chi-square 0.213, *P* = 0.347) (d). When the same analysis was performed for 1-year estimated survival, (e) radiological progression had a significant association with survival (log-rank Chi-square 62.54, *P* = 0.001), while (f) PFT loss did not make a significant difference (140.1 ± 7.3 months in patients with stable PFT vs. 144.8 ± 14.1 months those with PFT loss, log-rank Chi-square 0.001, *P* = 0.989). PFT: Pulmonary function test.

and progression. In other words, progression may occur under AFs, but it does not appear to be a major determinant of survival. This result can probably be evaluated more decisively with a longer follow-up.

In Raman's study, the rates of survivors at the 6th month and 12th month were reported as 81% and 80%.[13] We observed these rates to be higher (6th-month survival 98.2%, 12th-month survival 89.2%, and OS 77.5%). Our lower mortality rates may be related to the fact that, the proportion of CT-ILDs was higher and the fHPs was lower in our study.

The survival expectation obtained by Kaplan–Meier analysis was 147.8 ± 8.1 months. While the maximum survival expectation was determined in the CT-ILD group (166.5 ± 9.2 months), the minimum survival expectation was observed in the fHP group (87.6 ± 9.2 months) (*P* = 0.011). In a previous registry study, having the fHP subtype was identified as a risk factor associated with mortality.[9] In general, the estimated survival is higher in the N group. However, this result may be based on a multifactorial basis. P was used in only 61 patients. The fact that P is used more commonly in fHP, whose mortality rate is higher, also complicates the cause–effect relationship. In addition, the survival advantage of N actually appears only in patients with UIP. These results can be seen as confirmation of the INBUILD study results.[3] P appears to be disadvantageous in terms of the survival effects of the combination of AFs with anti-inflammatory treatments. However, in this case, it can also be interpreted as a result of the fact that N was used relatively more frequently in CT-ILD (anti-inflammatory treatments were combined more frequently in this group) and P in fHP.

Previous studies and guideline recommendations about progression vary, and the issue of which criterion is more guiding remains undetermined.[1,3,4] In addition, patients' characteristics such as age, gender, body mass index, and general condition may change their clinical responses to the progression. It is obvious that the definition of progression must be individualized according to the patient's personal characteristics and PPF subtypes.[12,24] As Johannson *et al*. mentioned, the definition of progression should not be considered only as an indication of AF, and more

personalized approaches should be investigated for different phenotypes.[25] In addition, it does not seem reasonable to apply the same temporal progression definitions to all patients. As Cottin *et al*. mentioned, the rate and duration of disease progression, and the expectations in this regard may differ significantly between phenotypes.[26,27] In order to interpret this complexity, we examined the effect of progression on estimated survival, and found no significant relationship. However, when looking at the subbreakdowns of the definition of progression, this situation changes at the point of radiological progression. Estimated survival time was found to be significantly lower in those with progression in radiological findings. In fact, this result is particularly consistent with the findings of previous studies on the sensitivity of progression definition.[1] Worsening of radiological findings indeed seems to be a more objective and independent criterion for assessing progression. In fact, there are studies that draw attention to this issue. In a retrospective cohort study conducted for the validation of the proposed criteria for PPF, 14 different progression criteria suggested in the literature were found to be significant for transplantation-free survival.[28] In that study, the strongest prognostic indicator was determined to be a 10% or greater loss in FVC.

Conclusion

AFs were well tolerated in patients on PPF treatment. The majority of patients had CT-ILD, and survival in these patients was better than for other subtypes, especially fHP. On the other hand, N, which was used more frequently in this subtype, had more positive effects on survival in combination with anti-inflammatory treatments than P. In terms of N versus P comparison, although real-life data showed that N was more preferred within its indications and guideline recommendations, AEs or overall mortality did not show a significant difference between them. N was also found to be significantly advantageous, especially in patients with UIP, in terms of FVC loss and estimated survival. While PFS during the entire follow-up period was in favor of N, CEFS had no significant difference between drugs. The major limitation of our study was that it was a retrospective cohort. This has definitely affected the level of objectivity at some points, such as the unbalanced distribution of AF drugs and PPF subtypes. It would be beneficial to ratify these results with longer-term studies. In addition, the heterogeneous definition approach that we criticized regarding PPF can be seen as a limitation of our study. In other words, large-scale analyses for different PPF subtypes will make the situation clearer.

Statement of ethics

Approval was obtained from the faculty local ethics committee. Since the study was a retrospective data review, an informed consent form was not obtained.

Ethical statement

Gulhane clinical investigations ethical committee.

Authors' contributions

NO, AC, NM, AU, FC, and IH contributed to the design, data collection, analyze, and writing of the study; BAO, KE, AE, EY, BA, FU, TSO, SM, PPD, IB, and OOK contributed at data collection and interpretation. All authors reviewed and contributed to the final version of the article.

Data availability statement

No supplementary or multimedia data has been added.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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