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Disease progression in idiopathic pulmonary fibrosis under anti-fibrotic treatment

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Abstract. Idiopathic pulmonary fibrosis (IPF) is the most common progressive interstitial disease of unknown etiology. The course of the disease cannot be predicted with certainty. It is crucial to regularly monitor the disease using multiple assessments to evaluate its progression. Currently, there is no consensus on the exact definition of disease progression. Although nintedanib and pirfenidone can slow down the progression of IPF, the disease can still advance even under anti-fibrotic treatment. The aim of this review is to examine and summarize the current data regarding IPF progression in patients receiving anti-fibrotic treatment, while also highlighting the limitations of the tests used for assessing disease progression

Key words: IPF, disease progression, nintedanib, pirfenidone

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common subtype of idiopathic interstitial pneumonias. It is a chronic disease characterized by progressive fibrosis and carries a poor prognosis. The incidence of IPF ranges from 0.22 to 11.7 per 100,000 individuals, with variations influenced by age and the geographical location of the study (1–3). Although the exact cause of IPF remains unknown, several risk factors have been identified, including advanced age, male gender, smoking, genetic mutations, environmental or occupational exposures, and microaspirations. The average survival time for patients with IPF who do not receive anti-fibrotic treatment is typically between 2.5 and 3.5 years (4), and the 5-year survival rate has been reported as 20-30% in certain studies (5).

IPF exhibits a variable clinical course, ranging from asymptomatic to progressive respiratory failure. Predicting the disease's course is impossible. Disease progression in IPF is indicated by a decline in lung function, worsening dyspnea, and radiological changes. Forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) are commonly used parameters in the literature (6,7). A 10% reduction in FVC within 6-12 months has been associated with increased mortality (8). The GAP (gender, age, physiology) index is also used to assess prognosis (9). In the AIFR study, desaturation during the 6-minute walk test (6MWT) was the only parameter linked to survival or disease progression after 12 months of follow-up (6). Furthermore, bronchoalveolar lavage fluid cell distribution and certain interleukins have been investigated as predictors of IPF prognosis. High levels of neutrophils and eosinophils in BAL fluid have been associated with a poor prognosis (10–13). However, there is currently no definitive marker for IPF progression. While anti-fibrotic drugs like nintedanib and pirfenidone have been shown to slow disease progression, IPF can still progress despite their use. In this review, we aimed to examine and summarize the current data on IPF progression in patients undergoing anti-fibrotic treatment, while also discussing the limitations of the tests used to assess disease progression.

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Reduced rate of decline in FVC in phase studies

Nintedanib, an orally administered tyrosine kinase inhibitor originally developed as a cancer drug, targets key receptors involved in the pathogenesis of IPF, including vascular endothelial growth factor (VEGF), transforming growth factor β (TGF-β), and fibroblast growth factor (FGF) receptors (14). The efficacy of nintedanib in IPF was initially assessed in the TOMORROW study conducted by Richeldi et al (15). This multinational, randomized, double-blind, placebo-controlled study demonstrated a reduction in FVC decline in 68.4% of patients treated with nintedanib for 52 weeks (15). However, there were no significant differences observed in DLCO and the 6MWT between the nintedanib group (150 mg twice daily) and the placebo group. Subsequently, the INPULSIS study was conducted, involving 1,061 IPF patients from 24 countries (14). The findings of these studies indicated that nintedanib significantly slowed the annual decline in FVC, irrespective of sex, age, or race (14,16). In both the INPULSIS 1 and INPULSIS 2 trials, after one year of nintedanib treatment, less than 10% reductions in FVC were observed in 70.6% and 69.6% of patients, respectively (14,16). Additionally, nintedanib demonstrated efficacy in prolonging the time to first exacerbation. These positive results led to the approval of nintedanib for the treatment of IPF in Japan, the United States, and Europe. In the long-term efficacy study INPULSIS-ON (17), which investigated the effects of nintedanib over 192 weeks, the mean FVC of the entire cohort showed a 7.5% decrease from baseline. The study also reported a 5-year mortality rate of 24% in patients receiving nintedanib treatment. Overall, these phase studies demonstrate the ability of nintedanib to reduce the rate of FVC decline in IPF patients.

Pirfenidone, another oral anti-fibrotic drug, has been in use in the European Union since 2011 and in the USA since 2014. It was subsequently recommended in the ATS/ERS/JTS/ALAT guideline in 2015. Although its mechanism of action is not fully understood, it is believed to inhibit the TGF-beta pathway, thereby preventing fibroblast proliferation and their transformation into myofibroblasts (18). The first clinical study on pirfenidone was conducted in Japan following the phase 2 study by Raghu et al. in 1999 (19). This study involved 13 patients with IPF and showed that nine months of pirfenidone use reduced vital capacity decline and the number of exacerbations (20). In addition, CAPACITY (21), ASCEND (22), and EMPIRE (23) studies were conducted. In all three studies, pirfenidone demonstrated a reduction in FVC decline compared to the placebo group and showed a positive effect on progression-free survival. In the EMPIRE study, which examined the effect of pirfenidone on FVC levels and survival, it was reported that patients with a ≥ 10% decline in FVC did not have superior mortality outcomes compared to the group that did not receive anti-fibrotic treatment within the first two years. However, at the end of two years, there was a statistically significant improvement in survival (23). The EMPIRE study also suggested that a 10% reduction in DLCO has potential value in predicting mortality. In the ASCEND study, an increase in FVC values was observed in 22.7% of patients after 52 weeks of pirfenidone use. The CAPACITY study showed a 36% reduction in the rate of death and disease progression (21).

In these phase studies, the decline in lung function in the placebo groups was significantly greater than in the treatment arms. In the CAPACITY study, FVC decline was -11% at the end of 72 weeks, while in the ASCEND trial, it was -280 ml at 52 weeks. For nintedanib, the decline rates were -6% and -6.2% in the INPULSIS 1 and INPULSIS 2 trials, respectively, at 52 weeks.

Limitation of the tests using for disease progression in IPF

Pulmonary function test

There is no standardized definition for disease progression in IPF, although progressive pulmonary fibrosis is well defined in recently updated guideline (24). Many studies in the literature have utilized a decline in FVC (>10%) and DLCO (>15%) as criteria for disease progression (22,23,25–33). Other studies have considered lesser radiological progression, 6MWT, symptom worsening, and/or acute exacerbations [10,13,24,30,31]. A decrease in DLCO is often considered indicative of progressive disease, particularly when accompanied by a decline in FVC or an increase in fibrosis on high-resolution computed tomography (HRCT). Table 1 provides an overview of parameters used to define IPF

progression. However, no gold standard criterion for disease progression can be used in routine clinical practice, and each criterion has its limitations.

FVC is the most commonly used physiological parameter for monitoring patients with IPF. It has been reported that FVC can indicate the progression of IPF due to its easy accessibility, reproducibility, and association with mortality, making it an outcome criterion in clinical studies (34). The FVC maneuver is often used to measure airflow velocities. However, since the FVC maneuver requires patient cooperation and effort, it can be influenced by various factors. Several studies have reported that a 6-12 month decline in FVC is indicative of increased mortality (22,23,26,27,30–32). Nevertheless, there is no standardized definition in the literature on how to utilize observed decreases in FVC in clinical practice. FVC measurement in IPF follow-up has both advantages and disadvantages. Disadvantages include its reliance on patient effort, variability in test results, laboratory quality, and susceptibility to the impact of comorbid diseases (35). Additionally, many IPF patients are elderly and may have limited exercise capacity, which can affect their cooperation during the test. Moreover, a significant portion of IPF patients also have emphysema (36). Furthermore, different trials have used either absolute or relative changes in FVC to assess the progression of pulmonary fibrosis, reflecting different patient populations.

Diffusing capacity for carbon monoxide

DLCO is another parameter used to predict IPF progression. In the literature, a 15% decrease in DLCO in IPF patients has been reported as an indication of progression [26,27,32,33]. Various methods exist for measuring DLCO, and although there may be differences between laboratories, the single breath method has been proven effective in determining lung function in different lung diseases (37). However, it's important to note that low DLCO does not always indicate impaired diffusion capacity, as several non-respiratory factors can affect DLCO, such as smoking, menstrual cycle, and alcohol intake (38,39). Additionally, there are challenges in performing the DLCO test in patients with very reduced lung volumes and difficulty in breathing. It's also worth mentioning that persistent isolated reduction in DLCO may occur in pulmonary vasculopathy without an increase in pulmonary fibrosis, therefore should be used cautiously if only accompanied by worsening of symptoms. A decline in absolute DLCO measurements, in the absence of other explanations for the decline, may indicate progression, particularly when complemented by a decrease in FVC or an increase in the extent of fibrosis on HRCT.

Table 1. Parameters used in idiopathic pulmonary fibrosis progression.

Decline in FVC (≥10%)
Decline in DLCO (≥15%)
Radiologic progression
Decline in 6MWT (> 50 m)
Increased oxygen requirement
Exacerbations/hospitalizations
Worsening of pulmonary symptoms

FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-minute walk test.

Six minute walk test

6MWT is another parameter used for assessing disease progression in IPF, although it is also a non-standardized test. The primary measurement in the 6MWT is the distance walked by the patient in 6 minutes, and secondary measurements include monitoring oxygen saturation, heart rate, and dyspnea. Studies have shown that a decline of 16.5% in 6MWT distance within one year can indicate disease progression in IPF (22). Additionally, desaturation during the 6MWT has been identified as a prognostic factor in IPF (6). However, the 6MWT can be influenced by various factors such as body mass index, heart failure, respiratory failure, and muscle disease. The length of the track used for the test and the distance covered can also impact the results (40,41).

High-resolution computed tomography

HRCT plays a well-defined role in the diagnosis of IPF, but its role in demonstrating disease progression is less established. Progression of fibrosis is visually assessed by evaluating the percentage of lung volume containing fibrotic changes. An increased extent of fibrotic changes in both the transverse and coronal planes indicates progression. Quantitative CT methods have been developed to provide a more objective measure of fibrosis extent (42). Some studies have utilized quantitative

lung fibrosis scores derived from imaging features to predict progression-free survival in IPF patients. However, the use of radiological progression as a criterion for disease progression in clinical studies is often combined with other clinical and physiological parameters, and there is no clear definition of radiological progression across these studies [24,25,41]. Various types of quantitative CT analyses have been developed (AMFM, CALIPER, QLF/QILD, DTA) (43). All these quantitative CTs have produced a certain level of usefulness, but quantifiable parenchymal pattern may vary by software. Serial changes in DTA scores showed a significant correlation with changes in both FVC% predicted and DLCO% predicted (44). In a very recent study, Sun et al. showed that changes in CT-related parameters during follow-up may have better predictive performance compared with baseline imaging parameters and pulmonary function tests for disease progression in IPF (45). While the results to date are promising, its clear that further prospective clinical studies are warranted to determine the potential role of the quantitative CT in patients with IPF.

In IPF, acute exacerbation is defined as acute worsening of dyspnea accompanied by newly developed bilateral ground glass densities and/or consolidation on top of the radiological baseline of usual interstitial pneumonia (UIP) pattern (46,47). Non-parenchymal causes such as pneumothorax, pleural effusion, pulmonary embolism, and isolated heart failure or fluid overload must be excluded to define acute exacerbation of IPF (17,46).

IPF progression in phase studies and in real-life studies

Determining the true progression rate of patients with IPF under anti-fibrotic treatment is challenging due to the lack of a gold standard parameter for disease progression. However, based on the available literature, the progression rates in phase studies and real-life studies can vary. In the literature, it has been reported that patients receiving anti-fibrotic treatment demonstrated a minimum of 10% decline in FVC within the first year for 6.5-38%, within the second year for 4.4-47%, and within the third year for 6.6-54% (22,23,25–27,31–33,48). As for DLCO reduction, a 15% decline was observed in 7.4-38% of patients in the first year, 4.4-15% in the second year, and 6.6-15% for longer follow-ups (22,23,28,29). When clinical worsening and/or acute exacerbation are considered as criteria for IPF progression, the progression rate ranges from 2.6% to 11.8% (10,11,13,24,30,31).

Table 2 shows the proportions of patients who progressed despite anti-fibrotic treatment in both phase studies and real-life studies, categorized by years. It is evident that the progression rates of IPF vary depending on the progression criteria and follow-up period used in the studies. In phase studies, where strict criteria are used for patient selection, the IPF progression rate in the first year is around 10%. However, in real-life studies, the progression rates can be much higher, reaching up to 38% in the first year, 47% in the second year, and 54% after two years (14,16,17,22,23,25–33,48–54). These differences may be attributed to variations in the selected progression criteria and the evaluation period, as well as the differences in patient characteristics and management in real-life settings compared to controlled clinical trials. It is important to consider these variations and limitations when interpreting the progression rates reported in different studies, as the definition and assessment of disease progression in IPF are still evolving. Further research and long-term follow-up studies are needed to provide a more comprehensive understanding of IPF progression under anti-fibrotic treatment in real-life settings.

The efficacy of pirfenidone in the treatment of IPF has been investigated in several phase studies, which also provided data on IPF progression (21–23). However, IPF progression was not clearly defined in the CAPACITY and ASCEND studies. In the ASCEND study, 6.5% of patients using pirfenidone for 52 weeks exhibited a decrease of 10% or more in FVC, while 16.5% had a decrease of 50m or more in the 6MWT. In the CAPACITY study, a decline in FVC was detected in 21% of the patients, and pirfenidone demonstrated a 26% reduction in the risk of disease progression and mortality in progression-survival analyses (21). A post hoc analysis, which included the CAPACITY and ASCEND studies and focused on IPF patients with a baseline FVC value ≥80%, reported a progression rate of 17.9% based on a 10% decline in FVC and 21.4% based on a ≥50m decrease in 6MWT (53). In the EMPIRE study, the percentages of patients experiencing a ≥10% decline in FVC at 6, 12, 18, and 24 months were as follows: 5.3%, 10.7%, 16.6%, and 17.0%, respectively. Using a ≥15% decline in DLCO as the marker of progression, the percentages of patients who progressed at 6,

Table 2. Idiopathic pulmonary fibrosis progression rates under anti-fibrotic therapy.

			Progression rate (%)			Treatment
Study/author	**Study design**	**Progression criteria**	**≤ 1 yr**	**1-≤2 yr**	**2-3 yr**	
Richeldi (15)	Phase 2	Disease worsening, exacerbation	9.8	-	-	Nintedanib
Richeldi (14)	Phase 3	Disease worsening, exacerbation	10	-	-	Nintedanib
Crestani (17)	Phase 3	Worsening of symptoms, exacerbation	14.4	13.7	-	Nintedanib
King (22)	Phase 3	FVC 10 %↓	6.5	-	-	Pirfenidone
		6MWT 50 m ↓	16.5	-	-	
Song (50)	Phase 3	Worsening of symptoms, exacerbation	16	10.7	-	Nintedanib
Zurkova (23)	Phase 3	FVC 10% ↓	10.7	17.0	-	Pirfenidone
Taniguchi (55)	Phase 3	VC 10% ↓	4.6	-	-	Pirfenidone
		Worsening of symptoms	2.8	-	-	
Antoniou (25)	Retrospective	Died or FVC 10% ↓	35	47	54	Nintedanib
Oltmanns (26)	Retrospective	FVC 10% ↓or DLCO 15%↓	38	-	-	Pirfenidone
Feng (27)	Retrospective	FVC 10% ↓	7.4	9.5	-	Pirfenidone
		DLCO 15 %↓	7.4	10		
Vianello (28)	Case control	Worsening of symptoms and FVC and/or CT	25	-	-	Pirfenidone
Suzuki (29)	Retrospective	FVC 10% ↓, CT	-	45.9	-	Pirfenidone-Nintedanib
Milger (30)	Case control	FVC 10% ↓	28.5	-	-	Pirfenidone
			28.5	-	-	Nintedanib
Bando (31)	Retrospective	FVC 10% ↓	16.2	31.9	31.3	Pirfenidone
Cerri (32)	Prospective	FVC 10% ↓, DLCO 15% ↓	12	15	30	Pirfenidone
			11	17	33	Nintedanib
Vietri (33)	Retrospective	FVC 10% ↓, DLCO 15% ↓	-	4.4	6.6	Pirfenidone
Caro (49)	Retrospective	Exacerbation	6	-	-	Pirfenidone
Cilli (48)	Retrospective	FVC 10 % ↓	-	35.7	-	Pirfenidone
		FVC 10% ↓+ CT	-	26.8	-	
		FVC 10%	-	10	-	Nintedanib
		FVC 10 %+ CT	-	10	-	
Sakayori (56)	Retrospective	NA	6	-	-	Pirfenidone
Tzouvelekis (51)	Retrospective	NA	12.8	-	-	Nintedanib
Kato (52)	Retrospective	NA	18.2	-	-	Nintedanib

FVC: forced vital capacity; VC: vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-minute walk test; CT: computed tomography; NA: not available

12, 18, and 24 months were 6.1%, 11.3%, 11.5%, and 14.3%, respectively. A randomized controlled study conducted by Taniguchi et al. in Japan reported a progression rate of 4.6% when the progression criterion was a vital capacity ≥10% decrease and 2.8% when the criterion was symptom worsening (55). In a retrospective study by Bando et al., which included patients with two-year data under pirfenidone treatment, a decline of 10% or more in FVC values was observed in 31.9% of the patients (31). Furthermore,

other real-life studies with pirfenidone reported IPF progression rates ranging from 4.4% to 38%, using criteria such as FVC decrease, DLCO decrease, or exacerbations (22,23,29,30,44).

Regarding nintedanib, the TOMORROW study, the first phase study investigating its efficacy in the treatment of IPF, reported a one-year progression rate of 12.8% for a daily dose of 50 milligrams and 4.7% for a twice-daily dose of 150 milligrams (15). The overall one-year progression rate in the entire cohort was found to be 9.8% in the TOMORROW study. In the INPULSIS 1-2 study conducted by Richeldi et al., which accepted disease worsening and acute exacerbations as progression criteria, the progression rate was 10%, similar to the TOMORROW study (14). Subsequently, two separate INPULSIS-ON studies were conducted to investigate the long-term effects of nintedanib, which reported IPF progression rates of 10.7% and 11.8% in patients receiving long-term nintedanib (17,50). In a real-life study by Antoniou et al., which included a large number of patients, three-year data of patients receiving nintedanib treatment were presented. In this study, a reduction in FVC ≥10% or mortality was considered a progression criterion, and the first, second, and third-year progression rates were reported as 35%, 47%, and 54%, respectively (25). In another real-life study where IPF progression was reported as 12.8%, without clear criteria for progression, the FVC reduction of the entire cohort was reported to be approximately 5% after six months of nintedanib treatment, and approximately 6% from baseline at one year (51). These findings from various studies highlight the progression rates observed in IPF patients under anti-fibrotic treatment with pirfenidone and nintedanib, emphasizing the need to consider different progression criteria and follow-up periods.

Conclusions

IPF demonstrates considerable heterogeneity, and a subset of patients experience disease progression despite anti-fibrotic treatment. The variability in reported progression rates can be attributed to differences in selected criteria for disease progression. Notably, real-life studies tend to report higher progression rates compared to phase studies. The ability to predict which patients will experience disease progression remains elusive, underscoring the challenge of identifying prognostic factors in IPF. Furthermore, a standardized definition for disease progression in IPF is currently lacking, leading to the utilization of various physiological, radiological, and clinical criteria for assessing disease progression. However, each criterion has its own limitations, necessitating the development of more objective and reliable measures. It is crucial to establish standardized definitions and more objective criteria for assessing disease progression in order to improve prognostic accuracy and guide treatment decisions in IPF patients.

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