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REVIEW

Progressive pulmonary fibrosis (PPF)

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ABSTRACT

Progressive pulmonary fibrosis (PPF)

Progressive pulmonary fibrosis (PPF) is defined as the presence of at least two of the three criteria, which are worsening respiratory symptoms, functional decline, and radiological progression in patients with interstitial lung disease with radiological pulmonary fibrosis for known or unknown reasons other than IPF, within the previous year (1). A conditional recommendation has been made for nintedanib in the treatment of PPF, and further studies are needed for pirfenidone (1). In this review, the diagnostic and therapeutic approach to progressive pulmonary fibrosis with its new name, previously known as progressive fibrotic interstitial lung diseases, will be discussed, accompanied by updates.

Key words: *Progressive pulmonary fibrosis; interstitial lung disease; antifibrotic*

ÖZ

Progresif pulmoner fibroz (PPF)

İPF dışında bilinen ya da bilinmeyen nedenlerle, interstisyel akciğer hastalığı olan ve radyolojik olarak pulmoner fibroz gösteren olgularda, son bir yıl içinde, solunum semptomlarında kötüleşme, fonksiyonel bozulma ve radyolojik progresyon olarak tanımlanan üç kriterden en az ikisinin varlığı progresif pulmoner fibroz (PPF) olarak tanımlanmıştır (1). Tedavide nintedanib için koşullu öneri yapılmış olup, pirfenidon için ileri çalışmalara ihtiyaç vardır (1). Bu derlemede, önceden progresif fibrotik interstisyel akciğer hastalıkları olarak bilinen, yeni adlandırmasıyla progresif pulmoner fibrozda yenilikler, güncellemeler eşliğinde tanı ve tedavi yaklaşımı ele alınacaktır.

Anahtar kelimeler: *Progresif pulmoner fibroz; interstisyel akciğer hastalığı; antifibrotik*

INTRODUCTION

Interstitial lung disease (ILD) is characterized by inflammation and fibrosis of the lung parenchyma, and fibrotic interstitial lung diseases form a subset of interstitial lung diseases (ILD) (1). Progressive fibrotic interstitial lung diseases are characterized by worsening symptoms, a decline in lung function, radiological

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progression, poor response to treatment, poor quality of life, and early mortality (2-4). IPF is the most common, severe idiopathic interstitial pneumonia (IIP), and it is accepted as the prototype of progressive fibrotic ILD (PF-ILD). Some subtypes of ILD other than IPF can also show progressive fibrotic behavior. Although etiology is different between these ILDs, overlaps exist due to common pathological mechanisms, clinical and radiological presentation, and prognosis. It is not easy to differentiate and define PF-ILD. (2-4) Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline 2022 clarified the definition, diagnostic and therapeutic approach to PF-ILD and preferred using the terminology of Progressive Pulmonary Fibrosis (PPF) instead of PF-ILD (1). Because the disease includes not only the interstitium, ILD was extracted from the definition, and pulmonary was preferred. The disease course is progressively similar to IPF, and the term pulmonary fibrosis was already used widely by clinicians and patients, so naming PPF is helpful and easier in clinical practice. It is stated that the term PPF does not point out the diagnosis, and it can include diseases that can show IPF-like behavior and similar prognosis in common. Differential diagnosis of these diseases is challenging and can be idiopathic nonspecific interstitial pneumonia (iNSIP), fibrotic hypersensitivity pneumonitis (HP), connective tissue disease (CTD)-associated ILD, unclassifiable fibrotic ILD, sarcoidosis and ILD related to occupational exposures (1-5).

Epidemiology

The exact prevalence of PPF is unknown. The recent PROGRESS study, a real-world cohort of patients with ILDs, has identified a progressive phenotype in approximately 25% of fibrosing ILDs other than IPF (6). In another real-life study, the proportion of non-IPF ILDs with progressive fibrosing phenotype has been reported to range from 18% to 32% (7). The time from the onset of symptoms to death was 61-80 months. Median survival following ILD progression diagnosis was approximately three years in these patients (7).

Pathogenesis

Some ILDs are primarily considered fibro-proliferative disorders, in which alveolar epithelial injury and fibroblastic proliferation lead to fibrosis, while other ILDs are considered primarily inflammatory disorders in which the pathogenetic process shifts to a fibro-proliferative pathway (8). Repeated chronic epithelial or vascular injuries lead to cell destruction and unregulated repair. Fibroblasts proliferate, migrate from different sources to the injury site, and are activated to become myofibroblasts, which secrete increased amounts of extracellular matrix. As an increasing extent of the lung is lost to fibrosis, the lung volume is reduced and gas exchange impaired, resulting in worsening breathlessness and capacity for exertion, and ultimately in respiratory failure (2,9).

In addition to IPF, ILD subtypes such as idiopathic non-specific interstitial pneumonia (iNSIP); unclassifiable idiopathic interstitial pneumonia (IIP); rheumatoid arthritis-associated ILD (RA-ILD); systemic sclerosis-associated ILD (SSc-ILD); hypersensitivity pneumonitis (HP); sarcoidosis; and ILDs related to other occupational exposures have overlapping morphological features and common pathological mechanisms regardless of the trigger leading the concept of a progressive fibrosing phenotype (1-3). These diseases are rare, poorly investigated, and challenging to diagnose. Accurate diagnosis requires a multidisciplinary discussion between the pulmonologist, radiologist, and pathologist, and it is crucial for therapeutic decisions (1-3).

Definition

PPF was defined separately from IPF in Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults an Official ATS/ERS/JRS/ALAT Clinical Practice Guideline, on May 1, 2022. It was stated that the definition of PPF is irrespective of the underlying condition, and the criteria for PPF have been associated only with prognosis (1). PPF is defined in patients with ILD having radiological evidence of pulmonary fibrosis other than IPF and at least two of the following three criteria occurring within the last year as;

1. Worsening of respiratory symptoms

2. Physiological evidence of disease progression

3. Radiological evidence of disease progression (1) These criteria are shown in Table 1.

Radiological Evaluation

The gold standard imaging method for the diagnosis and follow-up of ILD is high-resolution computed tomography (HRCT) (1). As the extent of fibrotic

Table 1. Criteria for the definition of PPF

Clinical criteria	Physiological criteria (one of the following)	Radiological criteria (one of the following)
Worsening of respiratory symptoms	Absolute decline in FVC ≥5 within last year Absolute decrease in DLCO ≥10 within the previous year	Increased extent and severity of traction bronchiectasis New ground-glass opacities with traction bronchiectasis New fine reticulation Increased in the extent or coarseness of reticulation New or increased honeycombing Increased lobar volume loss

changes, honeycomb cysts, and traction bronchiectasis increase, mortality risk increases in IPF (10). It has been shown that a greater extent of fibrotic changes is predictive of progression and mortality also in PPF. These changes are defined as the evolution of ground-glass abnormality to reticular abnormality, the development of reticular abnormality to honeycombing, an increase in reticulation, and traction bronchiectasis/bronchiectasis (1,10-12) (Figure 1). Follow-up HRCT is indicated when there is clinical suspicion of worsening fibrosis. The optimal interval for follow-up HRCT to determine disease progression is unknown. Annual HRCT can be suitable for screening progression and complications, especially lung cancer. Radiological scoring systems as predictors of prognosis are not useful until validated; low-cost, automated scoring systems are available (1).

Differential diagnosis of NSIP, especially fibrotic NSIP and IPF, is challenging. CT findings positive for NSIP may have different outcomes. It was reported that 28% of patients with NSIP pattern progress to IPF pattern radiologically at three years or longer follow-up. (12). Unfortunately, there are no CT features at the presentation that distinguish patients with NSIP that maintain an NSIP pattern from those who progress to an IPF pattern. At presentation, NSIP is characterized by the predominance of GGO, lack of honeycombing, presence of relative subpleural sparing, and low prevalence of peripheral distribution of disease, findings that allow distinction from IPF in most patients (12).

Most connective tissue disease-associated ILDs (e.g., scleroderma, polymyositis, dermatomyositis, Sjogren's syndrome, and undifferentiated connective tissue disease) represent the NSIP pattern. Unlike these

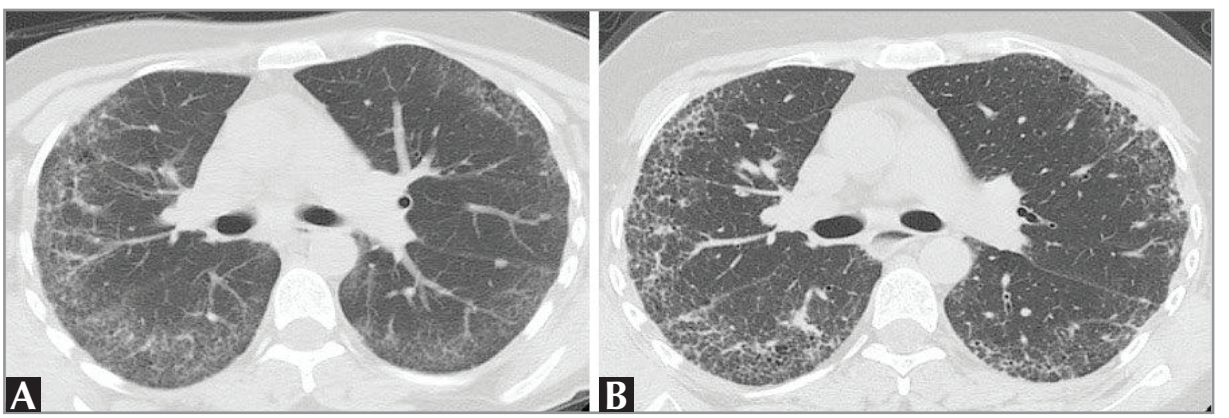


Figure 1. PPF in a 49-year-old woman with a histopathological diagnosis of idiopathic NSIP represents clinical deterioration, functional decline, and radiological progression at the end of the one-year follow-up despite corticosteroid therapy. **A.** Computed tomography shows ground-glass opacities, nodules, reticular densities, and traction bronchiectasis at diagnosis. **B.** Radiological progression as the increased extent of reticular densities and traction bronchiectasis and evolution of honeycombing during follow-up.

connective tissue disease-associated ILDs, a higher proportion of patients with rheumatoid arthritis (RA-ILD) have a UIP pattern radiologically (13,14). Definitive usual interstitial pneumonia pattern, the existence of traction bronchiectasis, and honeycomb fibrosis on HRCT were associated with worse prognosis in RA-ILD (14).

Almost half of the SSc patients had ILD at the time of diagnosis, and most of the ILD pattern was NSIP (15). It has been shown that a greater extent of lung fibrosis is associated with a short-term decline in lung function and increased mortality (16). Baseline HRCT and PFT should be made for all SSc patients (17). Thorax HRCT performed every 12-24 months can detect early progression even in subjects with stable pulmonary function (16).

Hypersensitivity pneumonia (HP), especially fibrotic HP, is another group of PPF that is difficult to distinguish from IPF radiologically (18). It was stated that when the extent of mosaic attenuation or air trapping is greater than reticulation and diffuse axial distribution of interstitial abnormality is present in combination, the specificity for HP is greater than 90% (19). The prognosis of fibrotic HP is worse, resembling IPF (18).

Despite a thorough multidisciplinary evaluation, approximately 10-15% of ILD patients have unclassifiable ILD (20,21). Unclassifiable ILD has a clinical course and prognosis that is intermediate between IPF and non-IPF ILDs (20,21). The greater extent of HRCT fibrosis and lower DLCO were associated with progression and mortality (20).

Functional Evaluation

Functional decline is the most critical component of PPF, reflecting disease progression. The functional evaluation was assessed by measuring the forced vital capacity (FVC) and diffusion capacity of the lungs for carbon monoxide (DLco). Physiological criteria for disease progression are defined as a:

1. Absolute decline in FVC of ≥5 within one year of follow-up.

2. Absolute decline in DLCO of ≥10 within one year of follow-up in recent IPF -PPF guideline (1).

FVC is the most commonly used functional parameter to follow IPF and PPF patients, associated with progression and mortality (1,9). The annual rate of FVC decline was evaluated as absolute or relative values of ≥5-10% and ≥10-15% for FVC and DLCO, respectively, in previous studies. (22-26). The absolute decline in FVC is calculated as the initial FVC measurement minus the final FVC measurement. An absolute decline in FVC of at least 5% and an absolute decline in DLCO of at least %10 accepted as meaningful for progression in the recent guideline (1). In all the subgroups, FVC decline was essentially linear over the long term, but it was too variable over the short time to enable recent change to be used to predict future change (9). Among 695 patients with SSc in a large cohort study, approximately one-third of patients had a DLCO of <50% within three years of the onset of Raynaud's phenomenon (27). Patients with other CTD-ILDs like RA or polymyositis/dermatomyositis can show rapid loss of lung function despite treatment (9). Also, patients with fibrotic HP can show rapid disease progression, especially if the inciting antigen cannot be identified and removed. FVC decline was found to be similar between patients with CHP and IPF and between patients with CTD-ILD and IPAF (5).

Treatment

Progressive fibrosing ILDs have been traditionally treated with corticosteroids and immunosuppressive therapies, and over a quarter of patients with PPF do not receive drug therapy. Corticosteroids and immunosuppressive therapies may not be effective and adequate, suggesting a need for efficacious treatment (28). Once fibrosis has become progressive, antifibrotic treatment would be required to slow disease progression (29). Similarities in pathobiological mechanisms leading to fibrosis between IPF and PPF provide a rationale to suggest that nintedanib and pirfenidone may be therapeutic options for patients with PPF (30). Further studies are required on the timing and sequence of antifibrotic drugs concerning corticosteroids and immunosuppressants in the PPF (31).

Nintedanib

Nintedanib is an anti-fibrotic agent shown to reduce the decline in FVC and slow disease progression in IPF patients with a large randomized controlled trial (INPULSIS) (32). The effect of nintedanib on patients with ILD associated with systemic sclerosis was shown in the SENSCIS trial. The annual rate of change in FVC was lower in the nintedanib group than in the placebo group p (-52.4 mL per year vs. -93.3 mL per year) (33).

An accurate initial ILD diagnosis is crucial to inform prognosis and ensure that patients receive optimal management, but diagnostic precision is less critical once progressive fibrosis occurs despite treatment. The clinical course of patients with progressive fibrosing ILD resembles patients with untreated IPF irrespective of underlying disease. This knowledge led to further studies about the influence of nintedanib on PPF progression, and the INBUILD trial (RCT) revealed that nintedanib reduces the rate of FVC decline and disease progression regardless of the type of underlying ILD (24,25). The effect of nintedanib versus placebo on slowing the rate of FVC decline was consistent across the five ILD subgroups, namely HP, autoimmune ILD, iNSIP, unclassifiable IIP, and other ILDs with a mean annual decline of significantly less than 107 mL/year (24). The effect of nintedanib on reducing the rate of decline in FVC was also consistent across patients with usual interstitial pneumonia-like fibrotic patterns and patients with other fibrotic patterns on HRCT (24).

The most frequent adverse event was diarrhea, reported in 70% of the nintedanib group, and nausea, vomiting, abdominal pain, decreased appetite, and weight loss were more frequent in the nintedanib group than in the placebo group. Adverse events reported in the subgroups were consistent with those reported in the overall population (24,25).

A conditional recommendation was made for nintedanib in the treatment of PPF in recent IPF-PPF guidelines (1).

Pirfenidone

Pirfenidone is an anti-fibrotic agent with anti-inflammatory, antioxidative, and antiproliferative effects. It reduces disease progression and rate of FVC decline and positively impacts exercise tolerance and progression-free survival in patients with idiopathic pulmonary fibrosis (34). Pirfenidone was recommended for the treatment of IPF in prior guidelines (35).

Because of the similarities in pathogenetic and clinical behavior between IPF and other progressive fibrotic ILDs, the RELIEF study was designed to assess the efficacy of pirfenidone in PPF patients (26). It was terminated early because of futility triggered by slow recruitment; however, imputations were conducted for missing data, with the primary analysis favoring the pirfenidone arm. Given the premature study termination, results should be interpreted with caution (26).

Additional research was recommended on the effect of pirfenidone in general and specific types of non-IPF ILD manifesting PPF in the recent IPF-PPF guidelines (1).

CONCLUSION

There have been promising developments in PPF. PPF was newly defined with clear criteria, and a conditional recommendation for nintedanib in the treatment of PPF was made in recent guidelines. Delays in diagnosis, treatment, and progression detection are major concerns in PPF. There is a need for research on validated biomarkers to predict disease progression and timing and sequence of anti-fibrotic drugs concerning corticosteroids and immunosuppressants in PPF.

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