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Editorial

Advantages of Early Antifibrotic Treatment in Progressive Pulmonary Fibrosis: How Significant is the Reduction in Morbidity and Mortality?

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Abstract

As a clinically important fibrotic phenotype, Progressive pulmonary fibrosis (PPF) occurs across a heterogeneous group of interstitial lung diseases (ILDs) other than idiopathic pulmonary fibrosis (IPF). Despite appropriate management, PPF is characterised by physiological deterioration, worsening respiratory symptoms, and radiographic progression usually accompanied by significant morbidity and mortality. The recognition that pulmonary fibrosis may progress irrespective of its underlying diagnostic category has led to increasing interest in early antifibrotic treatment. The principal aim of treatment is not reversal of existing fibrosis but preservation of viable lung parenchyma and lung function with delay in the clinical progression of the disease.

The INBUILD trial showed nintedanib significantly reduced the decline of forced vital capacity (FVC) in patients with PPF, thereby solidifying the concept that antifibrotic therapy reduces the rate of decline of progressive fibrotic disease. However, evidence remains considerably less certain for mortality reduction in non-IPF PPF than the evidence for slowing physiological progression.

The mortality benefit with antifibrotic treatment is better associated with IPF. Early treatment remains a defining strategy in reducing morbidity and preserving pulmonary functions. However, by contrast, established survival benefit across all forms of PPF is not clearly seen. Delaying treatment until severe physiological lung impairment develops may result in irreversible parenchymal lung damage without a significant therapeutic advantage.

Therefore, the aim of future studies should be to determine whether early therapeutic intervention results in reduced hospitalisation, reduced exacerbation of the disease process and consequent mortality. Attempts should also be made to identify which PPF subgroups derive the greatest benefit from antifibrotic treatment.

Keywords: *Early Treatment; Progressive Pulmonary Fibrosis; Pulmonary Fibrosis; Interstitial Lung Disease; Antifibrotic Therapy; Pirfenidone; Nintedanib; Forced Vital Capacity*

Introduction

Progressive pulmonary fibrosis is an important subject of discussion in modern-day treatment in respiratory medicine. Patients with autoimmune-associated or inflammatory disease usually receive immunomodulatory therapy, whereas antifibrotic treatment is principally reserved for patients with idiopathic pulmonary fibrosis (IPF). However, increasing evidence shows that several distinct types of ILDs acquire a common progressive fibrotic phenotype characterised by progressive deterioration despite appropriate treatment [1].

The 2022 international clinical practice guidelines from the American Thoracic Society, European Respiratory Society, Asociación Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) and the Japanese Respiratory Society have defined progressive pulmonary fibrosis (PPF) as a condition with the presence of at least two of the following three criteria, namely, worsening respiratory symptoms, physiological deterioration and/or radiological progression occurring within the preceding year, without a plausible cause, in a patient with ILD other than IPF [1]. This definition is an important step as it identifies disease progression according to disease behaviour rather than simply diagnostic criteria.

Moreover, the emergence of antifibrotic treatment forces one to ask if treatment should commence as soon as the progressive phenotype is recognised, or should clinicians wait until significant physiological deterioration occurs.

Since fibrotic lung injury is irreversible, even a small damage to functioning lung tissue reduces the vital capacity and consequently the physiological reserve leading to an increased risk of respiratory disability. Hence it is absolutely essential that treatment is commenced almost immediately the diagnosis is suspected.

PPF has clinically important implications

PPF encompasses a heterogeneous cluster of diseases which include idiopathic nonspecific interstitial pneumonitis, fibrotic hypersensitivity pneumonitis, connective-tissue disease-associated ILD, unclassifiable fibrotic ILD and occupational ILDs [1]. Most of these progressive forms share common pathways involving fibroblast activation, extracellular matrix deposition, persistent epithelial injury and a consequent destruction of lung architecture.

Disease progression with a deterioration in lung functions results in respiratory symptoms characterised by a dry cough, progressively increasing breathlessness resulting in exercise limitation and a reduced quality of life. Further progression of the disease process can result in hypoxemic respiratory failure requiring hospital admission. In patients with significant destruction of pulmonary parenchyma, lung transplantation is a final option to reduce mortality and improve the quality of life. However, it is not an easy decision as lung transplantation depends on a host of factors.

Therefore, there is a compelling rationale for early treatment before significant lung parenchymal destruction occurs.

Why early treatment is vitally important?

Unlike many inflammatory pulmonary diseases, pulmonary fibrosis cannot be reversed with currently available pharmacological treatment. The therapeutic endpoint of antifibrotic therapy is, therefore, to slow the further progression of the disease process, and not to restore the existing fibrotic lung tissue.

It is important to understand this distinction while treating a patient with PPF. If treatment is commenced after a patient has developed significant fibrosis and has substantially reduced lung functions, the treatment will have limited benefit as significant lung damage has already occurred. Slowing the disease process while useful will have limited clinical impact as a large part of the lung parenchyma has already been irreversibly damaged.

Conversely, early treatment will help slow the disease process while viable lung parenchyma is still present. Evidence from IPF too supports this principle [2].

Evidence that early antifibrotic treatment reduces morbidity

The strongest evidence supporting treatment of PPF comes from the INBUILD trial. This randomised, placebo-controlled trial included 663 patients with chronic fibrosing ILDs other than IPF who fulfilled criteria for progression despite appropriate management [3].

Nintedanib significantly slowed the decline in FVC. The adjusted annual rate of FVC decline was approximately 80.8 mL/year in the nintedanib group compared with 187.8 mL/year in the placebo group, yielding a between-group difference of approximately 107 mL/year [3]. The treatment effect was also observed in patients with a radiological usual interstitial pneumonia (UIP)-like pattern.

Therefore, a constant yearly preservation of approximately 100 mL in FVC can result in several hundred millilitres of preserved lung volume over many years. Although FVC is not a direct measure of survival, its decline is directly corelated with worsening of clinical symptoms and signs in patients with fibrotic lung disease.

A subsequent analysis of the entire INBUILD population reported that nintedanib reduced the risk of ILD progression and mortality compared with placebo, with a hazard ratio of approximately 0.66 [4]. These findings confirm that antifibrotic treatment not only improves spirometric functions but also significantly reduces the progression of the disease.

A systematic review and meta-analysis undertaken to inform the ATS/ERS/JRS/ALAT guidelines similarly found that nintedanib reduced annual FVC decline by approximately 107 mL/year compared with placebo [5]. The effect was observed across several PPF subgroups, although the certainty of evidence varied between individual ILD categories.

These trials have therefore arrived at one conclusion that nintedanib significantly slows physiological progression in PPF.

Some physicians may question whether an approximately 100-mL difference in annual FVC decline is sufficiently large to justify long-term treatment, particularly when antifibrotic therapy is associated with adverse effects and substantial cost.

This view if present would indeed be a short-sighted one because over many years a patient experiences the consequences of cumulative lung-function loss. A slower decline means the patient remains ambulatory without supplemental oxygen for longer, maintaining the ability to perform activities of daily living, remaining eligible for pulmonary rehabilitation or transplantation, and delaying the progression to advanced respiratory failure, thereby reducing the morbidity and mortality and improving the quality of life in these patients.

Furthermore, FVC is only one component of disease burden. Progressive fibrosis affects exercise capacity, symptoms, psychological wellbeing and health-related quality of life. A treatment that slows the underlying trajectory may therefore have benefits that are incompletely captured by a single pulmonary-function endpoint.

Therefore, data from the INBUILD trial can be interpreted as indication that antifibrotic therapy changes the natural course of PPF [3-5].

However, in the INBUILD trial, nintedanib did not demonstrate a statistically significant reduction in mortality [3,5]. The ATS/ERS/JRS/ALAT guidelines explicitly rated the certainty of evidence for mortality as low, largely because relatively few deaths occurred and the confidence intervals were compatible with both benefit and harm [1].

It must be remembered that PPF is not just one disease process. Therefore, mortality is determined not only by the rate of fibrotic progression but also by the age, underlying ILD, infection, comorbidities, pulmonary hypertension, malignancy, acute exacerbations and other potential causes of death.

The absence of statistically significant mortality benefit should therefore not be interpreted as evidence that antifibrotic therapy cannot increase survival in these patients. Hence, survival benefit remains indemonstrable in non-IPF PPF.

This is in contrast with IPF where the pool of evidence is much larger. Meta-analyses of antifibrotic therapy in IPF have reported reductions in acute exacerbations and mortality, thereby supporting the broader view that the alteration in fibrotic progression can ultimately influence clinically important outcomes [6].

Early treatment versus delayed treatment: Which is the more viable option?

A common clinical approach has been to monitor patients until the decline in FVC becomes substantial before introducing antifibrotic treatment. This strategy is understandable as antifibrotic treatment causes adverse effects, requires close monitoring and imposes significant treatment burden and financial costs.

However, there is a fundamental difference between early treatment and delay, namely: the adverse effects of antifibrotic treatment are potentially reversible while fibrotic lung damage once established, is not.

Most common side effects associated with Nintedanib include gastrointestinal adverse effects such as diarrhoea, abnormal rise of liver enzymes and other treatment-related events [1,3,5].

Reduction in medication dose and treatment spacing help improve tolerability. In contrast, lost lung parenchymal tissue cannot be regenerated once fibrosis has occurred.

The ATS/ERS/JRS/ALAT guidelines therefore conditionally recommend nintedanib for patients with PPF who have failed appropriate standard management for their underlying fibrotic ILD [1]. Importantly, standard management may include immunomodulatory therapy, antigen avoidance or other disease-specific interventions depending on the diagnosis [1].

Role of pirfenidone in non-IPF PPF

The evidence supporting pirfenidone in non-IPF PPF is less conclusive.

The RELIEF trial studied the role of pirfenidone in patients with progressive fibrotic ILDs other than IPF. Although the study indicated a slower reduction in FVC decline, it was discontinued prematurely because of problems associated with recruitment which limited the preciseness of its conclusions [7].

Similarly, another randomised trial in unclassifiable progressive fibrosing ILD provided supportive evidence for reduced decline in FVC [8].

For these reasons, the 2022 ATS/ERS/JRS/ALAT guidelines recommended further research into pirfenidone rather than making a conclusive treatment recommendation for PPF [1].

This evidence gap matters because early treatment strategies should ideally be supported by robust data across multiple disease phenotypes, not by extrapolation from IPF alone.

Importance of morbidity and quality of life in PPF

For many patients, the meaningful outcomes are whether they can walk for a reasonable distance without severe breathlessness, continue with their present occupation, live an independent life, sleep without severe cough, avoid hospitalisation and involve in their normal social activities.

A slower decline in lung functions can therefore help to delay deterioration and maintain a satisfactory quality of life.

Moreover, preserving physiological reserve may influence future therapeutic options. Patients with progressive disease may eventually require oxygen therapy, treatment for pulmonary hypertension, referral for transplantation or management of acute exacerbations. Maintaining better functional status for longer may improve the feasibility and timing of these interventions.

Hence, the importance of early medical intervention cannot be emphasized enough in terms of time gained while in a state of preserved function, rather than solely in terms of survival.

Limitations of current research studies

Despite positive results several uncertainties remain because the definition of PPF encompasses multiple diseases with different natural histories.

Also, most randomised controlled clinical trials have been of a relatively short duration in comparison to the duration of fibrotic lung disease.

Moreover, levels of FVC decline remains the dominant endpoint in most studies, while patient-centred outcomes such as quality of life, duration and frequency of hospitalisations and mortality are less consistently used as clinical endpoints.

To date, the right timing for initiating antifibrotic treatment remains undefined.

Access to antifibrotic therapy varies significantly between healthcare systems. Cost, monitoring requirements and adverse effects can influence treatment decisions and may limit the real-world effectiveness of therapies demonstrated to be efficacious in clinical trials.

What should be the criteria in clinical practice?

The available evidence supports a pragmatic approach.

Patients with fibrotic ILD should undergo a detailed assessment of clinical symptoms, pulmonary function testing and radiographic imaging. Once disease progression is confirmed, the physician should ensure that potentially reversible causative factors have been addressed and appropriate disease-specific therapy has been administered. In patients with a progressive fibrotic phenotype, antifibrotic therapy with nintedanib should be considered [1].

The discussion with patients should be clear and lucid in a language the patient and relatives clearly understand. The attending physician should explain that the main aim of treatment is to slow the progression of the disease process rather than reversing the fibrosis. They should also clarify that clinical and research evidence for a reduced rate of mortality in non-IPF PPF is currently unclear.

Following a clear discussion the patient and their relatives can weigh the expected preservation of pulmonary function, slowing of the disease process and improved quality of life against treatment side-effects such as cost of treatment, monitoring requirements, gastrointestinal toxicity, and treatment burden.

Conclusion

The case for early treatment of progressive pulmonary fibrosis, backed by scientific data, is gaining significant traction.

Various research evidence demonstrates that antifibrotic therapy, particularly nintedanib, significantly slows the decline in lung function and slows disease progression in patients with PPF [3,4,5,9]. This results in a significant reduction in morbidity and maintains quality of life in these patients since a progressive loss of pulmonary function would lead to dyspnoea, exercise limitation, oxygen dependence, reduced quality of life and respiratory failure.

The evidence for mortality benefits however is less clear. Unlike IPF, where antifibrotic treatment has demonstrated a more convincing effect on survival-related outcomes, randomised evidence has not established a statistically significant mortality reduction in the heterogeneous non-IPF PPF population [1,3,5,6].

Nevertheless, uncertainty regarding mortality should not discourage against early treatment. In an irreversible progressive fibrotic disease such as PPF, preserving pulmonary functions is of vital importance as fibrotic damage to the lung parenchyma leads to irreversible lung damage and significant reduction in quality of life and consequent increased mortality. Treatment with antifibrotic medications would be rendered ineffective in such situations.

Therefore, it is appropriate to accept that early antifibrotic treatment offers improved quality of life for a longer duration by slowing functional decline.

Further clinical trials are needed to determine how effectively early therapeutic intervention with antifibrotic therapy reduces the duration and frequency of hospitalisations, frequency of acute exacerbations, respiratory failure and death.

To summarise, early recognition and treatment of progressive pulmonary fibrosis is recommended as it helps preserve viable lung parenchyma and lung functions by reducing disease progression.

Even though antifibrotic therapy has shown a significant positive effect on disease progression, quality of life and overall morbidity, a definite reduction in mortality has not yet been conclusively established for the heterogeneous non-IPF PPF population. The clinical rationale for early treatment is, therefore, prevention of irreversible functional loss and maintaining of lung functions rather than an unequivocal reduction in mortality.

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