Antifibrotic therapy in progressive pulmonary fibrosis: a review of recent advances

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REVIEW

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Antifibrotic therapy in progressive pulmonary fibrosis: a review of recent advances

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ABSTRACT

Introduction: Progressive pulmonary fibrosis (PPF) is a manifestation of a heterogenous group of underlying interstitial lung disease (ILD) diagnoses, defined as non-idiopathic pulmonary fibrosis (IPF) progressive fibrotic ILD meeting at least two of the following criteria in the previous 12 months: worsening respiratory symptoms, absolute decline in forced vital capacity (FVC) more than or equal to 5% and/or absolute decline in diffusing capacity for carbon monoxide (DLCO) more than or equal to 10% and/or radiological progression.

Areas covered: The authors subjectively reviewed a synthesis of literature from PubMed to identify recent advances in the diagnosis and characterisation of PPF, treatment recommendations, and management challenges. This review provides a comprehensive summary of recent advances and highlights future directions for the diagnosis, management, and treatment of PPF.

Expert Opinion: Recent advances in defining the criteria for PPF diagnosis and licensing of treatment are likely to support further characterisation of the PPF patient population and improve our understanding of prevalence. The diagnosis of PPF remains challenging with the need for a specialised ILD multidisciplinary team (MDT) approach. The evidence base supports the use of immunomodulatory therapy to treat inflammatory ILDs and antifibrotic therapy where PPF develops. Treatment needs to be tailored to the specific underlying disease and determined on a case-by-case basis.

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Antifibrotics; nintedanib; pirfenidone; pulmonary fibrosis; progressive pulmonary fibrosis; interstitial lung disease

1. Introduction

Interstitial lung diseases (ILD) are a heterogenous group of parenchymal lung disorders with varying degrees of inflammation and fibrosis [1,2]. Etiological factors can include exposure to allergens, toxins or drugs, and underlying autoimmune diseases, although in many cases, the etiology is unknown, or idiopathic [3]. Lung inflammation is characterised by an acute inflammatory cell infiltrate accompanied by cytokine and chemokine release, with incomplete resolution of this process leading to chronic inflammation [4]. Pulmonary fibrosis is thought to arise from repeated subclinical alveolar epithelial and endothelial injury resulting in fibroblast activation, proliferation and abundant myofibroblasts, leading to abnormal tissue repair with excess extracellular matrix deposition. This ultimately leads to the destruction of normal lung architecture, and patients experience impairment of lung function, respiratory symptoms, and reduced survival [5]. Idiopathic pulmonary fibrosis (IPF) is the archetypal, invariably progressive, fibrotic lung disease characterised by decline in lung function, worsening dyspnoea, and quality of life, and early mortality [6].

It is increasingly recognised that other ILD subtypes can develop into a progressive fibrotic phenotype, despite conventional therapies [7]. These include idiopathic interstitial pneumonias, autoimmune ILDs, exposure related, ILDs with cysts and/or airspace filling and pulmonary sarcoidosis. Shared mechanistic and clinical features have been identified between these progressive fibrotic ILDs and IPF; worsening respiratory symptoms, decline in lung function, and early mortality are comparable [8–15]. Therefore, the term progressive pulmonary fibrosis (PPF) was developed to describe non-IPF progressive fibrotic ILDs [7]. While the definition of PPF has historically varied, the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociacion Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) clinical guideline further defined PPF as requiring at least two of the following in the previous 12 months: worsening respiratory symptoms, absolute decline in forced vital capacity (FVC) more than or equal to 5% and/or absolute decline in diffusing capacity for carbon monoxide (DLCO) more than or equal to 10% and/or radiological progression [16].

The treatment of PPF has dominated research activity in the field of ILD in recent years, with several observational studies and randomised controlled trials (RCT) having been conducted. The authors subjectively reviewed a synthesis of literature from the PubMed database to identify recent advances in the diagnosis, treatment recommendations and management challenges of PPF. Literature published by January 2024 was included if considered relevant or robust. We provide a comprehensive summary of recent advances in the diagnosis, management and treatment recommendations for PPF.

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Article highlights

- Recent advances in defining the criteria for progressive pulmonary fibrosis (PPF) and licensing of treatment are likely to support further characterisation of the PPF patient population and improve our understanding of prevalence.
- The accurate and timely diagnosis of PPF remains challenging with the need for a specialised interstitial lung disease (ILD) multidisciplinary (MDT) approach.
- Robust clinical trial data to evaluate the efficacy and safety of new and current therapies is lacking, in part due to the relatively low prevalence of specific fibrosing ILD subtypes.
- The evidence base supports use of immunomodulatory therapy to treat inflammatory ILDs and antifibrotic therapy where PPF develops. Treatment needs to be tailored to the specific underlying disease and determined on a case-by-case basis.
- We expect earlier identification of progression and improved diagnosis of PPF with technological advances and use of biomarkers to guide clinical practice.

2. Epidemiology

Reports on the incidence of PPF are highly variable, with estimates ranging between 10.4% and 60.6% of the ILD patient population [17]. In real-world studies, a progressive phenotype has been observed in approximately 25–33% of patients with fibrosing ILDs other than IPF [18]. It has been suggested 13% of patients with fibrotic idiopathic non-specific interstitial pneumona (iNSIP), 24% of connective tissue disease associated interstitial lung disease (CTD-ILD) and up to 87% of patients with hypersensitivity pneumonitis (HP) develop PPF [19]. Prospective registry data of patients with ILD in Canada reported an incidence of PPF in 50% within 24 months of diagnosis [20]. A French study suggested an overall incidence of 4.0 to 4.7 per 100,000 person-years, with an increasing prevalence over 8 years up to 19.4 per 100,000 people in 2016 [21]. In a more recent review, prevalence of PPF was 2.2 to 20.0 per 100,000 in Europe and 28.0 per 100,000 in the U.S.A. [22].

3. Diagnostic approach

The gold standard for ILD diagnosis requires a specialised multidisciplinary team (MDT) approach where experts, including respiratory physicians, rheumatologists, thoracic radiologists, pathologists and ILD specialist nurses, review clinical symptoms, exposure history, serology, and radiology as per the ATS/ERS/JRS/ALAT clinical guidelines. Lung biopsy is reserved for when high-resolution computed tomography (HRCT) findings are inconclusive and knowledge of histological phenotype can add value in determining the diagnosis [16].

The definition of PPF has evolved, as demonstrated in Table 1. Whilst a number of clinical trials have sought to define PPF as part of the inclusion criteria, using FVC decline and/or

Table 1. Diagnosis of Progressive pulmonary fibrosis (PPF).

Author and year of publication	Diagnostic criteria
Flaherty et al. 2019 [23]	Meet at least one of the following criteria for progression of ILD within 24 months, despite standard treatment: • relative decline in the FVC of at least 10% of the predicted value • relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on HRCT • worsening of respiratory symptoms and an increased extent of fibrosis
George et al. 2020 [24]	Meet at least one of the following criteria for progression of ILD within 24 months, despite standard treatment: • relative 10% or more decline in FVC • relative decline in FVC of 5% or more with a decline in DLCO of 15% or more • relative decline in FVC of 5% or more with increased fibrosis on HRCT, as assessed by an expert thoracic radiologist • relative decline in FVC of 5% or more with progressive symptoms • progressive symptoms with increased fibrosis on HRCT, as assessed by an expert thoracic radiologist
Behr et al. 2021 [25]	Meet the following criteria based on at least three measurements within 6–24 months, despite conventional therapy: • CTD-ILD, HP, iNSIP, or asbestos-induced lung fibrosis • FVC 40–90% predicted • DLCO 10–90% predicted and annual decline of FVC of at least 5% predicted
Raghu et al. 2022 [16]	Meet at least two of the following three criteria occurring within 1 year with no alternative explanation: • worsening respiratory symptoms; • physiological evidence of disease progression (either of the following): a. absolute decline in FVC > 5% predicted b. absolute decline in DLCO (corrected for Hb) >10% predicted • radiological evidence of disease progression (one or more of the following): a. increased extent or severity of traction bronchiectasis and bronchiolectasis b. new ground-glass opacity with traction bronchiectasis c. new fine reticulation d. increased extent or increased coarseness of reticular abnormality e. new or increased honeycombing f. increased lobar volume loss.

Definition of abbreviations: PPF = progressive pulmonary fibrosis, ILD = interstitial lung disease, FVC = forced vital capacity, HRCT = high-resolution computed tomography, DLCO = diffusing capacity for carbon monoxide, CTD-ILD = connective tissue disease associated interstitial lung disease, HP = hypersensitivity pneumonitis, iNSIP = idiopathic nonspecific interstitial pneumonia.

combinations of worsening respiratory symptoms, DLCO decline and radiologic progression in fibrosis, there have been some differences. Despite the ATS/ERS/JRS/ALAT guideline standardisation of the PPF definition, there remain a number of issues with the diagnostic criteria. These include phenotype variability in ILD subtypes, potential for relative decline in FVC of 10% or more to be the strongest predictor of progression, lack of sensitivity and specificity when using combinations of diagnostic criteria, and the potential for isolated DLCO decline to represent worsening pulmonary hypertension or vasculopathy, rather than PPF [18,23]. Of note, the ATS/ERS/JRS/ALAT guidelines assess progression over 12 months and use absolute FVC decline. This contrasts with the INBUILD assessment of progression over 24 months and relative FVC decline [14,16]. The ATS/ERS/JRS/ALAT committee preferred to use absolute change in FVC because it forecasts poorer outcomes and is regarded as an important predictor of mortality in IPF [24]. Progression can be defined by clinical parameters, lung physiology, and radiological imaging with recommendations to monitor at least every 3–4 months in the first year after diagnosis, unless clinically indicated otherwise [7]. Early recognition of PPF is important as treatment options become available where fibrosis becomes progressive.

4. Risk factors for progression

Although the pathogenesis of pulmonary fibrosis is incompletely understood there are several recognised risk factors. Patient risk factors which increase risk of progression include advancing age, male gender, autoantibodies, and/or presence of a short telomere syndrome [25]. Radiological findings which increase risk of progression include extensive fibrotic lung disease defined by ILD extent on HRCT of >20% or indeterminate on HRCT, usual interstitial pneumonia (UIP) pattern, and the presence of traction bronchiectasis [11,25–30]. Patients with lower baseline DLCO are at increased risk of progression [31,32]. Absence of regression or stabilisation with treatment can also increase the risk of developing PPF [25].

Each ILD subtype may demonstrate differing risks of progression, based on clinical, biochemical, molecular, physiological, histological, and/or radiological features [7]. For example, the risk of progression is greater in HP where the antigen is unknown [33], rheumatoid arthritis-associated interstitial lung disease (RA-ILD) where the patient is a smoker, male, and/or anti-cyclic citrullinated peptide (anti-CCP) antibody positive [11,34,35], in systemic sclerosis associated interstitial lung disease (SSc-ILD) where the patient has Black American ethnicity, anti-topoisomerase I (anti-Scl70) antibody, gastro-esophageal reflux disease (GORD), and shorter disease course [36,37]; and in pleuroparenchymal fibroelastosis (PPFE) [25]. Additionally, the risk of progression is higher when an initial ILD diagnosis cannot be made (i.e. unclassifiable ILD) [21].

An accurate MDT diagnosis of ILD and its subtype is therefore critical to enable risk stratification regarding the likelihood and suspected rate of progression. This is based on knowledge of individual patient-level risk factors and the nature of different ILD subtypes. For example, SSc-ILD and HP would warrant a higher index of suspicion for PPF compared to pulmonary sarcoidosis, where PPF is less common [38]. Evaluating the risk of progression is important to inform prognosis, treatment and monitoring frequency and patients at high-risk for progression should be monitored more closely [11].

5. Management

PPF is a manifestation of a heterogenous group of ILD diagnoses for which there is no standardised management regimen. Treatment needs to be tailored to the specific underlying disease and determined on a case-by-case basis.

5.1. Immunomodulatory therapy

Systemic immunomodulatory therapy such as corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, tacrolimus, and rituximab may be considered to slow the progression of disease in inflammatory ILDs, despite limited evidence. Corticosteroids are frequently used as first-line therapy as they interfere and/or inhibit leukocyte, fibroblast, and endothelial cell function and suppress humoral factors [39]. Mycophenolate is the most widely used first-line steroid sparing agent as it is effective in inhibiting inosine monophosphate dehydrogenase and exerting a cytostatic effect on lymphocytes, and it is well-tolerated [40–42]. Azathioprine is often used as second-line immunomodulatory therapy that inhibits purine synthesis and DNA replication in lymphocytes [43].

The greatest evidence base for the use of immunomodulatory therapy in ILD is in SSc-ILD. The prospective trials of immunomodulatory therapies for SSc-ILD, namely scleroderma lung studies (SLS I and II) and the focuSSced phase 3 trial, demonstrated stabilisation of lung function with cyclophosphamide, mycophenolate, or tocilizumab, respectively [44–46]. Rituximab is a monoclonal antibody that targets CD20 on B-lymphocytes and a number of studies have demonstrated the efficacy of rituximab in disease stabilisation and improved lung function in SSc-ILD [47–49].

HP is an immune-mediated reaction to an antigen and the cornerstone of treatment is antigen remediation [50,51]. However, identification of the antigen can be challenging and HP is often managed with corticosteroids. Morbidity associated with corticosteroids has led to the use of alternative immunomodulatory therapy, such as mycophenolate or azathioprine. A retrospective study of 70 patients with HP treated with mycophenolate or azathioprine found improvements in DLCO [51]. As with HP, corticosteroids are the mainstay of therapy in RA-ILD and have been shown to improve or stabilise the disease [52,53] There have been several small studies that have demonstrated stabilisation and/or improvement in symptoms, lung function, imaging, and survival with the use of tacrolimus, mycophenolate, and cyclophosphamide in RA-ILD [40,54–59].

There is some evidence to support the use of cyclophosphamide, rituximab, and/or mycophenolate and rituximab in the treatment of CTD-ILD [60,61]. The use of immunomodulatory therapy in the treatment of iNSIP has been extrapolated from its use in CTD-ILD, which often has the same radiological pattern. Treatment with systemic corticosteroids is also recommended for the management of pulmonary sarcoidosis [62], and there is evidence from largely observational studies to support the use of

methotrexate, azathioprine, leflunomide, and mycophenolate mofetil in this patient cohort [63–66]. Additionally, a phase II RCT of infliximab demonstrated improvement in FVC in patients with pulmonary sarcoidosis [67].

On the basis of this limited evidence base, immunomodulatory therapy remains the standard of care for the treatment of CTD-ILD, iNSIP, HP, and pulmonary sarcoidosis and should be considered as first-line therapy. However, immunomodulatory therapies are associated with risks, including increased risk of infections. In IPF, concerns were raised over the use of triple therapy with prednisolone, azathioprine, and N-acetylcysteine, where the treatment arm was discontinued early due to excess deaths; subsequently immunomodulatory therapy is not recommended in patients with IPF [68]. There are theoretical concerns that immunomodulatory therapy may not be beneficial and may even be harmful in the later stages of PPF pathogenesis when the disease becomes predominantly fibrotic; this however needs to be substantiated. There are also specific concerns regarding the use of immunomodulatory therapy in patients with short telomeres, who are at risk of developing PPF [69]. The use of immunomodulatory therapy in PPF requires further evaluation in clinical trials. A case-based approach and review are required to assess the added effectiveness of immunomodulatory therapy to baseline corticosteroid treatment. Despite the use of immunomodulatory therapy, high morbidity, and mortality associated with these ILDs remain.

5.2. Antifibrotics

Antifibrotic therapies currently licensed for the treatment of IPF include nintedanib and pirfenidone. Nintedanib is a tyrosine kinase inhibitor that binds and blocks platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor 1 (FGFR-1), and vascular endothelial growth factor receptor 2 (VEGFR-2) and thus is thought to interfere with fibroblast proliferation, migration, differentiation and the deposition of extracellular matrix components in the lung [70]. The exact mechanism by which pirfenidone slows the progression of pulmonary fibrosis is poorly understood but it is thought to regulate the activity of beta transforming growth factor (TGF-β), and inhibit fibroblast proliferation and collagen synthesis [71]. Nintedanib was licensed for the treatment for IPF following two phase 2 clinical trials, INPULSIS 1 and 2, which demonstrated that nintedanib reduced the annual rate of decline in FVC at week 52 compared with placebo [72]. Pirfenidone was licensed for the treatment of IPF following three phase 3 clinical trials, CAPACITY 004, CAPACITY 006, and ASCEND, which demonstrated that pirfenidone reduced the annual rate of decline in FVC at week 52 compared with placebo [73].

With increasing recognition of the shared clinical features between IPF and PPF, there was inevitable interest in the application of antifibrotics for the treatment of PPF. Nintedanib was licensed for the treatment of PPF following a phase 3 clinical trial, INBUILD, which demonstrated that nintedanib reduced the annual rate of decline in FVC over 52 weeks. INBUILD excluded those on treatment with azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids at a dose of >20 mg/day. However, initiation of these treatments was allowed after 6 months of the trial in patients with clinically significant deterioration of ILD or connective tissue disease [23]. Immunomodulatory treatments are commonly used to treat pulmonary and extra-pulmonary disease in SSc-ILD, CTD-ILD, and pulmonary sarcoidosis so it is unclear what effect this may have had on recruitment of patients with active systemic inflammatory disease. A greater percentage of patients on nintedanib had adverse events, such as diarrhoea or liver enzyme elevations, leading to a permanent dose reduction (33.1% vs. 4.2%) and discontinuation (19.6% vs. 10.3%) when compared to placebo. No significant difference was found in number of acute exacerbations, progression of ILD, deaths, or quality of life according to King's brief interstitial lung disease score [26].

Pirfenidone is not yet licensed for the treatment of PPF due to lack of supporting clinical trial data. Pirfenidone was studied in two phase 2 clinical trials. The first enrolled 253 patients between 18 and 80 years of age with progressive fibrosing unclassifiable ILD; progression was defined as an annual decline of FVC of at least 5% predicted despite conventional therapy, based on at least three measurements within 6 to 24 months of enrollment. The primary endpoint used home spirometry and provided unreliable results due to technical issues with home spirometry monitoring that could not be analysed. The secondary outcome compared predicted mean decline in FVC measured by site spirometry, which demonstrated predicted mean change in FVC was lower in patients given pirfenidone when compared to placebo over 24 weeks [74]. The second study enrolled 127 of the planned 374 patients with PPF, as defined in Table 1. Despite being underpowered and early termination of the trial due to poor enrollment attributed to the COVID-19 pandemic, this trial found pirfenidone resulted in a lower FVC per cent decline than placebo at 48 weeks. Although not statistically significant, these findings may have clinical relevance. No safety concerns were noted regardless of concomitant immunosuppressant status [75].

Whilst these trials demonstrated consistently reduced FVC decline with antifibrotic therapy, end points relating to reduced rates of exacerbation, death, and quality of life were not met. All trials noted acceptable and similar safety profiles to those expected from other studies with these therapies [26,76]. From the evidence available, it can be concluded that nintedanib has a valuable role in the reduction of FVC decline in PPF. Due to methodological issues with the pirfenidone studies in PPF, the conclusions taken from these studies need to be taken with caution, but there appears to be reduction in lung function decline with pirfenidone. Clinical impact on progression, mortality and quality of life with antifibrotics remains unproven.

5.3. Concomitant therapy

Although the evidence is limited, recent studies with pirfenidone and nintedanib show that both therapies reduce PPF progression and have acceptable tolerability when added to immunomodulatory therapy. Analysis of patients with

unclassifiable ILD and SSc-ILD where pirfenidone was used in combination with mycophenolate mofetil demonstrated benefit [75]. In the INBUILD study, of the 332 patients assigned to the nintedanib arm, 36 patients (10.8%) were initiated on immunomodulatory therapy over the 52 weeks [26]. Although the trials were not designed as dual immunomodulatory and antifibrotic trials, safety, and tolerability of antifibrotics was acceptable and in line with data in IPF [26,76]. The efficacy of nintedanib in SSc-ILD, was investigated in the SENSCIS trial, a double-blind, international RCT. Enrolment did not require evidence of PPF. 576 patients were enrolled and annual decline in FVC was lower with nintedanib compared to placebo. Nearly half of the participants were concurrently taking mycophenolate mofetil. A prespecified subgroup analysis of those concomitantly receiving mycophenolate showed the annual rate of decline in FVC in the group that received both mycophenolate and nintedanib was lower (26.3 mL/year) than in those who received nintedanib alone (55.4 mL/year), suggesting that treatment with combined immunomodulatory and antifibrotic therapy may be advantageous [77]. Real-world experience from the UK suggests concomitant immunomodulatory and antifibrotic therapy is commonly prescribed in patients with PPF [78].

Inflammatory ILDs managed with immunomodulatory therapy may or may not develop PPF. When immunomodulatory therapy is efficacious in inflammatory ILDs, it is continued. Where the criteria for PPF is met, antifibrotic treatment may help to preserve lung function. There remains a clinical dilemma regarding whether to intensify or discontinue the immunomodulatory therapy, introduce an antifibrotic agent or use a combination of these two approaches in patients demonstrating progression. Further trials are required to study the benefits of combination therapy. Treatment decisions should consider the time from disease onset due to the potential of immunomodulatory therapies to be more effective early in the disease course, response to therapy, tolerability, and underlying ILD diagnosis. This is particularly significant for SSc-ILD or CTD-ILD where immunomodulatory therapy is often prescribed for pulmonary and extra-pulmonary indications. Where combination therapy with antifibrotics and immunomodulatory therapy is recommended at diagnosis, sequential addition would be advisable.

5.4. Non-pharmacological management of PPF

Despite significant recent advances in antifibrotic therapies, PPF continues to confer poor prognosis, debilitating symptoms, including breathlessness and cough, and impaired quality of life. Palliative and supportive care includes education for patients and caregivers, pharmacological and non-pharmacological management of symptoms to improve and maintain quality of life and advanced care planning. The evidence for palliative and supportive care in ILD is scarce and limited to IPF. Persistent breathlessness is often managed with a combination of pharmacological therapies, including opioids, and non-pharmacological interventions, including breathlessness techniques and use of a handheld fan [79,80]. The pathophysiology and mechanism of cough in IPF is complex and poorly understood. Treatment includes opioid therapies and management of comorbidities that can influence cough, such as GORD [81]. The phase 2 multicentre PACIFY COUGH study demonstrated that low dose-controlled release morphine is effective in reducing awake cough frequency and improving quality of life in patients with significant IPF-related cough. Treatment was generally well tolerated by most participants [82]. There is limited evidence supporting the safety and efficacy of opioids for the management of cough in PPF. The psychological impact of PPF has not been studied specifically but given the similarities in symptom burden and mortality, patients with PPF should access palliative care in the same way as patients with IPF.

Maintaining physical exercise capacity through pulmonary rehabilitation or other exercise programs, prescribing long-term oxygen therapy for patients with resting hypoxaemia, and ambulatory oxygen for patients with exertional hypoxaemia are considered part of the routine supportive care of patients with PPF [7]. Pulmonary rehabilitation aims to improve quality of life and enable daily activities and patients with PPF should be assessed for severity of disease, progression of disease, patient's perspective and needs, comorbidities, and availability of pulmonary rehabilitation services locally [83]. Resting hypoxaemia can develop in advanced ILD, and is associated with breathlessness and reduced survival. There is limited evidence to support the use of long-term oxygen therapy (LTOT) in patients with PPF and significant resting hypoxaemia but it is often recommended [84]. Severe exertional hypoxaemia is frequent in patients with PPF and contributes to exercise intolerance, impaired quality of life and reduced survival. Despite limited supporting evidence, ambulatory oxygen therapy (AOT) can be used by patients with PPF during exercise and/or activities of daily life [85,86]. Further research is necessary to develop guidelines for supplemental oxygen use in PPF.

Symptoms and quality of life in patients with IPF can be significantly influenced by comorbidities such as GORD [87,88], pulmonary hypertension [88–91], obstructive sleep apnoea [92–94], cardiovascular diseases [95,96] and lung cancer [97,98]. Some studies have reported a significant association between comorbidities and survival in IPF [89,90,95,98]. A retrospective observational cohort study found the IPF comorbidities profile was similar to PPF [99]. Patients with PPF should be evaluated and treated for existing comorbidities to improve outcomes. Lung transplantation is an important consideration for patients without significant comorbidity who are eligible and continue to decline despite treatment with licensed therapies. Early discussion around transplant with the patient, and involvement of the transplant team when appropriate, is vital to pursue lung transplantation successfully.

6. Future advancements

6.1. Unanswered questions

The recent advances in the diagnosis and antifibrotic treatment for PPF have improved access to care but morbidity and mortality remain high. Robust clinical trial data to evaluate the efficacy and safety of new and current therapies is lacking, in

part due to the relatively low prevalence of specific fibrosing ILD subtypes. It is yet to be determined what drives PPF in patients with ILD and whether biomarkers can be identified to predict which patients are likely to develop PPF before lung function decline. Equally, the optimal time to initiate, intensify, and/or stop immunomodulatory and antifibrotic therapy in patients with PPF is unknown, with variable real-world practice. There is a lack of clinical trial data comparing the efficacy of nintedanib with pirfenidone and the safety of co-prescribing. Additionally, the evidence for palliative and supportive care in PPF is scarce and recommendations are extrapolated from the management of IPF.

6.2. Ongoing and upcoming clinical trials

The licensing of nintedanib for the treatment of PPF has led to continued interest in investigating novel antifibrotic therapy for patients with PPF. Several phase III studies are planned, in progress or completed, as demonstrated in Figure 1. FIBRONEER-ILD is an ongoing phase III antifibrotic study investigating phosphodiesterase 4b inhibition (PDE4bi) in patients with PPF; the related phase II study in patients with IPF showed a stabilisation of FVC in the treatment arm compared with placebo [100]. Inclusion criteria for the ILD (PPF) study are based on the INBUILD criteria, and this study allows participants to continue nintedanib, as well as selected immunomodulatory therapy (prednisolone ≤15 mg, methotrexate, and azathioprine) during the study period [101]. A multicentre phase III RCT investigating the antifibrotic activity of a lysophosphatidic acid receptor 1 (LPA1) antagonist in patients with PPF is also in progress. This study also allows for concurrent nintedanib but permits a wider range of immunomodulatory therapies including mycophenolate, azathioprine, tacrolimus, biological immunomodulatory therapies, such as anti-tumour necrosis factor (anti-TNF) and interleukin-1 (IL-1) inhibitors, and janus kinase (JAK) inhibitors, provided the doses are stable prior to recruitment. The results of the phase II study are awaiting formal publication. However, early available data suggests a 74% relative reduction in FVC decline in the higher dosing group compared to placebo [102]. The use of oral antifibrotics can be limited due to adverse effects, particularly gastrointestinal. The ATLAS trial demonstrated the safety and efficacy of nebulised pirfenidone in patients with IPF. The data on safety and tolerability was promising

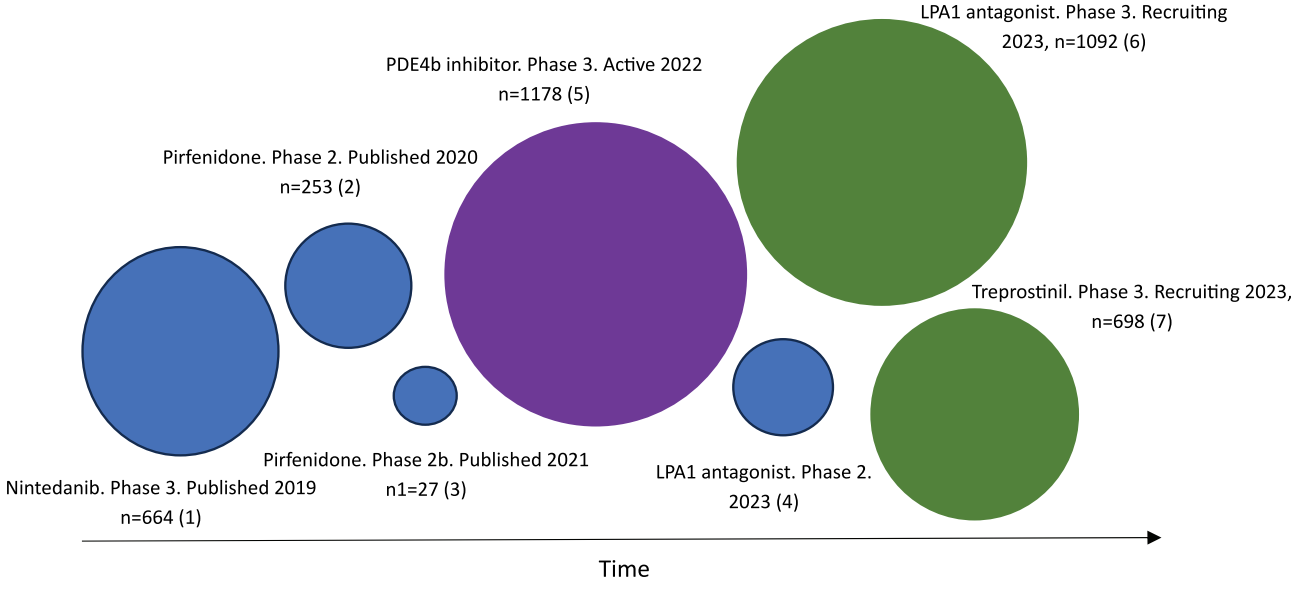

Figure 1. Phase 2 and 3 randomised controlled trials of antifibrotic therapy in Progressive pulmonary fibrosis (PPF).

Blue: completed study. Date is year of completion/publication.

Purple: active study, no longer recruiting. Date is year recruitment started.

Green: study in recruitment. Day is year recruitment started.

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and a potential phase IIb/III is planned in the PPF population [103]. The TETON-PPF phase III study evaluating the safety and efficacy of inhaled treprostinil in subjects with PPF is ongoing following on from the positive effect of nebulised treprostinil on FVC identified on post-hoc analysis of the INCREASE study [104,105].

6.3. Future directions

The prevalence data for PPF is limited. Clarity about the definition of PPF is likely to lead to improved tools for the diagnosis and characterisation of this patient population, including clinical and radiological features of disease. Given the differing risks of progression and mortality associated with each ILD subtype, further studies to better phenotype patients with fibrosing ILDs are required. Robust clinical trial data to support the use of immunomodulatory therapy in fibrosing ILDs is lacking and many patients with fibrosing ILDs progress despite conventional treatment; the long-term effectiveness and safety of treatments is not known. Future research should address knowledge gaps around optimal timing for antifibrotic initiation, duration of therapy, and concomitant use of antifibrotic and immunomodulatory therapy in PPF. The relatively low prevalence of individual subtypes of ILD, and specifically those with PPF within those groups, presents a challenge to designing robust clinical trials to evaluate the efficacy and safety of new and current therapies. A new approach to trial design that will enable multiple therapies to be assessed at the same time may improve access to a number of clinical trials [106].

The antifibrotic therapies licensed or undergoing phase 3 clinical trials for the treatment of PPF have been shown only to slow decline in lung function, and none have shown improvement in fibrosis. However, growing evidence from pre-clinical models suggests that fibrosis may be reversible, particularly with removal of the underlying cause of injury [107]. Future treatments should aim to stabilise the disease, manage symptoms and comorbidities, improve quality of life and reverse fibrosis. A prerequisite for future personalised therapy for PPF is the development of biomarkers that can guide diagnostic, prognostic, radiological and therapeutic approaches. Various biomarkers have been evaluated to identify individuals at risk of developing IPF, including MUCB 5 promoter gene [108]. Further studies are needed to validate the role of biomarkers in PPF before they can be used in clinical practice.

With earlier identification and diagnosis of ILD, we expect antifibrotic therapies to be recommended for use at earlier signs of progression in PPF. The use of home monitoring devices and applications to relay patient reported outcome measures are likely to improve monitoring of disease, allowing earlier identification of progression and timely access to treatments, without the need for frequent hospital visits, lung function tests and HRCT scans. Additionally, utilisation of artificial intelligence software may increase, with postulated roles in interpretation of imaging to predict disease subtypes and responsiveness to therapy, and interpretation of data from home monitoring devices. Further studies in the treatment of PPF should focus on reducing the burden of disease with the development of novel pharmacological and non-pharmacological therapies for palliative and supportive care. It is likely that ongoing developments in lung transplantation and treatment of comorbidities will lead to improved management options for patients with PPF.

7. Conclusion

Significant advances have been made in understanding the pathophysiology of pulmonary fibrosis, defining the criteria for PPF diagnosis and recommending the use of nintedanib as a treatment option for these patients. Some studies have demonstrated pirfenidone may also be beneficial in this patient group. There are a number of promising antifibrotic therapies in the pipeline that could be used instead of, or in addition to, the currently available treatments for PPF. However, significant gaps in knowledge around the management of PPF remain, including when to prescribe antifibrotic therapy, and whether to prescribe, continue and/or discontinue immunomodulatory therapy. Future research must consider biomarkers and other diagnostic tests for earlier identification of disease and progression and treatments that reverse fibrosis. We can expect technological advances to further improve diagnosis of underlying disease, monitoring and earlier identification of progression. Ultimately, this will lead to timely access to treatments and improved patient outcomes.

8. Expert opinion

The estimated prevalence of PPF varies widely. Recent advances in defining the criteria for PPF diagnosis and licensing of treatment are likely to support further characterisation of the PPF patient population and improve understanding of prevalence. Accurate diagnosis of the underlying ILD is requisite to appropriate prescribing, monitoring progression and response to treatment, and risk stratification for PPF. The diagnosis remains challenging with the need for a specialised ILD MDT approach to review clinical symptoms, exposure history, serology, radiology, and histopathology where necessary. Although certain risk factors for progression have been identified, it remains unclear why some patients with inflammatory ILDs progress to a fibrotic phenotype whilst others do not. The development of biomarkers that can guide diagnostic, prognostic, radiological, and therapeutic approaches will lead to improved outcomes in patients with PPF. Additionally, the use of artificial intelligence software to interpret imaging and other investigations, home monitoring devices, and applications that relay patient reported outcome measures have the potential to identify progression earlier and improve diagnosis of PPF. This will support the use of targeted treatments to reduce burden of disease and ameliorate quality of life.

PPF is a manifestation of a heterogenous group of ILD diagnoses and treatment needs to be tailored and

determined on a case-by-case basis. The evidence base supports the use of immunomodulatory therapy to treat inflammatory ILDs and antifibrotic therapy where PPF develops. There remains a clinical dilemma regarding whether to intensify immunomodulatory therapy, introduce an antifibrotic agent or use a combination of these two approaches in patients demonstrating progression. The use of current treatments may be limited due to adverse effects, such as gastrointestinal and infection. Robust clinical trial data to evaluate the efficacy and safety of new and current therapies is lacking, in part due to the relatively low prevalence of specific fibrosing ILD subtypes. Despite licensing and improved access to nintedanib therapy in PPF, the diagnosis continues to confer poor prognosis, debilitating symptoms, including breathlessness and cough, and impaired quality of life. The evidence for palliative and supportive care in this patient cohort is scarce; more well-designed studies and expert guidance are needed to evaluate the efficacy and safety of supportive and palliative interventions.

In five years, we expect to have a better understanding of the prevalence of PPF and further improvements in the diagnosis and identification of progression. This will likely be supported by the use of technological advances in addition to the use of biomarkers to guide clinical practice. With earlier diagnosis and identification of progression, antifibrotic therapies may be recommended for use at earlier signs of progression in PPF. There are a number of clinical trials ongoing to assess the efficacy and safety of novel treatments for PPF and improved access to multiple treatment options is likely. Ongoing developments in lung transplantation and treatment of comorbidities will lead to improved management options for patients with PPF. Ultimately, we expect ongoing interest in the development of novel treatments to manage and/or reverse pulmonary fibrosis, ameliorate quality of life and improve survival.

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