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Progressive pulmonary fibrosis: a need for real world data to solve real world clinical problems

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Clinical trials and real world evidence are urgently required to inform timely diagnosis and optimal management of progressive pulmonary fibrosis, argue Huajian Liu and colleagues.

Despite greater recognition and new licensed treatments, the real life challenges facing clinicians supporting patients with progressive pulmonary fibrosis are increasing. As a concept, progressive pulmonary fibrosis is still relatively new, and it remains a challenging diagnosis to establish. Recent, large scale, clinical trials have provided useful information, but questions still exist regarding epidemiology and optimal management strategies for progressive pulmonary fibrosis. In this article, we contend that real world data are likely to have a key role in answering these questions.

Interstitial lung diseases are a heterogenous group of disorders with varying degrees of inflammation and fibrosis of the lung. Idiopathic pulmonary fibrosis (IPF) is the archetypal progressive fibrotic lung disease for which there is currently no cure. Recently, the term "progressive pulmonary fibrosis" has been used to represent non-IPF interstitial lung diseases that develop into progressive fibrosis despite receiving conventional treatment.[1]

Definitions of progressive pulmonary fibrosis vary between studies, but consensus guidelines have defined the disorder as the presence of a non-IPF interstitial lung disease with radiological evidence of pulmonary fibrosis and progression in the past 12 months, evidenced by at least two of the following: symptom progression, physiological lung function decline (forced vital capacity (FVC) >5% or diffusing capacity of lungs for carbon monoxide (DLCO) >10%), or radiological progression.[1] Owing to the heterogeneous nature of interstitial lung diseases, epidemiological data have been sparse, especially with progressive pulmonary fibrosis being a relatively novel concept. Estimates of the development of the disorder vary according to the type of study and subtype of interstitial lung disease, and can range from 10% to 60%.[2 3] Prospective registries might provide more accurate estimations of progressive pulmonary fibrosis with subtypes of interstitial lung disease such as hypersensitivity pneumonitis and unclassifiable interstitial lung disease having the greater propensity to progress (with 58% and 51% of patients developing progressive pulmonary fibrosis within two years of diagnosis, respectively).[4]

Progressive pulmonary fibrosis has shared pathogenic mechanisms and symptoms with IPF. Insidious progression of breathlessness, cough, and fatigue have a clinically significant impact on patients' wellbeing and quality of life. Furthermore, a considerable economic burden is associated with progressive pulmonary fibrosis, with an annual cost per patient in Europe of €81 286 (£69 530; $88 797), almost double that compared with non-progressive interstitial lung diseases, with the largest portions of cost being hospital admissions for exacerbations, and loss of income from inability to work.[2] The prognosis of progressive pulmonary fibrosis has also been likened to that of IPF with mean survival estimates of 3.7 years from diagnosis.[5]

Owing to the high symptom and economic burden and poor prognosis in progressive pulmonary fibrosis, a robust multidisciplinary assessment is paramount in the diagnosis and monitoring of interstitial lung diseases. However, the assessment for progressive pulmonary fibrosis varies between countries, with the UK faring worst when it comes to the frequency of clinical reviews, and physiological and radiological monitoring of interstitial lung diseases compared with other countries such as Japan, Germany, and the US.[3] These differences in practice might be attributable to local availability and differing pressures on healthcare resources. Interstitial lung diseases and thus progressive pulmonary fibrosis are competing for resources and funding with the likes of more common diseases such as cancer, cardiovascular diseases, and diabetes. These economic constraints coupled with the need for early detection of progressive pulmonary fibrosis highlight the importance of risk stratifying patients to identify those at the highest risk of progression. This risk stratification ensures that finite resources can be appropriately targeted to those individuals at the greatest risk of developing progressive pulmonary fibrosis. Risk factors are defined as clinical (advanced age, male sex, and subtype of interstitial lung disease), biological (specific autoantibodies and genetics), physiological (FVC decline >10% and lower baseline FVC and DLCO at diagnosis), and radiological (usual interstitial pneumonia pattern).[6]

Treatment of interstitial lung diseases is often tailored towards the inflammatory component of the disease, but unanswered questions exist about the continued use of immunosuppressants in progressive pulmonary fibrosis. Despite limited evidence in all interstitial lung diseases except those associated with systemic sclerosis, 90% of patients in a UK study began treatment with immunomodulatory treatments.[7] Once fibrosis and progressive pulmonary fibrosis develop, the ongoing use of these treatments should be evaluated on a case-by-case basis. Distinguishing inflammation from fibrosis in

the context of progressive pulmonary fibrosis can challenge clinicians, demonstrating a need for reliable biomarkers to help differentiate between the two processes. Furthermore, immunomodulatory treatment such as prednisolone and mycophenolate could increase the risk of infection, particularly in the later stages of fibrotic disease. Coupled with the finding that immunosuppression was harmful in a trial in IPF and the shared pathogenesis between progressive pulmonary fibrosis and IPF, concerns exist regarding the use of immunosuppressants in this context, requiring further evaluation in a clinical trial.[8]

More evidence indicates support for the use of antifibrotic treatments, with nintedanib now licensed for progressive pulmonary fibrosis in the UK, as well as elsewhere in Europe and in the US. The INBUILD study was a randomised, placebo controlled, phase 3 trial of the safety and efficacy of nintedanib for 52 weeks in non-IPF progressive pulmonary fibrosis, where eligible patients needed to demonstrate progression over two years.[9] The primary endpoint of decline in FVC was lower in the nintedanib arm than in the placebo arm, with a relative risk reduction of 57%, equating to a difference of 107 mL/year. The side effect profile was similar to that seen in IPF studies with diarrhoea and liver function abnormalities being the the most common adverse events. The study recruited participants with a heterogenous subtype of non-IPF interstitial lung diseases with progressive pulmonary fibrosis: hypersensitivity pneumonitis (26%), autoimmune interstitial lung diseases (26%), idiopathic nonspecific interstitial pneumonia (19%), unclassifiable interstitial lung disease (17%), and other interstitial lung diseases (12%). Immunosuppression treatment was not allowed at the start of the study but could be initiated six months into the trial. The National Institute of Health and Care Excellence (NICE) approved nintedanib for progressive pulmonary fibrosis in the UK, based on the INBUILD criteria of disease progression as opposed to the globally adopted guidelines for progressive pulmonary fibrosis, thereby adding further heterogeneity in diagnosis worldwide.[1 9]

Although licensed in IPF, the evidence base for pirfenidone in progressive pulmonary fibrosis is less robust. In a randomised trial in unclassifiable interstitial lung disease with evidence of progression defined as either >5% absolute decline in per cent predicted FVC or clinically significant worsening of symptoms within the preceding six months, the primary endpoint in home spirometry measurements was not achieved, reportedly owing to technical issues.[10] The secondary endpoint of laboratory based FVC favoured the use of pirfenidone over placebo, with a difference of 95.3 (35.9 to 154) mL.[9] Furthermore, despite being underpowered because of poor recruitment and early closure, the RELIEF study, a randomised, placebo controlled phase 2b trial assessing the safety and efficacy of pirfenidone in non-IPF progressive pulmonary fibrosis, demonstrated a lower FVC decline with pirfenidone than placebo (36.6 mL *v* −114 mL).[11] Progression was defined as an annual decline of predicted FVC of at least 5% despite conventional treatment, based on at least three measurements made 6-24 months before enrolment.

Despite the evidence base for nintedanib in progressive pulmonary fibrosis and some suggested potential for pirfenidone, consensus is still lacking regarding the optimal time to initiate, intensify, or stop both immunomodulatory and antifibrotic treatments for progressive pulmonary fibrosis, with notable variations in clinical practice.[3 12]

A recent real world study in the UK suggested a greater prevalence of progressive pulmonary fibrosis than initially estimated by NICE, and up to 20% of patients who initiated nintedanib for progressive pulmonary fibrosis had advanced disease with an FVC of <50%.[13] This observation further highlights the urgent need for robust prognostic tools to identify patients who would benefit most from treatment, while recognising the challenges of an increased economic burden on services with finite resources. Clinical trial and real world data are lacking that compare antifibrotic treatments or assess the efficacy of combined antifibrotics or antifibrotics with immunosuppression. This question would be best investigated further by a clinical trial in the first instance for robustness.

Real world studies have begun to shed light on the true UK prevalence of progressive pulmonary fibrosis, placing an imperative on appropriate investment in UK services for interstitial lung disease to ensure that adequate resources are available for the early detection of the disease.[12] Having a clear guideline definition of progressive pulmonary fibrosis will support the development of robust, standardised pathways of diagnosis and improve understanding of the epidemiology of the disease. The development of progressive pulmonary fibrosis remains heterogenous, with its diagnosis and management likely to benefit from a precision medicine approach. For this purpose, validated biomarkers that can reliably direct diagnostic, theragnostic, and prognostic approaches are urgently sought. Further potential is recognised in the application of artificial intelligence software to identify and quantify radiological progression; digital applications to relay patient outcomes reported in real time; and home devices that could monitor and detect progressive pulmonary fibrosis early, resulting in timely access to treatments. In future, these technologies could focus healthcare resources on those individuals most in need and improve efficiency and use.

However, clinical trial data alone are not sufficient to allow for the development of improved pathways of diagnosis, monitoring, and treatment for patients

with progressive pulmonary fibrosis, owing to potential underestimation of disease prevalence, heterogeneity of the patient population with medical comorbidities, as well as economic limitations and competing pressures on healthcare resources in different healthcare services. More real world data are required to overcome these challenges to allow for improved service delivery for patients.

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