Progressive pulmonary fibrosis: all roads lead to Rome (but not all at the same speed)

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Shareable abstract (@ERSpublications)
Large observational cohorts show that eventually, a majority of patients with fibrotic ILD will experience disease progression. Highest rates of progression are seen in patients with idiopathic pulmonary fibrosis and fibrotic hypersensitivity pneumonitis. https://bit.ly/3QcnVKJ

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Fibrosing interstitial lung diseases (ILDs) encompass a number of diverse conditions, overlapping in their clinical presentations, and imaging and histopathological patterns [1]. Idiopathic pulmonary fibrosis (IPF) is the prototype of fibrosing ILD, and is characterised by irreversible progressive pulmonary disease, accounting for loss of lung function, exercise intolerance and complications, especially acute exacerbation and respiratory failure leading to early mortality [2]. A significant proportion of patients with fibrosing ILDs other than IPF will develop a progressive phenotype comparable to untreated IPF [3]. Such progression can occur despite conventional treatment which, depending on the underlying condition, may include close monitoring, antigen eviction, glucocorticoids, immunosuppressive therapy and pulmonary rehabilitation. Progressive pulmonary fibrosis (PPF) [1, 4], also referred to as "progressive fibrosing ILDs" (PF-ILD) or fibrosing ILDs with a progressive phenotype [5], is characterised by a disease course similar to that of IPF, with worsening respiratory symptoms, decline in lung function and early mortality [6, 7]. Although not every patient develops a progressive phenotype, collectively PPFs have a prevalence of up to 70 per 100 000 persons [8, 9], have significant impact on patients' survival [10] and quality of life, and place a considerable humanistic burden on both patients and caregivers, and a substantial economic burden on healthcare systems, patients and society [8].

In the large INBUILD trial in patients with PF-ILD despite management, antifibrotic therapy using the tyrosine kinase inhibitor nintedanib attenuated the rate of decline in forced vital capacity (FVC) [11], decreased the proportions of subjects who have ILD progression (absolute decline in FVC ⩾10% predicted) or died, and decreased the proportions of those who had an acute exacerbation of ILD or died [12]. Pirfenidone was also found to reduce FVC decline in patients with PF-ILD due to connective tissue disease (CTD)-associated ILDs, fibrotic nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis or asbestos-induced lung fibrosis [13, 14]. Therefore, is it of utmost importance that patients who develop PF-ILD and may benefit from antifibrotic therapy be identified early. Identification of baseline risk factors associated with the progressive phenotype will contribute to earlier and better-informed management decisions. Despite a handful of retrospective studies of patients with PF-ILD [6, 15–23], outside of clinical trials no large, prospective study has been conducted to assess the natural course of disease and factors associated with an increased risk of disease progression.

In this issue of the *European Respiratory Journal*, Hambly *et al.* [24] report the prevalence and characteristics of a large cohort of patients with PF-ILD (including IPF) enrolled in the Canadian registry for pulmonary fibrosis (CARE-PF) in eight specialised centres between 2015 and 2020. The ILD diagnosis was established by the treating ILD specialist, and reviewed in multidisciplinary meetings when necessary. Out of 2746 patients with fibrotic ILD including IPF, exactly 50% had criteria for PF-ILD within 24 months of diagnosis: 59% of patients with IPF, 58% of those with fibrotic hypersensitivity pneumonitis,

51% of those with unclassifiable fibrotic ILD, 45% of those with CTD-associated ILD, and 39% of patients with other ILD diagnoses [24]. Variables associated with disease progression were increasing age, male sex, a history of gastro-oesophageal reflux, and more compromised lung function (baseline FVC <70% of predicted value, and diffusion capacity for carbon monoxide <75% of predicted).

The authors, and all collaborators and patients who participated in this study, should be commended for a tremendous collective research effort that leads to a significant leap forward in our understanding of PF-ILD/PPF. Up to now, it was assumed that IPF, the prototypical PF-ILD, had a rate of progression as high as 95% [1], yet criteria of progression used in non-IPF fibrosing ILDs had not yet been applied to IPF, as they are not used in clinical practice in IPF in the absence of demonstrated utility. Here, Hambly *et al.* [24] found that "only" 59% of patients with IPF met criteria of disease progression within 2 years of the diagnosis in a real-world setting, where the diagnosis of IPF was made by treating ILD physicians in specialised centres. This progression rate of IPF is strikingly equal to that found in another recent study of 397 patients with IPF, 45% of them receiving antifibrotics, out of a total of 844 patients with fibrotic ILD from Japan [22]. This observation does not rule out the dogma built on clinical experience and confirmed by many cohorts, including some with early disease [25, 26], that IPF is *almost* always a progressive disease at some point. But it does suggest that disease progression, whatever its definition, may occur with variable interindividual rate in IPF, as it does in non-IPF fibrotic ILDs.

Importantly, 68% of patients with IPF were receiving antifibrotics, while patients with other fibrotic ILDs were not, as nintedanib was not yet approved in the indication of PF-ILD. It is therefore conceivable that apparently similar progression rates reflect at least in part differences in treatment (*e.g.* 59% of patients with IPF experienced progression despite 68% of them receiving antifibrotics, while 46.8% of non-IPF fibrotic ILDs progressed, none of them receiving antifibrotic therapy). In addition, 60% of patients with PF-ILD were receiving immunomodulatory therapy [24], in contrast with the INBUILD trial in which few participants were receiving immunosuppressive therapy [11, 27]. However, the precise impact of treatment on results could not be assessed due to study design [24].

Nevertheless, these findings by Hambly *et al.* [24] support the concept that IPF and PF-ILD share commonalities in disease behaviour. In addition, the study shows that different underlying fibrotic ILDs are, on average, associated with varying rates of disease progression, as previously suggested by several retrospective studies [6, 10, 23]. Indeed, data are accumulating, suggesting that, after IPF, fibrotic hypersensitivity pneumonitis and unclassifiable ILD have the highest rate of disease progression among non-IPF fibrotic ILDs (figure 1) [6, 20, 22, 24, 28].

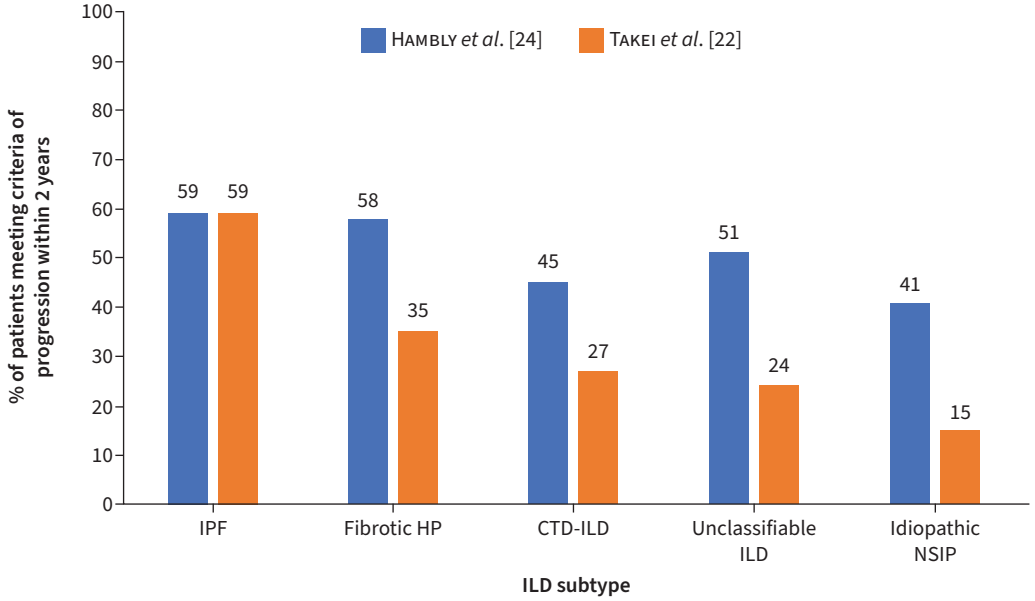

FIGURE 1 Proportion of patients who met criteria of disease progression by subtype of interstitial lung disease (ILD) in two large cohorts. IPF: idiopathic pulmonary fibrosis; HP: hypersensitivity pneumonitis; CTD-ILD: interstitial lung disease associated with connective tissue disease; NSIP: nonspecific interstitial pneumonia.

In this study, the authors defined disease progression, the primary outcome, using criteria similar to those of the INBUILD trial [11], which are based on a combination of physiological (FVC), clinical and radiological criteria. However, all-cause mortality and lung transplantation were also included in the definition of disease progression, to account for patients who may have had rapid clinical deterioration not captured by serial assessment of physiological, clinical, and radiographic variables. Although events of death or lung transplantation indisputably identify patients with progressive disease, they are more appropriate as endpoints (to describe the outcome of patients with PF-ILD) than as criteria to identify patients with a progressive phenotype and who are likely to benefit from antifibrotic therapy: death results from disease progression rather than it being a variable defining disease progression. However, death accounted for only 4% of PF-ILD cases, and a sensitivity analysis that excluded death within 24 months of diagnosis as a PF-ILD event found similar progression rates as the pre-defined, primary analysis. Acute exacerbation of pulmonary fibrosis, another relevant event associated with high mortality risk, was not included as a criterion of disease progression, due to the anticipated high rate of missing data in this multicentre study conducted in Canada, where patients may be admitted to emergency in hospitals remote to the study centres. Whether recently published consensus criteria [4] similarly identify subjects with an increased risk of disease progression or death in prospective, observational cohorts, remains to be studied. The findings by Hambly *et al.* [24] further suggest that in clinical practice, flexibility should be exerted when assessing disease progression, and that consensus criteria may be refined in the future, based on increasing knowledge from large cohort studies.

Another key difference that distinguishes the CARE-PF cohort from previous studies is that progression was assessed only over the first 2 years of follow-up from the diagnosis, in contrast for example to the PROGRESS study, in which progression was assessed at every hospital visit using overlapping windows of 24 months prior to each hospital visit, during a median follow-up time of 46.2 (25.3–73.3) months [6], which is more comparable to clinical practice.

In another study recently published in the *European Respiratory Journal*, Oldham *et al.* [28] retrospectively analysed a multicentre longitudinal cohort of 1227 consecutive patients with diverse fibrotic ILDs, the largest group (~40%) being patients with CTD-associated ILD. The authors determined the mean annual change in FVC following ILD diagnosis, and 1-year change in FVC after satisfying a variety of previously published criteria of disease progression. They found that the 1-year change in FVC after satisfying criteria of disease progression was highly heterogeneous, largely depending on the ILD subtype, with greater FVC decline in patients with fibrotic hypersensitivity pneumonitis or non-IPF idiopathic interstitial pneumonia (including unclassifiable ILD and idiopathic nonspecific interstitial pneumonia) when compared with those with CTD-associated ILD, paralleling previous observations [6]. Interestingly, in this study, progression of fibrosis on computed tomography was an infrequent but stronger predictor of subsequent FVC decline than observed, previous, categorical FVC decline, reminiscent of comparable studies in IPF [29, 30]. Altogether, the studies by Hambly *et al.* [24] and Oldham *et al.* [28] indicate that the course of fibrotic ILD is inherently complex: there is more than one way to assess disease progression, and observed disease progression does not always predict subsequent disease progression.

In conclusion, these studies carry important messages for clinicians. Disease progression in essence is a time-dependent event. Therefore, monitoring the evolution of fibrotic ILDs is crucial, and should rely on multicompartmental assessment (physiological, but also clinical and radiological assessment, pending validated biomarkers). Assessment of disease progression has strong therapeutic implications. Apart from clinical trials, which by essence require well-defined, objective eligibility criteria, some flexibility is needed to assess disease progression, so that clinicians can integrate in the decision-making process, not only consensus criteria of progression but also key variables such as clinical events, ILD subtype, radiological pattern, long-term disease behaviour, disease severity, patients' preferences, *etc*. The superb studies published in the *European Respiratory Journal* inform us on disease progression in the real-world setting, demonstrating that eventually, a majority of patients with fibrotic ILDs (~50% at 2 years, and more later on) will experience disease progression, sometimes several years after the ILD diagnosis. The time to satisfying progression criteria is variable: from one patient to another, and depending on the ILD subtype, disease progression occurs at variable speed.

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