Progressive fibrosing interstitial lung disease: we know it behaves badly, but what does that mean?

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The criteria used to define progressive fibrosing interstitial lung disease identify a rapidly progressive phenotype that behaves like idiopathic pulmonary fibrosis, regardless of the underlying diagnosis https://bit.ly/3bW5DIV

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The concept behind the INBUILD clinical trial was simple: if nintedanib slows progression of idiopathic pulmonary fibrosis (IPF) [1], then it might also slow progression in other forms of fibrotic interstitial lung disease (ILD) [2]. This was recently shown to be the case [3], with nintedanib slowing the rate of ILD progression in a diverse cohort of patients without IPF who met specific criteria for recent worsening. This study was a major advance, identifying a new treatment for a group of patients who previously had limited options.

IPF is notable for its rapid rate of progression and high risk of mortality compared to most other ILD subtypes [4]. Similar rapid progression and early mortality is also present in some patients with a variety of non-IPF ILDs, with this population recently labelled as having progressive fibrosing ILD (PF-ILD) [5]. The importance and clinical relevance of PF-ILD as a specific subgroup was largely based on the presumption that previous progression would predict a higher likelihood of also having future progression. This theory was the underlying basis for the eligibility criteria used in the INBUILD trial, which enriched the study population for this progressive phenotype in an attempt to enroll patients with a high likelihood of benefit from nintedanib.

Recent studies have defined PF-ILD in a variety of ways, generally based on a combination of physiological, clinical and radiological criteria. The most common physiological parameter used to define ILD progression is forced vital capacity (FVC), with both observational cohorts and clinical trials showing that a decline in FVC of more than 5% is associated with mortality in both IPF and non-IPF ILDs [6–8]. Clinical criteria for PF-ILD are usually based on worsening dyspnoea or cough, which are easily and routinely solicited in clinical practice. Given the impracticalities of specific questionnaires and exercise tests in most settings, recent trials have generally defined clinical worsening based on qualitative patient report in order to replicate real-world practice [3, 9]. Computed tomography (CT) has been used to demonstrate not only the presence and extent of fibrosis, but also to identify disease progression [3, 9, 10]; however, the inability to perform serial CTs at regular intervals has limited its routine use for this purpose. The recent INBUILD trial defined PF-ILD as having a 10% relative decline in FVC, or at least two criteria present out

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of a 5% relative decline in FVC, worsening symptoms and worsening CT [3]. This evidence of progression needed to be met over the preceding 24 months, despite treatment, with a second major requirement being the presence of clinically significant fibrosis based on CT. Although the criteria for PF-ILD used in INBUILD are somewhat arbitrary, the clinical relevance of this population was confirmed by the benefit of nintedanib observed in this trial.

In the present study published in this issue of the *European Respiratory Journal*, Brown *et al.* [11] extend the initial efficacy analyses of the INBUILD trial to show that patients with non-IPF PF-ILD have similar rates of progression and overall mortality compared to the IPF populations studied in the INPULSIS clinical trials [1]. The poor outcomes of PF-ILD are striking, but should not be overly surprising. IPF is the prototypical progressive ILD, with previous clinical trials showing rapid decline in FVC despite the absence of eligibility criteria related to pre-enrolment progression (figure 1) [1, 3, 9, 10, 12–19]. The INBUILD cohort of non-IPF patients had similar poor outcomes with enrichment of the study population for both disease severity and recent worsening [11]. These data confirm the ability of using recent disease behaviour to prospectively identify non-IPF ILD patients with a high risk of future progression, providing additional evidence that PF-ILD is a clinically useful concept.

Many previous cohorts have shown that patients with a usual interstitial pnemomia (UIP) pattern have worse outcomes compared to non-UIP patterns in a variety of clinical diagnoses [20, 21]. However, the relatively slow progression that is typically observed in unselected cohorts of patients with non-IPF ILDs (that mostly have non-UIP patterns of fibrosis) contrasts with the rapid rate of progression observed for patients with a non-UIP pattern in the INBUILD trial (figure 1). For example, the placebo group of the SENSCIS trial of systemic sclerosis-associated ILD (SSc-ILD) had a much slower annual rate of FVC decline (−93.3 mL) compared to patients with a non-UIP pattern in the INBUILD trial of PF-ILD (−160.1 mL) [10, 11]. These findings suggest that recent disease behaviour, at least as defined in the INBUILD eligibility criteria, substantially adds to the prognostic information conferred by both the clinical diagnosis and imaging pattern. An important caveat to this conclusion is that the rapid progression observed in the INBUILD clinical trial population occurred in the context of fibrosis affecting >10% of lung volume on CT. This eligibility criterion was used to increase the likelihood that the previous worsening was on the basis of ILD progression, rather than being due to alternative explanations (*e.g.* cardiac disease, variability in pulmonary function measurements). It is therefore important to note that this high risk of future progression does not necessarily apply to patients with very mild ILD.

The consistent response to nintedanib in IPF and PF-ILD implies at least some overlap in disease biology among the different ILD subtypes included in these trials [1, 3]; however, their similar disease behaviour

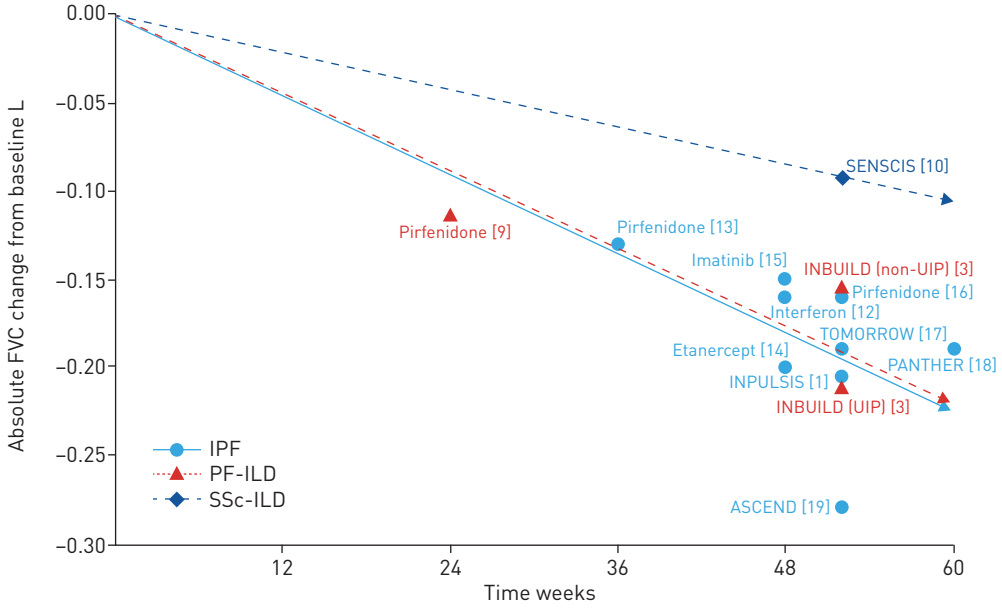

FIGURE 1 Decline in absolute forced vital capacity (FVC) from the placebo arms of selected interstitial lung disease (ILD) clinical trials. Lines of best fit are shown for illustrative purposes based on an unweighted average of FVC change from baseline. Different statistical methods were used across clinical trials (*e.g.* different approaches for handling of missing data), potentially contributing to variability in reported rate of FVC decline. Adapted and updated from Ley *et al.* [24].

does not provide any further evidence to support this claim. Nintedanib and pirfenidone are both relatively nonspecific antifibrotic medications, and these were therefore good candidates for testing in a variety of PF-ILD subtypes [3, 9, 22]. The relatively consistent benefits of nintedanib and pirfenidone across ILD subtypes may not be replicated with future ILD therapies that have different mechanisms of action, particularly if these medications are targeting more specific pathways. The next generation of medications currently under study in IPF will therefore require similar studies to INBUILD in order to justify expansion of clinical indications to additional ILD subtypes.

Although almost all patients with IPF worsen over time, it is still unclear what proportion of patients with other fibrotic ILDs will have progressive fibrosis. In the Scleroderma Lung Study, 13% of patients with SSc-ILD treated with placebo had progressive disease, defined by an absolute decline in FVC of >10% at 12 months [23]. Slightly fewer patients (8.3%) in the placebo arm in the SENSCIS trial progressed [10]; however, approximately half of the patients in this study also received mycophenolate, which likely attenuated the overall rate of progression. Additional studies are needed to determine whether similar percentages of patients with other fibrotic ILDs will meet criteria for PF-ILD, ideally including longitudinal follow-up to determine longer-term patterns of disease behaviour. This long-term trajectory of PF-ILD has significant implications for clinical management and for regulatory bodies attempting to establish funding criteria for this population.

The INBUILD clinical trial demonstrated the benefit of nintedanib in PF-ILD [3], while the present study further confirms that the criteria used to define PF-ILD identify a rapidly progressive phenotype that behaves like IPF regardless of the underlying diagnosis [11]. This finding has important implications beyond the demonstrated efficacy of nintedanib in PF-ILD, providing objective data that will inform other management recommendations and discussions with patients about their prognosis. Although these novel findings are interesting and clinically relevant, the similar outcomes of IPF and PF-ILD do relatively little to advance our biological understanding of these diseases. It is hoped that new therapeutics in the IPF pipeline will be effective in IPF, and that additional trials will confirm benefits that extend to the larger group of patients with other fibrotic ILDs. Through these types of clinical trials, and with additional mechanistic studies, it is anticipated that advances will be made to better understand and further slow the progressive fibrosis that defines this nebulous group of patients.

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