Comment on "The natural history of progressive fibrosing interstitial lung diseases"

To the Editor:

We have read with great interest the paper titled "The natural history of progressive fibrosing interstitial lung diseases" by Brown *et al.* [1]. This elegant study has used data from the INBUILD and INPULSIS trials to investigate the natural history of progressive fibrosing interstitial lung diseases (ILDs).

The cohorts in the two INPULSIS trials had a diagnosis of idiopathic pulmonary fibrosis (IPF), while in contrast the subjects in the INBUILD trial had progressive fibrosing ILDs other than IPF. The protocol-defined criteria for ILD progression despite management varied, and included a relative decline in forced vital capacity (FVC) ⩾10% of the predicted value; a relative decline in FVC 5–10% of the predicted value plus worsened respiratory symptoms; a relative decline in FVC 5–10% of the predicted value plus increased extent of fibrosis on high-resolution computed tomography (HRCT); and finally, worsened respiratory symptoms plus increased extent of fibrosis on HRCT. The researchers found that the adjusted mean annual rate of decline in FVC in the INBUILD trial (ILDs, n=331) was similar to that observed in the INPULSIS trials (IPF, n=423) (−192.9 and −221.0 mL per year, respectively; p=0.19). Furthermore, a relative decline in FVC >10% predicted was associated with a similarly increased risk of death in both the INBUILD (hazard ratio 3.64) and INPULSIS (hazard ratio 3.95) trials. Taken together, fibrosing ILDs that progress while on treatment have a similar outcome to IPF.

The early identification of a cohort of decliners may allow us to institute early measures to prevent end-stage lung disease. In the future, patients that remain stable may also allow dose adjustments in their treatment, thus limiting cost and side-effects. Several parameters of progression have been proposed and it would be interesting to determine these authors' rationale for their criteria. Indeed, this study does highlight the difficulty we find clinically and in research in defining progression in lung conditions that are progressive in their natural course, but quite variably so.

FVC is a measure of lung restriction secondary to tissue remodelling [2]. Various studies have proposed marginal decline (fall in FVC 5%–10%) [3], a relative decline in FVC by 10% (pre−post-FVC/pre-FVC×100%) and an absolute decline in FVC >10% (pre-FVC–post-FVC) to determine progression [4]. These proposals were based on analysis of IPF or combined IPF/non-specific interstitial pneumonia cohorts. Would the same parameters be predictive across different populations of progressive fibrotic ILDs, such as connective tissue disease ILD *versus* chronic hypersensitivity pneumonitis? Or, do we need to modify them for specific conditions? Equally, severity of disease may impact on the interpretation of lung function for progression.

We would also raise the possible problem that individual variability in repeated measurements may be within the marginal average decline of 5%–10% in different laboratories and may not represent a true decline. In addition, if we combine such apparent marginal relative decline with symptoms, we are concerned that this may reinforce a false-positive for progression since symptoms may be multifactorial and not attributable to progression in the specific ILD. For example, a cough could represent an upper respiratory tract infection, while dyspnoea may be a symptom of cardiac failure.

The measure of diffusing capacity of the lung for carbon monoxide (D_{LCO}), which we have used because it ought to be a sensitive reflection of interstitial lung dysfunction, is more variable than FVC, and does this explain why Brown *et al.* [1] have not reported this measure of ventilation/perfusion mismatch at the

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alveolar–capillary level? This is the site for the earliest changes in IPF and so D_{LCO} has been an important marker of progression in various studies [5]. Notably, baseline D_{LCO} was also predictive of mortality [3]. Further, our Australian IPF Registry of lung function data of predominantly untreated IPF patients has found that there may be a decline in either D_{LCO} or FVC or both, suggesting the use of one parameter such as FVC alone may miss real decline in some patients. The pattern of progression is also nuanced with patterns ranging over a year from stable; a linear decline; or general stability but with distinct episodes of decline that are not due to acute exacerbations. Further, we have found that the first 6 months of FVC measurement usually does not mirror the trajectory in the subsequent 6 months. This phenomenon is not often discussed in studies of progression of fibrotic ILDs and requires further focus.

The Brown *et al.* [1] paper highlights the need for a more defined evidence-based international consensus on the criteria of progression in ILD/IPF. What should these gold standard criteria be? More objective assessments of CT scan may fulfil this role for early disease. Although currently there may be variability between the subjective reporting of radiologists, artificial intelligence systems are likely to improve objectivity and accuracy. We further agree with the authors that progression should also incorporate an increase in symptoms, but only if other common causes can be explicitly excluded. Additionally, in the real clinical world, we suggest each laboratory takes into account the standard deviation of their own lung function testing that would then enable physicians to determine progression as a fall below the local standard deviation for FVC or D_{LCO}.

A diagnostic dilemma does arise when you have a single time-point decline in lung function that does not correlate with subjective clinical stability. Should decline be consistent over a period in time, but then what is the optimum duration? We suggest a decline in two consecutive tests (FVC and/or D_{LCO}), separated by at least 3 months apart for each test and larger than the local standard deviation for each measure, in order to constitute a recordable true decline. An even longer duration of individual monitoring will be needed to provide confirmation of consistency of information on the true trajectory of the illness. It would also be important to determine what is the best combination of parameters, that will give us the most accurate assessment, in a wide variety of ILDs. This may include combining D_{LCO} with FVC changes or adding the 6 min walk test or CT findings to the assessment of progression.

Finally, identifying the mechanisms of progression in individual patients needs to become an important element in their evaluation and management. The mechanisms of progression may include the extension of fibrosis, new inflammatory lung infiltrates, the worsening of co-morbidities or the presence of side effects of therapy. Such individualising of "treatable traits" will lead to more targeted management, and greater insights embedded within the outcomes of clinical trials. The manuscript by Brown *et al.* [1] has been not only informative, but also inspires thinking and hopefully further discussion around how to optimise the monitoring of progression of ILDs/IPF.

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