Reply to comment on "The natural history of progressive fibrosing interstitial lung diseases"

Reply to Y.P. Moodley and co-workers:

We thank Y.P. Moodley and co-workers for their thoughtful letter in response to our manuscript on the natural history of progressive fibrosing interstitial lung diseases (ILDs) [1]. We agree that early identification of patients with progression of their ILD is important to enable prompt implementation of appropriate treatment. The inclusion criteria for the INBUILD trial reflected current approaches used to identify patients with progressive ILD. However, we acknowledge that the pattern of progression of ILD varies among individual patients, and no single set of criteria will capture all of them.

A decline in forced vital capacity (FVC) of >10% of the predicted value has consistently been associated with early mortality across studies in patients with fibrosing ILDs, in idiopathic pulmonary fibrosis (IPF) and in non-IPF disorders alike. For subjects with a "marginal" decline in FVC of 5–10% of the predicted value, inclusion in the INBUILD trial also required worsening of symptoms and/or an increased extent of fibrosis on high-resolution computed tomography. Our rationale was that the problem of measurement variability can be constrained (although not eliminated) by combining lung function measurements with other, independent, clinically relevant variables. As the investigators were asked to enrol patients with progression of ILD (*i.e.* alternative explanations for worsening symptoms were considered and excluded), rejecting patients with a marginal decline in FVC accompanied by worsening of symptoms seemed unjustified.

We agree with Y.P. Moodley and co-workers that evaluation of ILD progression requires a multidimensional approach and repeated measures over time. In the INBUILD trial, we used a retrospective 2-year window to assess for progression of ILD. This duration allowed us to account for potential variability in clinical variable measurement and competing explanations for clinical decline. With regard to diffusing capacity of the lung for carbon monoxide (D_{LCO}), we believe that in real-world practice, clinicians can integrate trends in D_{LCO} measured in the same laboratory into a multidimensional assessment of disease progression. We did not use decline in D_{LCO} within the prior 2 years as an inclusion criterion in the INBUILD trial, as we believed that for many sites, repeated D_{LCO} measures from the same laboratory would not have been available, and inter-laboratory variation in D_{LCO} measurement is a recognised issue.

We agree that a variety of other measures of disease progression might have been used as inclusion criteria, but the INBUILD inclusion criteria were effective at identifying patients with future progression, as shown by an IPF-like rate of decline in FVC over 52 weeks of 193 mL per year in the placebo group. We believe that this indicates that experienced clinicians are able to identify patients with progressive ILD based on easily accessible clinical data. That said, we agree that this is an area ripe for additional investigation, and there remains a need to develop consensus criteria for the progression of fibrosing ILD. Developing artificial intelligence-driven computed tomography criteria to define progression is an intriguing idea that is worthy of further research, but may be challenging to make accessible to patients in the short term.

Y.P. Moodley and co-workers raise the important question of whether the categorical declines in FVC that have consistently been associated with mortality in patients with IPF are also associated with mortality in patients with other progressive fibrosing ILDs. This linkage has been observed in previous studies in

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No set of criteria will cover all patients, but the inclusion criteria used in the INBUILD trial were effective at identifying a population of patients with progressive ILD https://bit.ly/3mKkzzi

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patients with chronic hypersensitivity pneumonitis, systemic sclerosis-associated ILD, rheumatoid arthritis-associated ILD, and idiopathic non-specific interstitial pneumonia. In the current analyses, a relative decline in FVC >10% predicted was associated with an increased risk of death in the INBUILD and INPULSIS trials with similar hazard ratios (3.64 and 3.95, respectively).

We hope that these and future analyses of data from the INBUILD trial will continue to inspire discussion around how to optimise the monitoring and treatment of fibrosing ILDs in clinical practice.

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Reference

1 Brown KK, Martinez FJ, Walsh SLF, *et al.* The natural history of progressive fibrosing interstitial lung diseases. *Eur Respir J* 2020; 55: 2000085.