Worsening dyspnoea as a predictor of progression of pulmonary fibrosis

Received: 10 Dec 2023
Accepted: 12 Aug 2024

To the Editor:

Progressive pulmonary fibrosis (PPF), also known as progressive fibrosing interstitial lung disease (ILD), is a term used to describe progressive lung fibrosis in a patient with an ILD other than idiopathic pulmonary fibrosis (IPF) [1]. Patients with PPF often experience burdensome symptoms such as cough and dyspnoea and impairment in their quality of life [2]. Several studies have reported associations between symptoms and subsequent disease progression in patients with pulmonary fibrosis [3–5], but little is known about the relationship between changes in symptoms and outcomes including survival.

The INBUILD trial enrolled patients with an ILD other than IPF who met criteria for ILD progression within the prior 24 months, despite management in clinical practice [6]. Patients were randomised to receive nintedanib or placebo. Over 52 weeks, nintedanib slowed the decline in forced vital capacity (FVC), and reduced worsening of dyspnoea, fatigue and cough assessed using the Living with Pulmonary Fibrosis (L-PF) questionnaire [6, 7]. We used data from the placebo group of the INBUILD trial to investigate associations between L-PF questionnaire scores (at baseline and changes over time) and outcomes.

The L-PF questionnaire comprises two modules: symptoms (23 items) and impacts (21 items) [8]. The symptoms module includes domains for dyspnoea (12 items), cough (six items), and fatigue (five items). Total, module and domain scores range from 0 to 100, with higher scores indicating greater impairment. The L-PF questionnaire includes items that are relevant to and understood by patients with PPF [8]. In the INBUILD trial, the L-PF questionnaire was completed at baseline and weeks 12, 24, 36 and 52. Associations between L-PF questionnaire scores at baseline (categorised as below *versus* at least the median), and between changes in L-PF questionnaire scores from baseline to week 24 (categorised as less than *versus* equal to or greater than the minimal important change to the patient) and subsequent time-to-event endpoints were analysed using Cox regression models. Based on distribution- and anchor-based methods, meaningful change thresholds for the L-PF questionnaire dyspnoea and cough scores in the INBUILD trial were previously estimated to be 6 to 7 points and 4 to 5 points, respectively [9]. Meaningful change thresholds for the fatigue and impacts scores were estimated using question 21 of the L-PF questionnaire (“On average, over the last 7 days, how has your quality of life been?”) as an anchor. Over 52 weeks, mean changes in impact score were 13.3, 10.0 and 0.6 for a moderate decline (2 points), minimal decline (1 point) and no decline, respectively, in quality of life assessed using this question. Mean changes in fatigue score were 7.5, 10.7 and 1.0 for the same declines, respectively. Based on the average scores for a moderate or no decline, and for a minimal or no decline, meaningful change thresholds for the fatigue and impacts scores were estimated to be 5 to 6 points. The time-to-event endpoints analysed were death, ILD progression (decline in FVC % predicted ⩾10%), ILD progression or death, acute exacerbation of ILD or death, hospitalisation or death, and respiratory-related hospitalisation or death.

The placebo group comprised 331 patients. At baseline, mean±SD age was 66.3±9.8 years, 53.5% were male, FVC was 69.3±15.2% pred, and diffusing capacity of the lung for carbon monoxide was 47.9±15.0% pred. Mean±SD L-PF questionnaire cough, dyspnoea, fatigue and impacts scores were 40.0±26.5, 21.2±18.1, 40.9±19.6 and 44.4±21.7, respectively. The median follow-up time for the time-to-event endpoints was approximately 19 months. Data on ILD progression and ILD progression or death were available for 301 patients and data on other outcomes were available for 305 patients. Overall, 36 patients (11.8%) died, 88

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Among patients with progressive pulmonary fibrosis, worse dyspnoea at baseline and a worsening of dyspnoea over 24 weeks were associated with an increased risk of disease progression
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Cite this article as: Wijsenbeek MS, Swigris JJ, Spagnolo P, *et al*. Worsening dyspnoea as a predictor of progression of pulmonary fibrosis. *Eur Respir J* 2024; 64: 2302211 [DOI: 10.1183/13993003.02211-2023].

(29.2%) had ILD progression, 110 (36.5%) had ILD progression or died, 48 (15.7%) had an acute exacerbation or died, 116 (38.0%) were hospitalised or died, and 92 (30.2%) had a respiratory-related hospitalisation or died.

Correlation coefficients between changes from baseline in FVC % pred and in dyspnoea score were −0.15, −0.21, −0.28 and −0.35 at weeks 12, 24, 36 and 52, respectively. Correlation coefficients between changes from baseline in FVC % pred and in cough score were −0.12, −0.16, −0.09 and −0.25 at weeks 12, 24, 36 and 52, respectively. A baseline dyspnoea score of ⩾17.2 (median) *versus* <17.2 was associated with significantly increased risks of death (hazard ratio (HR) 2.21, 95% CI 1.15–4.25), ILD progression or death (HR 1.42, 95% CI 1.05–1.93), hospitalisation or death (HR 1.75, 95% CI 1.25–2.47) and respiratory-related hospitalisation or death (HR 1.76, 95% CI 1.20–2.59). There were no significant associations between a baseline cough score ⩾37.5 (median) *versus* <37.5 or between a baseline impacts score ⩾42.2 (median) *versus* <42.2 and risks of the outcomes. There were no significant associations between a baseline fatigue score ⩾43.8 (median) *versus* <43.8 and risks of the outcomes, except for associations with death (HR 1.98, 95% CI 1.04–3.74) and acute exacerbation or death (HR 1.86, 95% CI 1.10–3.13).

Change in dyspnoea score ⩾6 *versus* <6 points at week 24 was associated with increased risks of all the outcomes (figure 1). Findings were consistent when a threshold of 7 points was used. There were no significant associations between changes in cough score ⩾4 *versus* <4 at week 24 and the risks of the outcomes (figure 1), nor between changes in fatigue score ⩾5 *versus* <5 at week 24 and the risks of the outcomes. Findings were consistent when a threshold of 5 points for change in cough score or 6 points for change in fatigue score was used. There were no significant associations between changes in L-PF impacts score ⩾5 *versus* <5 at week 24 and risk of the outcomes, except for associations with an increased risk of death (HR 2.00, 95% CI 1.06–3.77) and acute exacerbation or death (HR 1.73, 95% CI 1.00–3.01).

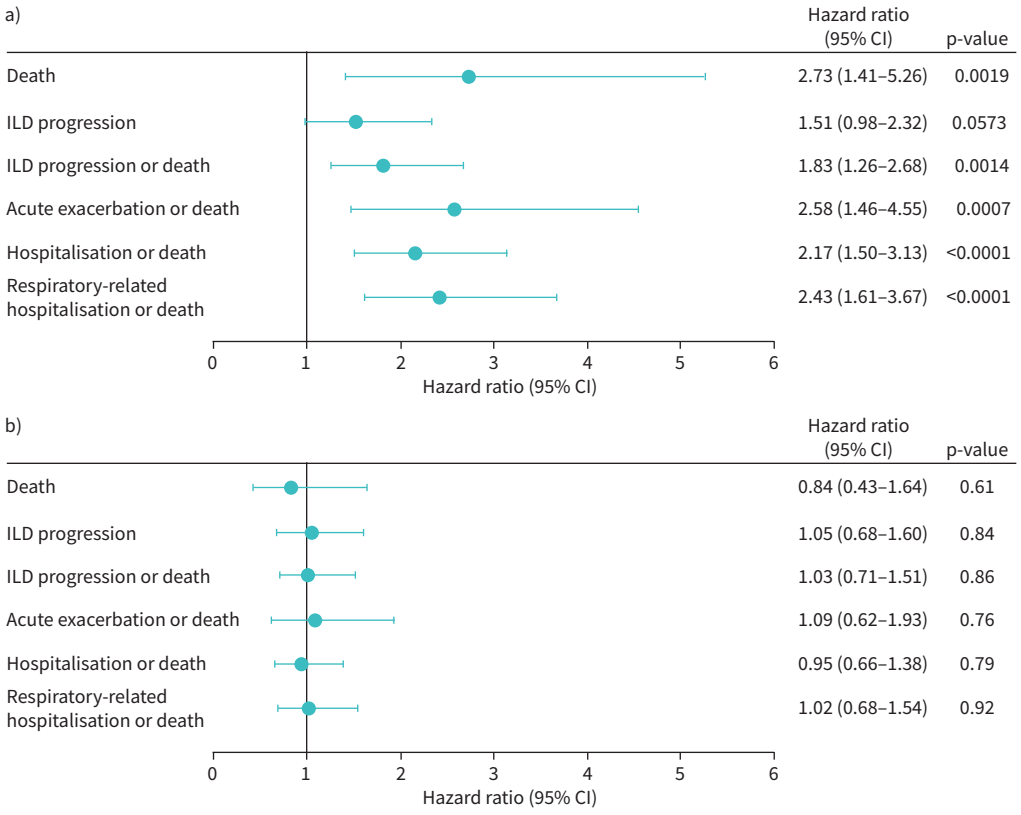

FIGURE 1 Associations between a) change in Living with Pulmonary Fibrosis questionnaire dyspnoea score (⩾6 *versus* <6) at week 24 and subsequent time-to-event endpoints, and b) change in Living with Pulmonary Fibrosis questionnaire cough score (⩾4 *versus* <4) at week 24 and subsequent time-to-event endpoints in the INBUILD trial. Interstitial lung disease (ILD) progression was defined as decline in forced vital capacity % predicted ⩾10%.

These analyses suggest that baseline and short-term changes in dyspnoea assessed using the L-PF dyspnoea score may identify patients at higher risk of worse outcomes. Previous studies in patients with ILDs have also shown that worsening dyspnoea is associated with worse outcomes. Among 424 patients in the INSIGHTS-IPF registry, a worsening of University of California San Diego Shortness of Breath Questionnaire score was associated with an increased risk of mortality during follow-up [10]. Among 81 patients with IPF, 6-month change in dyspnoea (based on the exertion required to precipitate dyspnoea) was predictive of mortality [11]. In a study of 150 patients with various ILDs, baseline and 3- to 6-month changes in dyspnoea, based on the Medical Research Council (MRC) dyspnoea score, were associated with disease progression (decline in FVC % predicted $\geqslant$10%, decline in 6-min walk distance $\geqslant$50 m, respiratory-related hospitalisation, lung transplant assessment, or death) or death over 18 months [12]. A recent prospective study performed in 199 patients with fibrotic ILDs found that MRC dyspnoea score at baseline and change in MRC dyspnoea score over a mean follow-up of 9.6 months were associated with mortality [13].

Consistent with our findings from the INBUILD trial, weak cross-sectional and longitudinal correlations between patient-reported outcomes and FVC % pred have been observed in studies in patients with IPF [14, 15]. These data underline that measures of symptoms and lung function assess different aspects of the severity of ILD and that measuring both is important in the assessment of disease progression.

In conclusion, among patients with PPF in the INBUILD trial, worse L-PF questionnaire dyspnoea score at baseline, and a worsening of L-PF questionnaire dyspnoea score over 24 weeks, were associated with an increased risk of progression. Assessment of dyspnoea may play an important role in identifying patients with PPF at high risk of short-term progression. Further work should examine associations between L-PF questionnaire dyspnoea scores and outcomes in other cohorts of patients with PPF.

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Acknowledgements: Writing assistance was provided by Julie Fleming and Wendy Morris of FleishmanHillard, UK, funded by Boehringer Ingelheim. Boehringer Ingelheim reviewed the manuscript for medical and scientific accuracy as well as intellectual property considerations. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. A graphical abstract for this manuscript can be found at https://www.globalmedcomms.com/respiratory/INBUILD_dyspnoea_and_ILD_progression.

Ethics statement: The trial was carried out in compliance with the protocol, the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonisation and was approved by local authorities. All patients provided written informed consent before study entry.

Conflict of interest: The authors did not receive payment for development of this manuscript. M.S. Wijsenbeek reports grants to her institution from The Dutch Pulmonary Fibrosis Patients Association, The Dutch Lung Foundation, The Netherlands Organisation for Health Research and Development, The Thorax Foundation, Sarcoidosis.nl, AstraZeneca/Daiichi-Sankyo, Boehringer Ingelheim and Hoffmann-La Roche, and consulting or speaker fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Galapagos, Galecto, Hoffmann-La Roche, Horizon, Kinevant Sciences, Molecure, NeRRe, Novartis, PureTech, Thyron, Trevi and Vicore. J.J. Swigris reports consulting fees from Boehringer Ingelheim and is an unpaid member of the Board of Directors

for Live Fully, Inc. and patientMpower. P. Spagnolo reports grants, personal fees and non-financial support from PPM Services and Boehringer Ingelheim, grants from Roche, personal fees from AstraZeneca, Chiesi, CSL Behring, Galapagos, Glycocore, JucaBio, Lupin, Menarini, Novartis, Pieris, Structure Therapeutics and Veracyte, and that his wife is an employee of AstraZeneca. M. Kolb reports grants from the Canadian Institute for Health Research, Roche, Boehringer Ingelheim and Pieris, and fees from Boehringer Ingelheim, Roche, the *European Respiratory Journal*, LabCorp, Bellerophon, United Therapeutics, Nitto Denko, MitoImmune, Pieris, Abbvie, DevPro Biopharma, Horizon, Algernon, CSL Behring and ShouTi. M. Kreuter reports grants, consulting fees and fees for speaking from Boehringer Ingelheim and Roche, and holds leadership or fiduciary roles with Deutsche Gesellschaft für Pneumologie, the European Respiratory Society and the German Respiratory Society. H. Nunes reports grants and consulting fees from Boehringer Ingelheim and Roche, and has been a trial investigator for Galapagos, Galecto, Gilead, Novartis and Sanofi, he has participated on an endpoint committee for Galapagos. W. Stansen and K.B. Rohr are employees of Boehringer Ingelheim. Y. Inoue reports grants from the Japanese Ministry of Health, Labour, and Welfare, and the Japan Agency for Medical Research and Development, payment for presentations from Boehringer Ingelheim, Kyorin, Shionogi, GlaxoSmithKline and ThermoFisher, and has served as a consultant or steering committee member for Boehringer Ingelheim, Galapagos, Roche, Taiho, CSL Behring, Vicore Pharma and Savara.

Support statement: The INBUILD trial was supported by Boehringer Ingelheim. Funding information for this article has been deposited with the Crossref Funder Registry.

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