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# Analyses of the Efficacy and Safety of Antifibrotic Therapies in Non-IPF Pulmonary Fibrosis, Progressing Despite Management

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In the this issue of *AnnalsATS*, readers have been treated to systematic reviews of the efficacy and safety of pirfenidone (1) (pp. 1030–1039) and nintedanib (2) (pp. 1040–1049) in patients with non-IPF pulmonary fibrosis (nIPF) with fibrotic lung diseases progressing despite management. This possible use of antifibrotic agents has been of worldwide interest. Historical management strategies have failed to meet the needs of patients once progression has occurred despite treatment, with forced vital capacity (FVC) decline strongly predicting earlier mortality in individual fibrotic interstitial lung diseases (ILDs) other than idiopathic pulmonary fibrosis (IPF) (3). Both reviews were undertaken to inform recommendations made in an impending ATS/ERS/JRS/ALAT (American Thoracic Society/European Respiratory Society/ Japanese Respiratory Society/Latin American Thoracic Association) clinical guideline. Literature searches disclosed a single nintedanib trial, the INBUILD trial (4), and two pirfenidone trials, the UILD and RELIEF trials (5, 6), all placebo-controlled and meeting the criteria for inclusion. In summary, it was concluded that nintedanib is efficacious in attenuating disease progression in patients with nIPF despite management, regardless of the radiographic pattern of fibrosis. Conclusions on the use of pirfenidone were more guarded, with statistically significant treatment benefits offset by the view that the certainty of beneficial effects is low on the basis of trial limitations. Side effects for both agents mirrored those observed in IPF antifibrotic trials.

A major strength of this approach, novel in our field, is the separation between the breadth of analyses used to inform a guideline group (analyses restricted to hard data) and the ultimate distillation of guideline statements, in which additional considerations are often important. Current guideline terminology used in previous IPF guidelines (especially the separation between the strength of evidence and the strength of a recommendation) allows the informed reader a partial insight into the key distinction between data abstraction and analysis and final guideline recommendations. But the forensic and detailed dissection of trial data exemplified in both manuscripts is a very welcome departure from past guideline presentations.

Furthermore, the presentation of data in both manuscripts is lucid. The basis of differential conclusions on the strength of the pirfenidone and nintedanib data is laid bare. The authors have not fallen into the trap of overemphasizing whether studies are "officially" positive based solely on primary endpoint analyses but have captured the full breadth of trial variables with a balanced distillation of all available data. It should be acknowledged that analysis of the pirfenidone data was a difficult task. In the UILD study, the primary endpoint (serial home spirometry) did not provide meaningful data, but serial FVC readings in lung function laboratories (the usual primary endpoint in IPF trials) were appropriately emphasized (5). Interpreting FVC trends in the RELIEF study was a courageous attempt given premature trial termination and the consequent problems of underpowering and a large number of missing variables (6).

This said, there are caveats that merit careful consideration. In analyses of both agents, the authors state comparisons in FVC decline between active and placebo arms, expressed as mean differences in mls/year and, in the case of pirfenidone, mean differences as a percentage of predicted normal values (1, 2). At first sight, this appears logical as the decline in FVC, expressed as mls/year, constitutes the primary endpoint in most ILD trials. However, attenuation of decline with active treatment cannot exceed the decline observed in the placebo arm. A mean difference of 100 mls in FVC decline, favoring pirfenidone in the UILD and RELIEF trials, representing a difference of 2.3% of predicted normal values, appears to be a weak treatment effect. However, approximately 50% of the decline was prevented compared with that observed in the placebo arms of these trials, an effect very similar to pirfenidone effects observed in IPF trials. The apparent significance of mean



DOI: 10.1513/AnnalsATS.202204-323ED

absolute differences in FVC decline can be misleading. In the recent SENSCIS trial of nintedanib in scleroderma-associated ILD, an apparently unimpressive FVC treatment effect of only 40 mls favoring active treatment led to rapid regulatory approval for nintedanib in that disease because 43% of progression was prevented compared with FVC decline in the placebo arm (93.3 mls) (7). Thus, it can be argued that "percentage prevention of FVC decline" with active treatment is a helpful metric that might usefully have added context to the efficacy analyses in both current manuscripts (1, 2). An average FVC treatment effect of approximately 100 mls covers both smaller treatment effects in patients with less progressive disease and potentially major benefits in patients with rapid disease progression.

A notable feature of both meta-analyses was the stated desirability of defining treatment effects in individual fibrotic ILDs. In both manuscripts, most stated questions, before analysis, related to treatment effects in patients with hypersensitivity pneumonitis (HP), connective tissue disease-related ILD (CTD-ILD), idiopathic nonspecific interstitial pneumonia, sarcoidosis, occupational ILD or unclassified ILD, with each diagnosis considered separately. However, the hypothesis underpinning all three antifibrotic trials was that in nIPF patients with IPF-like progression despite management, irrespective of the underlying diagnosis (or in patients with unclassifiable disease in which no diagnosis can be made), an IPF-like treatment effect might be seen with antifibrotic therapy.

The emphasis on quantifying antifibrotic treatment effects in individual diseases risks misunderstandings that are not sufficiently confronted in either manuscript. Importantly, there is the potential misperception that data in each individual disease should be viewed as a separate small trial in that disease. This applies especially to analyses of the INBUILD trial of nintedanib. Ghazipura and colleagues evaluate individual diseases and conclude that treatment effects in attenuating FVC decline were significant in fibrotic connective tissue disease-related ILD, idiopathic fibrotic nonspecific interstitial pneumonia, and fibrotic occupational ILD, but not in fibrotic HP, fibrotic sarcoidosis, or unclassified fibrotic ILD (2). However, the evaluation of treatment-related mean differences in FVC decline in individual diseases in the INBUILD trial served only to establish that treatment effects are broadly uniform across disease subgroups (8). No significant or marginally significant differences in efficacy between disease subgroups were observed (treatment-by-subgroup-by-time interaction; $P = 0.41$). Diagnostic subgroups in INBUILD were seriously underpowered. In all five major diagnostic subgroups, FVC treatment effects lay immediately above or below "statistical significance", with chance having a defining role in this distinction.

In any case, the quantification of treatment effects in individual ILDs, described as "progressive fibrotic ILDs", risks an important separate misunderstanding that these analyses are applicable to individual fibrotic ILDs at first presentation. By and large, patients with fibrotic ILDs present because the disease is progressive with worsening symptoms. However, in all three antifibrotic trials, patients were selectively enrolled with disease progression despite management, tailored by individual clinicians to the underlying ILD diagnosis. Patients studied in these trials are not representative of the spectrum of disease at first presentation, and it would perhaps have been helpful to emphasize this important caveat. For example, patients with fibrotic HP included in the INBUILD and RELIEF trials were explicitly the subgroup of patients with HP progressing despite management, including antigen eviction, in which this was achieved. In the INBUILD trial, over 50% of patients enrolled with fibrotic HP had computed tomography appearances indicative of underlying usual interstitial pneumonia (4).

However, in the two largest studies of histological findings at surgical biopsy in HP, each containing more than 100 patients, an underlying usual interstitial pneumonia histological pattern associated with a high risk of subsequent progression was present in only 11% of patients with fibrotic abnormalities at biopsy (9) and in only 10–15% of patients with fibrotic abnormalities on computed tomography (10).

In summary, the analyses performed by Ghazipura and colleagues are highly informative. Whether the focus on treatment effects in individual ILD diagnoses will promulgate confusion is likely to depend on the nature of final guideline recommendations, likely to be released in the near future. It is not yet known whether the guideline group will make differential recommendations for pirfenidone and nintedanib in pulmonary fibrosis progressing despite management. In some guidelines, recommendations tend to be made only when treatment effects are proven. However, clinicians most value decisive guidance when treatment benefits are likely but uncertain or imprecise, as provided in the recent ERS guidelines for the management of sarcoidosis (11).

Be that as it may, Ghazipura and colleagues have helpfully detailed ongoing pirfenidone trials likely to provide results in the near future. These are crucial studies, and it is essential that the guideline group provides a rapid update of treatment recommendations. The last multisocietal guideline for the treatment of IPF was released in 2015 (12). However, as made clear by the detailed analyses of recent trial data, 7 years is far too long a time interval for the provision of authoritative guidance on the optimal use of antifibrotic agents in nIPF pulmonary fibrosis. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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