# Broad Therapeutic Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a variably progressive disease that carries a poor prognosis. Recent international multicenter phase III clinical trials testing the efficacy of nintedanib (1) and pirfenidone (2) have shown that medical therapy, specifically antifibrotic agents, can reduce the rate of lung function decline in patients with IPF. In the United States, these groundbreaking findings were quickly followed by U.S. Food and Drug Administration fast-track priority review, orphan product designation, and drug approval for both pirfenidone and nintedanib (3). Nintedanib, a small-molecule tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor, was tested in two simultaneous phase III trials (INPULSIS-1 and INPULSIS-2) (1). Compared with placebo, nintedanib consistently slowed disease progression by significantly reducing the annual rate of decline in forced vital capacity (FVC) in both INPULSIS trials (1). Comparable reductions in disease progression were reported for pirfenidone, raising the possibility that overlapping mechanisms mediate these remarkably similar antifibrotic effects.

Importantly, as IPF is a highly heterogeneous disorder, it remains unclear whether patients with varying clinical or molecular phenotypes will selectively respond to antifibrotic therapies. For instance, a prior report suggested that treatment with antifibrotic agents may be more effective in patients with reduced disease severity (4). In this issue of the *Journal*, Costabel and colleagues (pp. 178–185) (5) report prespecified analyses conducted to evaluate the therapeutic effect of nintedanib on the primary and key secondary endpoints in patient subgroups, using pooled data from the two INPULSIS trials (1). Treatment effects, examined against sex, race, age, baseline FVC percentage predicted ($<$70% vs. $>$70%), baseline St. George's Respiratory Questionnaire, smoking status, and systemic corticosteroid and bronchodilator use did not differ significantly for the primary (annual rate of decline in FVC) or key secondary (time to first acute exacerbation and change from baseline in the St. George's Respiratory Questionnaire) endpoints. Thus, it appears that nintedanib provides therapeutic benefit to a broad range of phenotypes of patients with IPF.

This study suggests that in patients with more severe disease, nintedanib reduces the risk for acute exacerbations of IPF (AEIPF) and maintains health-related quality of life. Although enrollment to the phase III clinical trials testing the efficacy of nintedanib and pirfenidone was limited to patients with mild to moderate disease, this important finding provides a rationale for the approval of nintedanib without restriction for physiologic criteria and its use in late-stage disease until additional studies in patients with IPF with severe disease are available. However, the findings can also be interpreted as suggestive, rather than conclusive. The total number of AEIPF was small, and the protective effect of nintedanib was statistically significant in one of the INPULSIS studies, but negligible in the other (1). It can also be argued that "acute events" reported in a pharmaceutical study in which disease progression is very closely monitored at regular intervals are not necessarily synonymous with acute events encountered in routine practice. AEIPF matter because of their high associated mortality in clinical series. The missing piece of the jigsaw in the INPULSIS trials is the outcome associated with AEIPFs. This question is important because favorable mortality trends with treatment are marginally stronger for pirfenidone, despite the absence of a reported effect on AEIPFs, than for nintedanib. This apparent paradox may reflect imprecision resulting from the low number of events (both deaths and AEIPFs), but it is also possible that mild AEIPFs are reported more frequently in pharmaceutical populations than in other settings. The dilemma arising from these caveats relates to the required level of proof of benefit with regard to infrequent, but often lethal, events. Certainly, the reported AEIPF protective effect of nintedanib provides "proof of concept." However, taken together, the low event numbers and lack of evidence of a mortality benefit associated specifically with AEIPF prevention indicate that further validation is required.

Uncertainties also exist on the question of very early treatment. The widespread use of high-resolution computed tomography (HRCT) in clinical and research settings has increased the detection of subclinical ILD in at-risk populations (6). We anticipate that the future availability of genetic testing (i.e., telomerase mutations, MUC5B polymorphism) and other predictive biomarkers (i.e., SPD, CCL18, MMP7) will enhance our ability to diagnose IPF at earlier stages and identify those patients at risk for disease progression. This study provides evidence that antifibrotic therapies can reduce disease progression and frequency of acute exacerbations in patients with IPF with preserved lung function and suggest that secondary prevention clinical trials should be considered in at-risk populations (i.e., familial interstitial pneumonia, rheumatoid arthritis interstitial lung disease) (7). However, extrapolating from these results to the current management of individual patients with IPF is not straightforward.

The use of an FVC severity threshold in the current study is justified by the fact that some regulatory bodies (such as the U.K. National Institute for Health and Care Excellence [NICE]) have specified that funding for antifibrotic therapy will be reimbursed only in patients with IPF with FVC levels lower than 80%. The finding of an equivalent treatment benefit above and below an FVC threshold of 70% held true when an alternative FVC threshold of 80% was examined in the INPULSIS cohort (data presented in abstract form at the 2015 European Respiratory Society meeting). This observation in a large IPF cohort severely undermines the logic of the NICE FVC threshold, but is difficult to rationalize. The superficial interpretation is that treatment benefits on serial FVC trends are independent of disease severity. However, an alternative explanation exists: that FVC levels are

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simply a poor measure of disease severity when compared with diffusing capacity of the lung for carbon monoxide ($D_{LCO}$) levels or composite indices (8, 9). To understand the limitations of FVC as a severity measure is to understand that there are four distinct subgroups of patients with IPF when FVC levels exceed thresholds of 70 or 80% of predicted:

1. IPF is genuinely subclinical, confirmed by lack of symptomatic limitation, preservation of, or mild reduction in, $D_{LCO}$ levels and the presence of limited abnormalities on HRCT.
2. IPF is clinically important and sometimes severe, especially in those unidentifiable patients (often with very physically active backgrounds) in whom premorbid FVC values exceed 120% of predicted. This scenario can reasonably be suspected when an FVC level higher than 80% is associated with significant exercise limitation and major reduction in $D_{LCO}$ levels or the presence of extensive disease on HRCT.
3. Extensive IPF on HRCT is associated with overt emphysema, prominent exercise limitation, spurious preservation of FVC levels, and major, even devastating, reductions in $D_{LCO}$ levels
4. Finally, IPF is not present, but there is normal limited, age-related subpleural reticulation (seen on HRCT in more than 50% of healthy subjects aged older than 75 years [10]) with $D_{LCO}$ levels normal (or reduced in patients with smoking-related lung damage).

The multidisciplinary evaluation of the clinical significance of IPF in an individual patient, integrating symptoms, FVC and $D_{LCO}$ levels, and HRCT evaluation, is the "bread and butter" of the routine assessment of IPF severity. The use of the NICE and other similar FVC thresholds to restrict access to antifibrotic agents is both ill informed and discriminatory against patients with smoking-related lung damage and those with high premorbid pulmonary function variables, who must progress to advanced disease before the use of antifibrotic therapy is endorsed. However, although the findings in the current study based on an FVC threshold of 70% provide "proof of concept" for the use of nintedanib in early disease, it is essential that further work is undertaken to define efficacy in each of the FVC subgroups detailed here (with the obvious exception of elderly patients with normal age-related abnormalities on HRCT).

In conclusion, the findings in the current study provide "proof of concept" for broadening the criteria for treatment of patients with IPF to those with more advanced disease and also to very early disease, as well as underlining the fact that rigid FVC thresholds, limiting access to antifibrotic agents, are discriminatory. However, more work is essential to define more precisely the efficacy of antifibrotic therapy in both advanced and subclinical IPF. ■

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

Athol U. Wells, M.D.
*Interstitial Lung Disease Unit*
*Royal Brompton Hospital*
*London, United Kingdom*

Ivan O. Rosas, M.D.
*Pulmonary and Critical Care Medicine*
*Brigham and Women's Hospital*
*Boston, Massachusetts*
and
*Harvard Medical School*
*Boston, Massachusetts*

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# Diagnosis of Post-extubation Stridor: Easier with Technology Support?

The transition from invasive ventilator support to spontaneous breathing without a tracheal tube is a complex process, and children who require reintubation after extubation failure are at increased risk for adverse outcomes, including duration of ventilation and of pediatric intensive care unit length of stay and higher mortality (1). Because of the small size of pediatric upper airways and the dramatic effect of the radius in Poiseuille's law, upper airway obstruction plays a major role in extubation