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Patient-centered Outcomes in Idiopathic Pulmonary Fibrosis Clinical Trials

In 2018, we will mark a decade of commercially available therapy for idiopathic pulmonary fibrosis (IPF)—pirfenidone was approved for use in Japan in 2008. Since that time, evidence of the efficacy of both pirfenidone and nintedanib in IPF has continued to accumulate. Five large phase 3 clinical trials (CAPACITY I and II, ASCEND, and INPULSIS I and II) have provided convincing evidence that these two drugs slow disease progression as defined by a reduction in the rate of FVC decline over 1 year (1–3). These findings have been appropriately lauded, and the U.S. Food and Drug Administration has also weighed in, emphasizing the now-recognized primacy of FVC as the preferred primary endpoint in IPF clinical trials, noting that "the relationship between FVC and mortality trends in both sets of clinical trials strengthened our ability to rely on FVC as a clinically relevant efficacy measure in IPF" (4).

Nevertheless, the choice of primary endpoint in IPF trials has been subject to additional nuanced debate (5, 6). Although declines in FVC over time likely do represent progression of IPF in many cases and indeed may be distressing to patients and their healthcare providers, FVC is simply a physiological measurement and not a "patient-centered" outcome. A pharmacologically induced reduction in the rate of FVC decline has no tangible benefit from the patient's perspective. Evidence that antifibrotic therapy positively influences one or more patient-centered outcomes would have both a meaningful impact on patient care and important implications for future clinical trials in IPF.

In this issue of the *Journal*, Ley and colleagues (pp. 756–761) provide new evidence that directly addresses this knowledge gap (7). They performed randomized comparisons of pirfenidone versus placebo using data from three phase 3 trials of pirfenidone (the two CAPACITY trials and ASCEND). They examined the effect of allocation to a pirfenidone arm on the risk of respiratory hospitalization, nonrespiratory hospitalization, and all-cause hospitalization using time-to-event analyses. They found that pirfenidone was associated with a lower risk of respiratory-related hospitalization at 1 year (a 5% absolute risk reduction, which corresponds to a number needed to treat of 20) but was not associated with all-cause or nonrespiratory hospitalizations. Pirfenidone was also associated with a lower

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risk of death after hospitalization of any kind at 1 year (but not at 72 wk).

These findings have two important implications. First, clinicians can now convey to their patients that IPF treatment may result in a reduction in the rate of respiratory hospitalization, a patient-centered and clinically relevant outcome for patients with IPF. This information is likely to influence decisions to initiate therapy during the decision-making process involving patients and their providers. In the future, developers of clinical practice guidelines will also likely incorporate this information during the evidence-synthesis process, possibly influencing recommendations for treatment of IPF. Third-party payers should also pay close attention to this demonstrated benefit of antifibrotic therapy, as healthier patients who stay out of the hospital are less costly to the healthcare system.

Second, these findings have the potential to influence the selection of endpoints for clinical trials. The incorporation of respiratory hospitalization (with and without its inclusion in a composite time-to-event endpoint) as a key secondary endpoint should be strongly considered by trialists. Respiratory hospitalization has a number of advantages as an endpoint. Like an FVC decline, in many cases it is a direct result of a worsening of the underlying disease process. It is likely to be easier to measure and adjudicate than acute exacerbations, and FVC measurements can be obtained even if the participant is not alive at the end of the study. Missing landmark endpoints threaten the validity of any clinical trial in which patients are likely to die, become too sick to make a return visit, or undergo lung transplantation before the landmark is reached. Perhaps most importantly, respiratory hospitalization is a patient-centered outcome that is directly relevant to one of the most important goals of our patients: living a healthier life.

All-cause mortality and all-cause nonelective hospitalization have previously been proposed as clinically meaningful endpoints in IPF trials. Some have noted that the sample size required to achieve adequate power for these endpoints would make such trials impractical (4, 5). The study by Ley and colleagues supports the possibility of using respiratory hospitalization as a primary endpoint in IPF trials. Given the 5% absolute reduction in the 1-year risk of respiratory hospitalization (from 12 to 9.0%) observed in the current study, future studies would need to enroll 588 participants (294 per arm) to have sufficient power (80%) to detect a similar reduction in the risk of respiratory hospitalizations at 1 year (this calculation assumes a 2-yr enrollment period and a 5% dropout in both arms). This sample size rivals those of other phase 3 IPF trials, including the ASCEND trial. When included in a composite time-to-event endpoint along with other important endpoints (such as FVC decline and death), an even smaller sample size might be possible. Although it seems that FVC will remain the primary endpoint for many phase 3 trials in the near future, confirmation of the usefulness of a respiratory hospitalization endpoint in these trials could influence the decision to use patient-centered primary endpoints in IPF trials designed just a few years down the road.

The randomized comparisons, large sample size, appropriate analytic approach, and clinically relevant outcomes are major strengths of the study by Ley and colleagues. Minor limitations, such as the *post hoc* nature of the study and the unexamined variability of the measurement and definition of respiratory hospitalization, only marginally detract from the strength and implications of the findings. One major barrier to implementation of this endpoint is the absence of a standard definition of a respiratory hospitalization. Although this can be overcome through central or local adjudication, there is also concern that non-IPF–related hospitalizations may be captured, and that regional differences in the use of and indications for hospitalization may add variability to this measure. Consensus regarding the definition and measurement of respiratory hospitalization should be a short-term goal of clinical trialists. Methods to account for regional propensities for hospitalization should also be considered.

We have come a long way in 10 years. Patients are increasingly engaged in making decisions about the role of IPF therapy in their lives. We must continue to focus our current and future efforts on gaining new knowledge about the relevance of these therapies for the day-to-day lives of our patients. ■

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Anna J. Podolanczuk, M.D., M.S.
David J. Lederer, M.D., M.S.
Department of Medicine
Columbia University Medical Center
New York, New York

ORCID ID: 0000-0001-5258-0228 (D.J.L.).

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