Broad Adoption of Antifibrotics in Idiopathic Pulmonary Fibrosis: Still a Long Way to Go

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In October 2014, two antifibrotic medications (nintedanib and pirfenidone) were approved by the U.S. Food and Drug Administration (FDA) for treatment of idiopathic pulmonary fibrosis (IPF) after landmark trials showed a significant reduction in the decline in lung function as measured by forced vital capacity compared with placebo over 1 year (1, 2). Follow-up *post hoc* analyses of these trial data have since demonstrated that the benefits of antifibrotics are consistent across disease severity, may reduce respiratory-related hospitalizations, and could possibly improve survival (3–5). The benefits of these antifibrotics are clear; and although they are associated with unpleasant side effects in a number of patients, these are not life-threatening and do not linger after cessation of the drugs. Considering that in a large number of patients, the benefits generally outweigh the potential risks and adverse effects, it is important to know what the real-life use of antifibrotics in IPF has been over the past 5 years. Previously published data from longitudinal registries of IPF in the United States have shown that treatment rates vary, ranging from 58–70% (6, 7). However, registry participants are typically highly selected patients referred to tertiary care specialized interstitial lung disease centers. Therefore, treatment rates from registry studies may not truly reflect real-life practice outside of academic institutions. Establishing the true rate of uptake of antifibrotic medications in IPF across institutions and populations is important for identifying gaps and inequalities in medical care and in access to medications.

In this issue of *AnnalsATS*, Dempsey and colleagues (pp. 1121–1128) have sought to evaluate the adoption, persistence, and out-of-pocket costs of antifibrotic medications (both pirfenidone and nintedanib) in the United States since their approval in 2014 (8). This is a retrospective observational study, in which the authors used deidentified United States–based administrative claims data from private and public (Medicare Advantage) health insurance plans. This database contains claims data from diverse racial and ethnic groups spanning all 50 states. There were 10,996 subjects with IPF identified in the data set using *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision* and *Tenth Revision* diagnostic codes and included in this study (out of a possible 21,444,770 covered patients). The authors also looked at all prescriptions of either nintedanib or pirfenidone and added the claimants who had filled such a prescription even if they received their diagnosis of IPF at a later date. Of the patients with IPF, a total of 2,901 (26.4%) received either nintedanib or pirfenidone during the study period. Those who were younger and had fewer comorbidities were more likely to receive treatment. Importantly, there were sex-based differences in medication initiation whereby women were significantly less likely to be prescribed medications than men (22% vs. 30%). The number of patients who were started on antifibrotics increased over time, peaking in the last quarter studied in 2019, presumably as prescribers became more familiar with these novel medications. During the duration of the study, 10.5% switched from one drug to the other. Treatment discontinuation occurred in 43% of patients who had been started on treatment, with a mean duration of treatment of under 1 year (302 d). This was not due to imminent death or reaching end-stage disease, as the mean time from treatment end to death was over 500 days.

It is disappointing to see that in this first large-scale, real-life study of drug usage in IPF, only 26% start therapy and that nearly half of those discontinue treatment fairly early on. This study is based on administrative data in which cases are identified using diagnostic codes, which may limit the diagnostic accuracy and therefore miss some cases of IPF. However, the authors included patients who had filled prescriptions of antifibrotics before the diagnostic code was added to their chart and then added those subjects to their cohort, making it likely that there was no substantial underestimation of the uptake of antifibrotics. This raises the key question as to why the observed adoption rate is so low even 5 years after approval of antifibrotics for IPF by the FDA. Many factors are likely contributing: approximately 21% of patients experienced at least one of the common side effects associated with antifibrotic medications, which had a role to play in the discontinuation of treatment in some. Side effects and having to manage them may also deter some patients or their physicians from initiating treatment. In some cases, patients continue to smoke despite their diagnosis, which may make some physicians reluctant to start therapy as well.

Perhaps the most important reason that uptake has been low, and that discontinuation has been so high, may be the prohibitively high cost of medications in the United States. The authors of this study looked at the out-of-pocket cost of antifibrotics for patients. They report that the global cost for either antifibrotic is approximately U.S. $9,000 per month, or about U.S. $108,000 per year per patient. Out-of-pocket fees by the patients (copays) vary on

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the basis of the type of health insurance and coverage provided, and details can be found in the online supplement of the authors' article. Patients with commercial insurance paid lower out-of-pocket costs than those with public coverage (commercial, U.S. $123 to U.S. $173/mo; Medicare Advantage, U.S. $434/mo). This would mean that patients would have to pay between U.S. $1,476 and U.S. $5,208 per year just to afford 1 year of prescriptions for the treatment of IPF. These out-of-pocket costs are staggering and possibly unaffordable for patients, especially when added to the costs of their other medications for the average of four comorbidities they may suffer from. Considering that, according to the U.S. Census Bureau, the median annual income for a family in the United States in 2019 was U.S. $68,703 (9), the out-of-pocket cost of antifibrotics could be between 2.1% and 7.6% of the total annual gross income of the household. Median earnings were lower for women than for men, which may contribute to the sex difference in medication initiation identified in this study.

This study has shown that antifibrotic uptake remains low in the United States and that discontinuation of treatment is high for those who do start medications. This may be in large part due to the high out-of-pocket cost for patients, but it is likely that other barriers and discrepancies exist but were not captured by this analysis. As more clinical trials looking at novel IPF treatments are combining drugs and looking at additive benefits of different medications, it will become even more difficult for patients who would benefit from those drugs to afford them. Exorbitant costs should not be a barrier toward a standard of care in a developed country with state-of-the-art medical advances and therapies. Policy changes to control the prohibitive costs of those medications are needed to ensure affordability for all who need them. Further barriers to access to care such as sex, race and ethnicity, or socioeconomic status also need to be identified and addressed in future studies to ensure appropriate care for all. ■

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A Bold First Toe into the Uncharted Waters of Evaluating Proprietary Clinical Prediction Models

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Would a clinician prescribe a new medication in the absence of any data about its efficacy or safety? Of course not. Regulatory authorities like the Food and Drug Administration (FDA) and good clinical judgment would prevent such a blunder. Then why would a health system deploy a clinical prediction model, designed to inform high-stakes decisions for patients at risk for critical