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Toward Realizing the Full Potential of Registries in Interstitial Lung Disease

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The past two decades have seen a revolution in our understanding of interstitial lung disease (ILD), with the emergence of idiopathic pulmonary fibrosis (IPF) as the prototypical fibrotic ILD. We have learned that targeting a putative inflammatory mechanism with immunosuppressive therapy provides no benefit in IPF and in fact leads to harm (1); accordingly, current treatment directly targets mechanisms of fibrosis (2, 3), but until recently, their use has been limited to IPF. At the same time, non-IPF ILDs, for which a given individual diagnosis may affect few patients, nonetheless comprise a large number of patients in total. This has frustrated both clinicians and patients, with little evidence to guide the use of existing therapies and little progress with respect to new treatments. Recently, however, antifibrotic therapy has been shown to reduce disease progression across a broader range of fibrosing ILDs, with nintedanib now approved for treatment of both systemic sclerosis-associated ILD (4) and progressive fibrosing ILD (5) and an additional study suggesting a benefit of pirfenidone in unclassifiable fibrosing ILD (6). In short, current evidence now supports a role for antifibrotic therapy based on a progressive fibrosing ILD phenotype while recognizing that specific diagnoses remain likely to impact disease behavior and perhaps treatment response, and that underlying causes (such as rheumatologic diseases or environmental exposures) must still be addressed.

In such an environment, the means to systematically understand disease behavior across a broad range of ILD is more crucial than ever. In this issue of *AnnalsATS*, Wang and colleagues (pp. 1620–1628) describe the broadly inclusive Pulmonary Fibrosis Foundation Patient Registry (PFF-PR) (7), which represents an ambitious attempt to address that need. The registry has enrolled over 2,000 patients in under 5 years, including over 300 with collagen vascular disease–associated ILD, over 150 with hypersensitivity pneumonitis, and over 200 with non-IPF idiopathic interstitial pneumonias. Importantly, this provides the opportunity to study relatively large subgroups of rare ILDs across multiple centers.

What can ILD registries teach us? Wang and colleagues provide some interesting initial insights on diagnosis, management, and treatment patterns, reporting that 60% of IPF patients were treated at the time of enrollment (7). Hopefully, the authors will pursue further analyses that will help us understand who we currently treat and, more importantly, who we *should* treat relative to diagnosis and disease course. Approximately 30% of patients were diagnosed with the help of a surgical lung biopsy, despite a general trend toward more reliance on imaging in ILD classification (8). Surprisingly, only 41% were diagnosed with the help of formal multidisciplinary discussion, despite evidence for its benefit and a general understanding that such discussion should be considered standard of care, particularly at the expert care centers participating in the registry. It will be interesting to see whether these patterns change over time,

DOI: 10.1513/AnnalsATS.202008-1077ED

both with steady improvements in imaging-based diagnosis and with the partial shift to disease behavior rather than underlying diagnosis as a driver of treatment choice in fibrotic ILD.

Such reports will be compared with interest to those from a number of other IPF registries from around the world (9). To date, much of what we have learned has been limited to IPF, but several registries, such as the ILD-PRO (Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease Prospective Outcomes Registry) and CARE-PF (Canadian Registry for Pulmonary Fibrosis) (10, 11), have included other ILD diagnoses. The PFF-PR provides an interesting first look at the characteristics of this broader ILD population and is well positioned to document the use and outcomes of antifibrotic therapy for progressive fibrosing ILD across multiple centers.

Though the multicenter design, size, and scope of ILD diagnoses included in the PFF-PR represent clear strengths, the registry does have some limitations. As the authors acknowledge, enrollment of patients with non-IPF ILDs has been restricted to achieve a target 60% enrichment for IPF. This detracts from the unique strength of the registry being inclusive of a broad ILD population and limits the ability to draw conclusions about the relative prevalence of individual forms of ILD. The registry is limited to U.S. expert centers and, as such, is unlikely to be fully representative of ILD management in other international regions or at other less specialized centers.

Although registries provide value by documenting disease course and outcomes among patients who fall outside the narrow inclusion criteria of clinicals trials, such as those with more severe lung function impairment or high comorbidity burden, they cannot by themselves determine treatment effects in these patient groups in the way that a randomized trial could. But one hopes that registries like the PFF-PR can begin to bridge this gap. Though not a specific objective stated by the authors, a large, inclusive, and efficiently managed ILD registry provides an invaluable opportunity to efficiently facilitate prospective interventional studies in a challenging patient population. Historically, clinical trials in IPF have enrolled patients with a limited and relatively moderate range of disease severity, and sample sizes sufficient to power for truly patient-centered outcomes (such as hospital admissions or mortality) have been unrealistic (12). Until recently, patients with more uncommon ILD subtypes or unclassifiable ILD have seldom been included in randomized studies at all. But the PFF-PR could provide a pragmatic framework for so-called registry randomized trials, in which a randomized intervention is inserted into the framework of the existing registry, capitalizing on efficiencies in data collection and patient visits. Clearly, such studies would require additional infrastructure related to safety monitoring, but the efficiencies are likely still worth pursuing. Here, we can learn from our colleagues in cystic fibrosis research, who have leveraged registries to enable pragmatic clinical trials and arguably enabled insights that would be difficult to achieve in a traditional stand-alone trial, by incorporating past individual disease behavior gleaned from the registry into analyses of individual treatment effects (13). Wang and colleagues point out that enrolled patients have been asked about their willingness to participate in add-on studies. The ILD community, including clinicians and the patients and caregivers whom the PFF represents, needs the PFF-PR investigators to seize that opportunity to more efficiently study potential new therapies, existing therapies in new or expanded patient populations, or even treatment regimes based on multiple drugs and/or timing relative to disease course.

The PFF-PR, with other registries close behind, arrives at an exciting time in the treatment of fibrotic ILD. Existing antifibrotic therapies are now being deployed among a larger and more diverse population of patients with ILD, and we can hope that other effective therapies will provide more options in the not-too-distant future. In this context, understanding an increasingly complex disease patient population, learning who should be treated with which drugs, and efficiently conducting prospective studies will present important challenges. Let us hope that the PFF-PR and others are up to the task. ■

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

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