Insights from the INSIGHTS-ILD Registry: real-world heterogeneity in treatment patterns for patients with fibrotic interstitial lung disease

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An interim analysis of the INSIGHTS-ILD registry provides important real-world insights into clinical characteristics and practice patterns for patients with non-IPF fibrotic ILD https://bit.ly/4fXcHpn

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Pulmonary fibrosis frequently complicates interstitial lung disease (ILD). While idiopathic pulmonary fibrosis (IPF) remains the prototypic progressive fibrotic ILD, estimates support that up to 40% of individuals with non-IPF fibrotic ILD will develop a progressive fibrosing course [1]. This recognition has led to the recent American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Asociación Latinoamericana de Tórax clinical practice guideline defining an entity termed progressive pulmonary fibrosis (PPF), with diagnostic criteria designed to capture individuals with declining pulmonary function, progressive fibrotic changes on computed tomography (CT) and worsening respiratory symptoms [2]. While there have been variations in the terminology of what is currently referred to as PPF, the implications of having PPF are significant. First, the development of PPF is associated with reduced transplant-free survival [3]. Second, meeting criteria for PPF has therapeutic relevance. The results of the INBUILD trial support that individuals with progressive fibrosis benefit from treatment with nintedanib [4]. In individuals that met criteria for disease progression over the prior 24 months, nintedanib reduced the decline in forced vital capacity over 52 weeks compared to placebo.

Despite a growing recognition of PPF, significant gaps remain in our understanding of this clinically relevant phenotype. Until recently, there was no uniform definition of PPF. Differing criteria have been utilised to define progressive disease [2, 4]. Depending on the definition employed, prevalence estimates and associations with transplant-free survival vary [3]. The definition of PPF has been met with some criticism due to the lack of validation of the diagnostic criteria and the time requirement over which progression is needed to occur [5, 6]. Future refinements of the diagnostic criteria of PPF hinge on "real-world" data from patients with non-IPF fibrotic ILD. Registry data is therefore essential to better understand disease course and treatment selection in patients with and at risk for PPF.

In this issue of *ERJ Open Research*, Behr *et al*. [7] provide real-world insights into clinical characteristics and practice patterns for patients with non-IPF fibrotic ILD from an interim analysis of the INSIGHTS-ILD registry. The INSIGHTS-ILD registry contains data from patients enrolled across more than 30 specialty centres in Germany. Key registry inclusion criteria include a non-IPF fibrotic ILD diagnosis, age ⩾18 years, ILD on high-resolution CT involving >10% lung parenchyma, diffusing capacity for carbon monoxide ⩽80% predicted and current immunomodulatory or antifibrotic therapy. Both incident and prevalent cases were included. Data on 655 patients were presented with the most common ILD aetiologies being hypersensitivity pneumonitis (31.2%) and non-IPF idiopathic interstitial pneumonia (22%), followed by connective tissue disease related-ILD (13%) and unclassifiable ILD (13%). This cohort had a slight male predominance (54%) with a mean age of 65.9 years. Physiologic impairment was common, with a mean forced vital capacity of 69.8% predicted and diffusing capacity for carbon

monoxide of 33.8% predicted. In the 24 months prior to enrolment, 56% of patients met at least one of the INBUILD criteria for progressive fibrosis. Clinical diagnoses were confirmed by multidisciplinary discussion in 78.4% of cases. The majority (76.1%) of patients underwent bronchoscopy with bronchoalveolar lavage and approximately half underwent a biopsy procedure as part of diagnostic ascertainment, most commonly with transbronchial biopsy.

Use of immunomodulatory treatment was common, with 62.6% of patients receiving prednisone, followed by azathioprine (14.4%) and mycophenolate mofetil (MMF) (11.1%). Half of the patients received antifibrotic therapy with the majority (96%) receiving nintedanib. The patients receiving antifibrotic therapy were slightly older and more commonly male with an increased prevalence of comorbidities, reduced pulmonary function and shorter 6-minute walk distance. Notably, approximately 40% of patients not receiving anti-fibrotic therapy retrospectively satisfied one or more criteria for progressive fibrosis defined in the INBUILD trial, and conversely approximately one out of three patients who did not satisfy any of these progressive fibrosis criteria received "off-label" antifibrotic therapy.

These findings provide important "real-world" insights into the current management of patients with non-IPF fibrotic ILD. First, there was discordance between administration of nintedanib and guideline recommendations. The start of registry enrolment predated publication of the PPF criteria and treatment recommendations, likely explaining some of these discrepancies; however, nintedanib had already received approval from the European Commission for progressive fibrotic ILD. Little has been known about adoption rates of antifibrotic therapy for the expanded indication of PPF. Within the INSIGHTS-ILD registry, adoption of antifibrotic therapy was relatively high with approximately 72.7% of individuals that met at least one INBUILD criteria for progressive disease receiving an antifibrotic. This is in comparison to data from a large United States insurance claims-based cohort in which only 25% of individuals with IPF received nintedanib or pirfenidone [8]. Future data from the INSIGHTS-ILD registry may elucidate common themes regarding provider rationale for treatment initiation, barriers to antifibrotic adoption and discontinuation rates.

Second, the frequency of corticosteroid and corticosteroid-sparing agent use was higher in the no antifibrotic therapy group compared to the antifibrotic therapy group. Currently, the initial treatment of many non-IPF ILDs includes immunomodulatory therapy with corticosteroids or corticosteroid-sparing agents; however, treatment selection is stylistic and often provider-dependent making registry data critical. A better understanding of practice patterns in different regions is crucial to defining an accepted standard of care for initial management of non-IPF ILD, especially given the paucity of clinical trial-derived data in this area. Additionally, it remains unclear what should be done with immunomodulatory treatment once PPF develops. The use of many of these agents (rituximab, MMF and azathioprine) was an exclusion for participation in the INBUILD trial. Given that nintedanib and pirfenidone share some side effects (diarrhoea and nausea) with certain commonly utilised immunomodulatory medications such as MMF, understanding real-world immunomodulatory and antifibrotic treatment discontinuation rates and reasons for discontinuation will be important.

The findings by Behr et al. [7] also provide insight into the frequency and type of comorbidities present in individuals with fibrotic ILD. In this patient cohort, there was an average of 1.8 comorbidities per patient with the most common being arterial hypertension (47.8%) followed by pulmonary hypertension (17.8%). Much of what is known about the occurrence of comorbidities in patients with pulmonary fibrosis originates from IPF literature; however, comorbidity estimates in non-IPF fibrotic ILD likely differ from IPF due to differences in age, sex and underlying drivers of ILD subtypes. Comorbidities such as pulmonary hypertension are often part of exclusion criteria for ILD clinical trials. Indeed, the INBUILD trial excluded participants with significant pulmonary hypertension, severe systemic hypertension, the need for therapeutic anticoagulation or high-dose antiplatelet therapy and recent myocardial infarction or stroke [4]. However, these conditions are not absolute contraindications to initiating nintedanib. Assessing the use of nintedanib in a broader patient population may provide important insights into clinical practice considerations, such as adjustments to therapy or adverse events, that may not have been captured in prior clinical trials.

There are some limitations in the interpretation of these data. Incident cases represented the minority of enrolments into the registry at less than 10%. Demographics and treatment patterns are expected to differ based on the variations in enrolment time within a patient's ILD course. Additionally, the registry enrolled patients from pulmonary specialty centres in Germany. The characteristics of these patients and their management may therefore be different from those in non-specialty settings. Most diagnoses were made through multidisciplinary discussions consistent with current guidelines; however, the performance of

multidisciplinary discussion is contingent upon access to multiple subspeciality providers. Lastly, regional practice variations in treatment selection may limit broader generalisability, and comorbidity profiles may influence clinical outcomes.

There are many pressing questions in caring for patients with non-IPF fibrotic ILD. Does the timing of initiation of ILD-directed treatment influence outcomes? Would upfront combination immunomodulatory and antifibrotic treatment more favourably modulate disease course in comparison to current practice? While these answers would be best informed by a randomised clinical trial, longitudinal data from this registry may provide an important window into some of these questions. Further insights from this registry may assist with refining the current treatment of patients with fibrotic ILD to improve outcomes and delay the development of PPF.

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References

1 Olson A, Hartmann N, Patnaik P, *et al.* Estimation of the prevalence of progressive fibrosing interstitial lung diseases: systematic literature review and data from a physician survey. *Adv Ther* 2021; 38: 854–867.
2 Raghu G, Remy-Jardin M, Richeldi L, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022; 205: e18–e47.
3 Pugashetti JV, Adegunsoye A, Wu Z, *et al.* Validation of proposed criteria for progressive pulmonary fibrosis. *Am J Respir Crit Care Med* 2023; 207: 69–76.
4 Flaherty KR, Wells AU, Cottin V, *et al.* Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.
5 Johannson KA, Kolb M, Fisher JH, *et al.* Progressive pulmonary fibrosis: putting the cart before the horse. *Am J Respir Crit Care Med* 2022; 206: 1294–1295.
6 Cottin V, Brown KK, Flaherty KR, *et al.* Progressive pulmonary fibrosis: should the timelines be taken out of the definition? *Am J Respir Crit Care Med* 2022; 206: 1293–1294.
7 Bher J, Kreuter M, Guenther AU, *et al.* Real-life characteristics and management of patients with fibrosing interstitial lung disease: INSIGHTS-ILD registry. *ERJ Open Res* 2025; 11: 00926-2024.
8 Dempsey TM, Payne S, Sangaralingham L, *et al.* Adoption of the antifibrotic medications pirfenidone and nintedanib for patients with idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2021; 18: 1121–1128.