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EDITORIAL

Fibrotic ILDs: translating research advances into clinical practice

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Fibrotic interstitial lung diseases (ILDs) remain among the most challenging respiratory conditions. From idiopathic pulmonary fibrosis (IPF) as the primary fibrotic ILD to non-IPF fibrotic ILDs of different causes and origins, these disorders may develop from inflammatory or immunomodulatory pathogenic processes. Their biological complexity, heterogeneous clinical presentation, overlapping clinical features, and unpredictable course demand a multidimensional and multidisciplinary approach that spans genetics, environmental exposures, advanced imaging, and emerging antifibrotic therapies. Furthermore, once the fibrotic process has been established, regardless of the ILD type, it may progress until respiratory failure and death. Thus, diagnostic and therapeutic improvements remain an unmet need in pulmonary fibrosis. This issue of *BRN Reviews* brings together four complementary reviews that capture some of the latest developments shaping the field and highlight how these advances are already modifying clinical practice.

A striking theme is the central role of genetics in both disease susceptibility and progression. Growing evidence regarding the role of genetics, especially telomere regulator genes (TRGs), surfactant protein genes, and the *MUC5B* promoter polymorphism, has identified pulmonary fibrosis as a disease of inherited vulnerability or predisposition. These insights are no longer confined to research laboratories: telomere testing is entering clinical practice, informing prognostication, and helping in patient management. Genetic counselling is becoming essential for families affected by early-onset disease or identified through screening programs, and clinicians increasingly confront ethical questions about the limits of predictive testing, among others.

Genes, however, represent only part of the story. Environmental exposures remain powerful drivers of fibrotic ILDs. Hypersensitivity pneumonitis (HP) clearly represents this interplay. Advancing in antigen identification

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and characterizing patients who develop progressive fibrosis despite antigen avoidance is of outmost importance to improve therapeutic strategies and patient outcomes. Diagnostic features from chest high-resolution computed tomography (HRCT), bronchoalveolar lavage (BAL), and emerging molecular biomarkers help clinicians to differentiate those cases with predominant inflammation or fibrosis, guiding treatment decisions, predicting immunosuppression effect, and optimizing follow-up monitoring. Fibrotic HP requires a closer monitoring than non-fibrotic HP, in order to early identify progressive pulmonary fibrosis that benefit from anti-fibrotic medications. Integrating exposure histories with histopathology and molecular signatures enables a dynamic treatment plan that can shift as new information emerges.

On the other hand, the clinical and pathogenic features of IPF, the archetype of fibrotic ILD, have been widely investigated, which has been crucial for the advances in clinical practice not only for IPF but also for progressive pulmonary fibrosis (PPF). Updated guidelines refine diagnostic criteria and treatment approach, while artificial intelligence tools applied to HRCT are enhancing early detection and prognostic assessment. To date, antifibrotic monotherapy remains the treatment backbone, but combination therapy in clinical trials with experimental drugs targeting senescence pathways and lung remodelling have enabled a new era where patients will receive combination of anti-fibrotic drugs that have demonstrated a better effect than monotherapy. Furthermore, IPF and PPF also require an integral approach, with a comprehensive care including an optimal management of comorbidities and emotional, nutritional and physical state. Among comorbidities, pulmonary arterial hypertension (PAH) and lung cancer are the most lethal complications of ILDs. Advances in PAH research have impacted diagnostic management and therapeutic approaches. The mechanisms linking ILD and pulmonary vascular remodelling are complex and multifactorial. Echocardiography remains the most widely used screening tool, but it lacks sensitivity and specificity, and right-heart catheterization, the gold standard for diagnosis, is only performed in those cases with high-probability of PAH. Therefore, PAH-ILD may be underrecognized in patients with mild-moderate PAH although some studies have shown that even mild PAH in ILD impacts on survival. Until recently, treatment for PAH-ILD was limited to optimizing oxygenation and the treatment of the underlying ILD, although case series with severe PAH-ILD treated with sildenafil, bosentan or mazicentan have been reported. Inhaled treprostinil was the first FDA-approved therapy to improve exercise capacity in mild-to-severe PAH-ILD (after the positive results of INCREASE clinical trial), representing a paradigm shift.

Taken together, research advances in fibrotic ILDs are modifying clinical practice, from diagnostic procedures to therapeutic strategies. Therefore, updating knowledge in this field is crucial to offer the best diagnostic and therapeutic options to patients.