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COMMENT

In pursuit of personalized medicine in fibrotic interstitial lung diseases. Divide and conquer

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In current clinical practice, "pulmonary fibrosis" is a commonly used term in medical records and radiology reports. For patients and their families, "pulmonary fibrosis" is an ominous term because searches on internet sources will convey a grim prognosis, particularly since "pulmonary fibrosis" is often conflated with "idiopathic pulmonary fibrosis." The recent advent of antifibrotic therapy has generated hope, as well as new terms including "fibrotic interstitial lung disease" (fILDs), "progressive fibrosing" ILD, and "progressive pulmonary fibrosis" (PPF) that group together distinct ILDs together based on their fibrosing behavior.[1,2] While these developments may signify progress in our understanding and management of patients with progressive ILDs, potential detriments loom for patients and future progress in this field.

Through 1980s and 1990s, the disease entity of "idiopathic pulmonary fibrosis" (IPF), also called "cryptogenic fibrosing alveolitis" (CFA), became deciphered to encompass several heterogeneous clinicopathologic entities associated with varying histopathologic patterns of lung injury, etiology, and clinical behavior.[3,4] The use of the term "cryptogenic fibrosing alveolitis" faded as the role of inflammation became de-emphasized, and the concept of "idiopathic pulmonary fibrosis" was narrowed to specifically mean usual interstitial pneumonia (UIP) pattern of lung injury in the absence of an identifiable cause, acknowledging that this predominantly fibrotic process can be encountered in other clinical contexts such as rheumatoid arthritis-related ILD. Thus, as the role of inflammation ("alveolitis") in the pathogenesis of IPF and other ILDs was downplayed, other mechanisms of lung damage gained prominence, including epithelial injury, aberrant repair, and fibrosis. Accordingly, the role of anti-inflammatory agents including glucocorticoids and "steroid-sparing" immunosuppressive agents declined, and the antifibrotic era emerged.

Increased understanding of mechanisms underlying parenchymal fibrosis led to the discovery of 2 antifibrotic drugs, pirfenidone and nintedanib, both of which were shown to slow the rate of decline in forced vital capacity (FVC) in patients with IPF.[2] Furthermore, subsequent studies demonstrated that nintedanib could slow the decline in FVC in patients with progressive non-IPF fILDs and this led to broadening indications for the use of antifibrotic therapy and, in turn, the grouping together of a heterogeneous spectrum of fILDs including fibrotic hypersensitivity pneumonitis, connective tissue-disease-related ILDs with fibrotic component, and several others.[5] In an analogous manner, some experts have proposed the histologic pattern of UIP to be a "stand-alone diagnostic entity", regardless of underlying etiopathogenesis.[6]

Adopting a "lumping-together approach" to ILDs with fibrotic predisposition, i.e., fILDs, seems reminiscent of a prior era when the glucocorticoids were widely used and ILDs were considered various forms of "alveolitis." Available treatment options have a tendency to distort and bias our concepts regarding the pathogenesis of diseases, such as

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ILDs. While the proposed entity of fILDs may be pragmatic for the time being in the antifibrotic era, this conceptual evolution also raises concerns. Because there are many ILDs that may result in parenchymal fibrosis, there is concern that antifibrotic therapy may be inappropriately or prematurely prescribed for patients who have not been properly evaluated for potential underlying causes such as exogenous agents (inhaled or ingested substances or medications), autoimmune or autoinflammatory disorders, neoplasms (e.g., histiocytoses), or other systemic disorders with lung involvement. Identification of the underlying cause or systemic disease should be the aim in the diagnostic evaluation of patients with ILDs, and often results in more effective therapy, including avoidance of inciting agent (e.g., drug-induced lung disease, hypersensitivity pneumonitis), targeted therapy, or antiinflammatory/immunosuppressive therapy.

Histopathologic UIP pattern forms the basis of diagnosing IPF, the prototype of fILDs, but is also seen in chronic forms of hypersensitivity pneumonitis (i.e., fibrotic hypersensitivity pneumonitis), lung involvement in patients with systemic rheumatic diseases (especially rheumatoid arthritis), drug-induced ILDs, pneumoconioses, and other disease processes. While the concept of UIP is seemingly straightforward, there are problematic issues in diagnosing this pattern. The inter-observer agreement for UIP pattern, both in pathology and radiology, is moderate even among experts. The pathologic distinction between nonspecific interstitial pneumonia (NSIP), fibrotic hypersensitivity pneumonitis, and UIP can be particularly problematic.[7] The inter-observer agreement is even lower among general pathologists.[8] Similarly, inter-observer agreement among radiologists as to the presence of UIP pattern on CT scans is variable. For example, agreement levels on the presence of honeycombing on CT scans are moderate even among expert chest radiologists.[9,10] To complicate this further, other histologic patterns of injury, such as NSIP, not uncommonly accompany UIP pattern in individual patients, as demonstrated on surgical lung biopsy specimens and lung explants.[11-14] While unifying "primary" and "secondary" (those with identifiable cause or underlying disease) UIP may simplify diagnosis and treatment strategies, this proposal seems a backward step that is likely to impede progress to a better understanding of the complex molecular and cellular mechanisms underlying the pathogenesis of distinct ILDs which can ultimately manifest UIP pattern in advanced stages[6] The use of newer techniques including immunohistochemistry and tissue transcriptomics analysis can place histopathology back in the forefront by providing significant pathogenetic insights that can inform underlying disease mechanisms, prognosis, and optimal management.[15]

While recognizing the value of antifibrotic agents, it is to be acknowledged that they are not a "game changer" in the treatment of fILDs. Despite the use of antifibrotic therapy, most patients with fILDs will continue to experience disease progression. In the Canadian Registry for Pulmonary Fibrosis, among 473 IPF patients receiving antifibrotics, 62% exhibited progression within 24 months of diagnosis.[16] Adverse effects associated with antifibrotic agents and difficulties in assessing the effect of this treatment in individual patients pose additional dilemmas.

Current tendency to lump together disparate ILDs with fibrotic predisposition should not distract us from the goal of individualized medicine. It is still important to delve into the individual context to identify the underlying cause(s) whenever possible, modifying factors, and comorbidities in the management of patients with ILDs. Current tendency to group disparate ILDs into "fibrotic interstitial lung diseases" and "progressive pulmonary fibrosis" in the era of antifibrotic therapy may be shortsighted and could potentially impede progress in understanding the complexities of ILD pathogenesis.

Conflicts of interest

None related to the present work.

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