Re-dimensioning the treatment paradigm in idiopathic pulmonary fibrosis

Author
Luca Richeldi
Unità Operativa Complessa di Pneumologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico A. Gemelli. Rome, Italy

Correspondence
Luca Richeldi
Catholic University of the Sacred Heart. Rome, Italy
E-mail: luca.richeldi@unicatt.it

Idiopathic pulmonary fibrosis (IPF), the prototypic disorder among the group of interstitial lung diseases (ILD), is a chronic progressive fibrotic lung disease characterized by an estimated median survival of approximately three years from diagnosis. Although the cause of IPF remains elusive, the main pathogenetic mechanisms have been explored and partly clarified in recent years. In areas of active fibrosis, fibroblasts proliferate and differentiate into myofibroblasts that produce excess extracellular matrix components including collagen and fibronectin under control of pro-fibrogenic stimuli such as transforming growth factor beta. As excess ECM is deposited scar tissue replaces healthy tissue, thereby destroying the complex and delicate alveolar architecture, thus leading to decreased lung compliance, disrupted gas-exchange, and ultimately respiratory failure and death.

After decades of failing clinical trials, finally a few years ago two molecules were shown to be safe and effective in reducing disease progression in IPF. This has been an historical and crucial turning point for the management of these patients, particularly after many years of using harmful empiric combinations of corticosteroids and immunosuppressive drugs. Nonetheless, despite the approval of these two anti-fibrotic therapies, nintedanib and pirfenidone, many questions remain unanswered. For example, why are these therapies effective when so many putative anti-fibrotic therapies failed in randomized controlled trials? Which study design will best enable future putative anti-fibrotic therapies to demonstrate efficacy in an era of approved therapies? Will patients with other progressive fibrotic lung diseases respond to treatments which have been shown to be safe and effective for IPF?

The results of many different studies would need to be discussed and analyzed to answer these questions and many of them would remain unanswered anyway. However, one major point is worth discussing. Recent genetic findings have the potential to transform our understanding of IPF, with increasing evidence that inherited genetic factors are significantly associated with the risk of developing pulmonary fibrosis. Genome-wide association studies have identified more than a dozen common genetic variants associated with IPF risk. Overall, dramatic advances have been made in our understanding of how the genetic background of an individual might impact on the probability of developing pulmonary fibrosis, the disease course, and potentially response to pharmacologic therapy. Findings suggesting the importance of defects in host defense pathways have the potential to inform our understanding of disease pathogenesis. It is now clear that all future clinical trials must control, and perhaps even consider stratifying, for the presence of prognosis-modifying genetic variants. Whether these findings will ultimately translate to clinical practice is however yet to be determined, and robust prospective studies are required to better understand whether genetic factors may influence the diagnosis and treatment of fibrotic ILDs.

Finally, recent reviews have identified the progress that has been made in clinical trial design in IPF, culminating in robust large scale phase III clinical trials demonstrating therapeutic efficacy. Following a period of debate, forced vital capacity was accepted as a clinically relevant primary efficacy measure in IPF, and in placebo-controlled trials this enabled demonstration of efficacy of both pirfenidone and nintedanib for regulatory approval. As a new era of clinical trials commences, a particular challenge will be selection of a new primary end-point with sufficient power to enable a feasible study size for late phase clinical trials which are anticipated to be either additive to standard of care (pirfenidone or nintedanib) or head-to-head.
References


