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Is personalised medicine the key to heterogeneity in idiopathic pulmonary fibrosis?

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonia of unknown cause, characterised by progressive worsening in lung function and dyspnoea with an associated prognosis similar to or worse than many cancers. As a better understanding emerges around the pathogenesis and mechanisms driving disease pathology, a host of novel agents are being tested both pre-clinically and clinically. However even with this deeper understanding and positive pre-clinical supportive data, negative trial outcomes are frequently reported, highlighting the problems faced in treating such a heterogeneous disease with a varied clinical course. Recently, two therapies that slow disease progression, nintedanib and pirfenidone, have been approved for the treatment of IPF, yet the clinical unmet need is still high for IPF patients given their failure to stop disease progression and their potential side-effect profiles. Efforts are being made to not only understand the underlying pathways and genetics that might influence the clinical course of the disease, but also the non-invasive biomarkers that reflect the activity of specific pathways which in turn may highlight progressive treatment plans for individual patients. The cumulative data may be based on the identification of subgroups of patients via biomarker analysis of ongoing clinical trials, or investigation of cohorts of patients over time to understand the relative role of these mediators in their disease progression. Below we review the ongoing quest for novel therapeutic approaches and highlight, where appropriate attempts have been made to identify patients for which a specific pathway or mediator may be driving disease progression.

Contents

Abbreviations: IPF, idiopathic pulmonary fibrosis; IL, interleukin; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; NAC, N-acetylcysteine; COPD, chronic obstructive pulmonary disease; ECM, extracellular matrix; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; 6MWT, 6 minute walk test; MMP, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; TGs, transglutaminases; LOXs, lysyl oxidases; LAP, latency associated peptide; CTGF, connective tissue growth factor; NSIP, non-specific interstitial pneumonia; SAP, serum amyloid P; MCP, monocyte chemoattractant protein; LPA, lysophosphatidic acid; HP, hypersensitivity pneumonitis; CTD, connective tissue disease; HRCT, high resolution computed topography; CRP, clinical, radiological and physiological; CPI, composite physiologic index; TOLLIP, toll interacting protein; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and ultimately fatal interstitial lung disease (ILD) with an unknown aetiology, a median survival of ~3 years (Raghu, Rochwerg et al., 2015) and estimated 5 year survival rate of ~20%; a mortality rate higher than that of a number of cancers (Bjoraker et al., 1998; Kim et al., 2006). IPF usually occurs in adult individuals of between 50 and 80 years of age and affects more men than women. The disease is highly heterogeneous with varying rates of clinical progression, decline in lung function and response to therapies. Lung tissue from patients with IPF shows a characteristic

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histopathologic pattern known as usual interstitial pneumonia (UIP), with areas of normal parenchyma interspersed with areas of paraseptal and subpleural fibrosis, and architectural distortion within these areas. This may be accompanied by the presence of honeycomb cysts, fibroblastic foci and immune cell involvement (Raghu et al., 2011).

Although clinical diagnosis of IPF has improved, it is still complex and requires exclusion of other known causes of ILDs which are evidenced by patterns of UIP, such as chronic hypersensitivity pneumonitis (HP) or connective tissue disease (CTD). In the right clinical setting, it is possible to make the diagnosis of IPF by high resolution computed topography (HRCT) alone, if it shows a typical UIP pattern. In the absence of a typical UIP pattern lung biopsies may be required to confirm diagnosis, however mortality can be associated and this may not be possible in patients with significantly impaired lung function and/or other comorbidities (Raghu, Rochwerg et al., 2015).

Once diagnosed, heterogeneity of disease progression impacts clinical management and treatment, as is evidenced by a clinical trials history that is littered with landmark negative trials (Table 1). Patients have varying rates of clinical progression indicative that different biological factors or drivers may be at play. Some patients deteriorate rapidly leading to death within months, others follow a slower decline in disease progression with limited progression of associated disability, yet some patients have periods of relative stability interspersed with periods of acute respiratory decline (Ley et al., 2011). Acute exacerbations of disease are reported in 5–15% of patients and lead to diffuse alveolar damage, and can progress to dramatic respiratory failure with a short-term mortality estimated at 50% (Collard et al., 2016). However there is currently no way of accurately predicting disease progression and determining prognosis. Consequently significant efforts are underway to try and understand the underlying pathways and genetics that might influence the clinical course of the disease in the hope that prognostic biomarkers of disease progression and new molecular targets to aid early diagnosis of the disease may be identified and ultimately enhance clinical success.

Being a rare disease, the ability to apply clinical prediction models used in many other indications to provide a more accurate prognosis and disease staging, is hampered due to small patient numbers. This impacts the feasibility to adequately power trials and to be able to validate endpoints and biomarkers for use in clinical trials ("Exploring clinical outcome assessments in rare diseases trials". Presented by Laurie B. Burke, FDA Rare Disease Workshop Series, June 14–15, 2011, L'Enfant Plaza Hotel, Washington, D.C.). The clinical, radiological and physiological (CRP) score was developed in IPF and was used to predict survival in the cohort from which it was derived (King et al., 2001), however this has not been further validated externally and takes into account parameters not routinely measured in clinical practice (King et al., 2001). In 2003, the composite physiologic index (CPI) was developed to help address the problem of co-existing emphysema and its impact on maintaining or artificially increasing the FVC. The CPI, which was derived against clinical/computed tomography and validated using split sample testing was reported as a more accurate prognostic determinant in UIP than an individual pulmonary function test (Wells et al., 2003). An abbreviated clinical model comprising of only four factors (age, respiratory hospitalisation, percent predicted FVC, and a 24-wk. change in FVC measurement) that predicted the overall risk of one-year mortality has been described (Du Bois et al., 2011), which may determine prognosis and guide clinical management. The GAP index, based on gender (G), age (A), and two lung physiology variables (P; FVC and DLCO) is also described and used in clinical practice to predict mortality (Ley et al., 2012). The highest stage of GAP (stage III), has been associated with a 39% risk of mortality at one-year, and a modified ILD-GAP Index has been developed and applied across ILD subtypes to provide survival estimates (Ryerson et al., 2014). Image based diagnosis may help to identify defined study populations (Raghu, Rochwerg et al., 2015). However, this lack of consistency in clinical trial endpoints and heterogeneity in outcome measures applied across clinical trials, again limits the feasibility to assess their validity. For example mortality, often used as a secondary endpoint, has been measured as all-causes mortality, IPF-specific mortality, time to death, progression free survival, or survival time, limiting the ability to validate this outcome (Raghu et al., 2012; Fregonese & Eichler, 2015).

The exact mechanisms involved in the initiation and progression of lung fibrosis are largely unknown, however significant advances have been made in recent years due to a dramatic increase in research efforts in this field. Evidence suggests that inflammation is not a prominent histopathological finding in UIP and that inflammation is not required for the development of fibrosis, as evidenced in in vivo models of fibrosis. Clinically, measures of inflammation have failed to correlate with disease stage or clinical outcome and when trialled, non-specific anti-inflammatories have not demonstrated significant clinical efficacy (Mapel et al., 1996; Idiopathic Pulmonary Fibrosis Clinical Research Network et al., 2012). The current paradigm for the fibrotic process in IPF is often defined as an aberrant wound healing response, involving dysregulated tissue repair and remodelling. The alveolar epithelium is subjected to wounding over an unknown prolonged period of time, leading to the activation of pro-fibrotic signalling pathways and elevation of pro-fibrotic cytokines (Myers & Katzenstein, 1988; Kuhn et al., 1989; Maher et al., 2007). This process leads to the migration and proliferation of fibroblasts, differentiation into myofibroblasts and production of extracellular matrix (ECM) (Maher et al., 2007; Sakai & Tager, 2013; Darby et al., 2014). Several origins of these fibroblasts have been proposed, including mesenchymal progenitor cells (Xia et al.,

Table 1
Main recent randomised negative clinical trials.

Agent	Number of patients included	Mean duration of treatment	Main result
Interferon	821	64 weeks	No effect (PMID 19570573)
Bosentan	616	12 months	No effect (PMID 21474646)
Macitentan	178	14.5 months	No effect (PMID 23682110)
Ambrisentan	492	34.7 weeks	Increased risk of disease progression (PMID 23648946)
Sildenafil	180	12 weeks	May benefit if right ventricular dysfunction (PMID 20484178; 23732584)
Warfarin	145	48 weeks	Increased risk of mortality (PMID 23634866)
Azathioprine	155	32 weeks	Increased risk of mortality (PMID 22607134)
Prednisone			
N-acetylcysteine			
N-acetylcysteine	264	60 weeks	No effect (PMID 24836309)
Etanercept	88	48 weeks	No effect (PMID 18669816)
Everolimus	89	180 days	Increased risk of disease progression (PMID 21362103)
Imatinib	119	80 weeks	No effect (PMID 20007927)
Co-trimoxazole	161	12 months	No effect in intention-to-treat analysis (PMID 23143842).
Carlumab (anti-CCL2)	126	52 weeks	Greater decline of FVC compared to placebo (PMID 26493793)