Practical Issues and Challenges in Idiopathic Pulmonary Fibrosis

Vincent Cottin^a Philippe Camus^b

^aHospices Civils de Lyon, Hôpital Louis Pradel, Service de Pneumologie – Centre de référence national des maladies pulmonaires rares, Université Claude Bernard Lyon 1, Université de Lyon, Lyon, et ^bCentre Hospitalier Universitaire de Dijon et Université de Bourgogne, Dijon, France

Idiopathic pulmonary fibrosis (IPF) is a devastating disease, with a median survival from diagnosis of only 3 years [1]. Although it is a rare and somewhat orphan disease [2], its incidence, prevalence and specific mortality are rising [3–6], further increasing the many challenges faced by both patients and chest physicians. Recent evidence-based recommendations have been produced jointly by the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Association, establishing standards for the diagnosis and management of IPF. Standardization of diagnosis criteria originally published in 2000 [7] and updated in 2011 [8] has set the stage for drug development, and one first drug (pirfenidone) has been approved in a number of countries, representing a significant achievement in the fight against IPF. However, IPF remains a diagnostic and therapeutic challenge [9–11], with often more questions raised than answers provided. Clinicians also face a number of practical situations and decisions that are not fully addressed by international guidelines [9, 12].

This issue of *Respiration* includes the first article of a thematic review series on *Practical issues and challenges in IPF* (table 1). This timely series authored by IPF experts will address selected practical issues, reviewing progress

made in recent years and established evidence, suggesting elements of discussion in areas where evidence is still lacking and reviewing challenges that remain. In this issue, Poletti et al. [13] review the current diagnostic approach of IPF and further discuss the heterogeneity of the disease that encompasses various clinical presentations, complications, comorbidities and phenotypes, especially regarding familial pulmonary fibrosis, rapidly progressing disease and subclinical ‘early’ IPF, with each of them raising specific challenges for clinicians. They further critically review elements on which to discuss the indication for lung biopsy, the potential future role for cryobiopsies (a novel endoscopic technique that is currently under evaluation for diagnosing the usual interstitial pneumonia pattern), evaluation of individual prognosis in clinical practice, and the controversial issue of *possible* IPF and its practical management.

In the next article of the series, Antoniou and Wells [in preparation] will review the current knowledge on acute exacerbations of IPF, a dreadful complication, which warrants active biologic and clinical research [14–19]. Hypotheses for etiology, a proposed approach for appropriate diagnosis and suggested management will be reviewed, as well as recently identified potential triggers such as viral infection, surgery, microaspiration, expo-

Table 1. Thematic review series on idiopathic pulmonary hypertension

Idiopathic pulmonary fibrosis: diagnosis and prognostic evaluation (Venerino Poletti, Forli, Italy)
Acute exacerbation of idiopathic pulmonary fibrosis (Athol Wells, London, UK, and Katerina Antoniou, Heraklion, Greece)
Idiopathic pulmonary fibrosis: from epithelial injury to disease monitoring – insights from the benchside (Bruno Crestani, Paris, France, and Martin Kolb, Hamilton, Ont., Canada)
Pulmonary hypertension in idiopathic pulmonary fibrosis (Vincent Cottin, Lyon, France)
Idiopathic pulmonary fibrosis: recent trials and current drug therapy (Luca Richeldi, Modena, Italy)
Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis (Jürgen Behr, Munich, Germany)
When pulmonary fibrosis is not idiopathic (Philippe Camus and Philippe Bonniaud, Dijon, France)

sure to peak air pollution, aerocontaminants and drugs. Crestani and Kolb [in preparation] will review the current understanding of IPF pathogenesis [20–22], with a particular focus on the mesenchymal-epithelial interplay, circulating stem cells [23] and immune dysregulation. In one of the next articles, Camus and Bonniaud [in preparation] will review the differential diagnosis of IPF, with the critical quest for identifiable causes of pulmonary fibrosis (e.g. drugs, occupational exposure and chronic hypersensitivity pneumonitis), the challenge of differentiating IPF from other chronic fibrotic lung diseases, especially nonspecific interstitial pneumonia, and the boundaries between IPF and connective tissue diseases, especially undifferentiated ones [24]. There is mounting evidence that pulmonary hypertension is frequent in patients with IPF [25], which is possibly related to common pathogenesis pathways between IPF and pulmonary hypertension, portending a poor outcome [26, 27], a topic that will be reviewed in the series as well [Cottin, in preparation]. Further, pulmonary hypertension may represent a potential target for therapy in IPF [28], warranting dedicated randomized clinical trials [29] with the hope of improving outcome through specific management of IPF-related pulmonary hypertension.

Two further articles by Richeldi et al. [in preparation] and by Behr et al. [in preparation] will focus on drug therapy and pulmonary rehabilitation in the management of IPF, respectively. Recent years have indeed witnessed an

increasing number of clinical trials in IPF [30, 31], and available data synthesized in international guidelines and Cochrane reviews need updating and critical review [10]. Among those, four key clinical trials supported the efficacy and tolerability of pirfenidone [32–35], which has been approved for the treatment of IPF in several areas of the world, including Japan, Europe and Canada, with a further phase III trial being currently conducted in North America. Richeldi et al. will review the place of drug therapy in the management of IPF and discuss key issues regarding the management of case scenarios corresponding to ‘probable’ or ‘possible’ IPF according to current guidelines [8, 9]. In addition, a number of promising drugs are currently evaluated in patients with IPF, including the triple tyrosine kinase inhibitor nintedanib [36], GS-6624 (an inhibitor of lysyl oxidase-like molecule-2), the antioxidant N-acetylcysteine, XAQ-576 (an anti-interleukin-13 monoclonal antibody), FG-3019 (a monoclonal antibody against connective tissue growth factor), STX-100 (a monoclonal antibody specific for anti- $\alpha_v\beta_6$ -integrin), BMS-986202 (a lysophosphatidic acid-1 receptor antagonist), IW001 (a type-V collagen inhibitor), PRM-151 (human pentraxin) and many others (www.clinicaltrials.gov). Results from at least three ongoing phase III IPF trials will be released in 2014, demonstrating the accelerating pace of clinical research in the field of IPF, with evolving views regarding which end-points are appropriate, feasible and clinically meaningful [37–40]. In the absence of a curative treatment for IPF, a realistic goal is to reduce the rate or pace of disease progression. Apart from drug therapy, active research is also ongoing to evaluate the place of pulmonary rehabilitation to improve patients’ symptoms, exercise capacity and quality of life [41].

Although most hot topics in IPF will be reviewed in this series, some other important aspects can be found elsewhere, including the development of biomarkers [42, 43], the impact of comorbidities including emphysema (syndrome of combined pulmonary fibrosis and emphysema) [44], gastroesophageal reflux [45, 46], lung cancer [47], sleep apnea, cardiovascular disease and diabetes mellitus [48], the increasing role of genetics in the pathogenesis and management of IPF [49, 50], comprehensive management and supportive care [51, 52], or possible approaches for earlier diagnosis and treatment [53]. We hope readers will enjoy this series on IPF, and that it will translate into better care for IPF patients.

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