IPF – Current Treatment and Future Targets

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Idiopathic pulmonary fibrosis is the most common and deadly of the "idiopathic" interstitial lung diseases. It is estimated that in the UK alone, IPF is responsible for 5,000 deaths per year, with a mortality rate greater than that of many common cancers (1). Despite a median survival of only 3 years from diagnosis, there is a wide variability in disease course in IPF (2). Some patients will have relatively prolonged periods of stability or only a gradual progression of disease, whereas others will have extremely rapid disease progression, leading to death in less than a year, and others still will experience acute exacerbations, periods of catastrophic worsening in their lung disease over only a few weeks, whose frequency increases with worsening disease severity.

Over the past decade, there have been a number of trials yielding negative or uncertain results, such that, until recently, IPF was an untreatable disease. The recent results of phase 3 trials on two anti-fibrotic drugs, pirfenidone and Nintedanib, respectively (3,4), have represented a major breakthrough for patients with IPF. They show that treatment with pirfenidone or nintedanib is associated with a reduction in FVC decline by roughly 50%, and the FDA has approved the use of both in IPF. The magnitude of effect is remarkably similar between the two drugs. However, neither halts disease progression, and ultimately the only treatment unequivocally linked to improved survival remains lung transplant. A number of targets are being investigated in ongoing trials, and there is now the challenge of future design of drug trials. The new drugs will be compared with pirfenidone or Nintedanib, but this will mean smaller longitudinal reductions in FVC, the currently most used primary endopoint. Combined endpoints are likely to be needed to increase the power of future trials in IPF.

Overall, although IPF is the most common of the idiopathic interstitial pneumonias, it represents only a subpopulation of patients with progressive fibrotic lung disease, with similar proportions being taken up by patients with CTD-ILD and sarcoidosis/hypersensitivity pneumonitis (5). Furthermore, there is substantial overlap between some ILD entities and IPF, particularly with subgroups of patients with fibrotic hypersensitivity pneumonitis, rheumatoid arthritis associated UIP, and undifferentiated connective tissue disease. Patients in these subgroups can experience relentlessly progressive fibrosis with absent or insufficient response to immunosuppressive treatment, and behave similarly to IPF. It is therefore likely that shared pathogenic mechanisms exist across a range of progressive fibrotic lung diseases. It is also increasingly recognised that at least 10-20% of ILDs cannot be classified with current criteria (5), either because a surgical biopsy is not possible or because even with histology it is not possible to reach a definitive conclusion.

In terms of clinical management of the individual patient, differentiating between relentlessly progressive lung disease such as IPF on the one hand, and ILDs where progression of fibrosis is driven by immune overactivity, such as connective tissue disease-associated ILD (CTD-ILD) on the other, has never been so important. In IPF, immunosuppressive therapy is not only ineffective, but associated with an increased risk of death and hospitalization, as demonstrated by the PANTHER-IPF clinical trial, a randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of a three-drug immunosuppressive regimen of oral prednisone, azathioprine and N-acetylcysteine in patients with IPF (6). By contrast, in many non IPF-ILDs, immunosuppression remains the mainstay of treatment, mostly studied in CTD-ILDs, but also used in hypersensitivity pneumonitis (HP), fibrotic sarcoidosis and others, with stabilisation of disease in the face of previous progression a realistic aim. This has been shown by the only two prospective placebo controlled trials in CTD-ILD, both in SSc-ILD (7,8), but also a series of retrospective studies including a large review of MMF in CTD-ILD overall (9) and case series/clinical experience in non CTD-ILD.

However, there is a subgroup of patients with non-IPF fibrotic ILD that continues to progress despite aggressive/intensive immunosuppression, behaving in an “IPF-like” fashion. There is also the relatively large group with “unclassifiable ILD”, who tend to have the second worse prognosis among ILD patterns, after IPF patients (5). Although there are multiple prognostic scoring systems (10,2), better markers are needed to allow us to identify key pathogenetic molecular pathways involved, and predict likelihood of response to anti-fibrotic versus immunosuppressive treatments, identify new treatment targets, and overall behaviour of the disease in the individual patient.

Much of the progress made in the understanding of pathogenesis of pulmonary fibrosis over the past ten years has come from the application of molecular biology to large populations of patients with pulmonary fibrosis (11). Genome wide association studies in families and in sporadic IPF have identified a number of significantly linked loci, with links to genes involved in cell senescence, innate immunity and epithelial adhesion. Among these, the MUC5B promoter variant is the strongest genetic factor identified so far for IPF (12-15). Interestingly, a striking similarity across different loci has been observed between sporadic and familial IPF, suggesting the genetic background is much more similar than previously thought (16). With regards to the highly significant association with the *MUC5B* gene, as the mucin it encodes is mainly expressed in the distal airways and honeycomb cysts of IPF biopsies, this association has highlighted a potential pathogenetic role of the bronchiolar epithelium, as initially proposed by Chilosi et al (17). Interestingly, while the *MUC5B* promoter variant is associated with the risk of developing IPF, it is associated with slower progression and better survival (14, 18), suggesting that it marks a subset of the disease, with potentially different response to treatment, and possible differences in pathogenesis. Disease subsets are also suggested by a recent whole-genome expression analysis in a large number of IPF biopsies (19), identifying two clear IPF subpopulations, based on a distinct molecular signature. One IPF group was characterized by upregulation of a large number of transcripts associated with cilium genes together with MUC5B and MMP7 over expression. Another study by DePianto et al investigating genome-wide transcriptomic analysis of lung biopsy tissue from IPF patients, and also peripheral blood markers, has identified clusters of bronchiolar related genes overexpressed in conjunction with lymphoid related genes such as CXCL3, also suggesting from a molecular perspective that IPF may in fact consist of more than one disease (20). Interestingly, the MUC5B genotype association is not seen in SSc-ILD or sarcoidosis related pulmonary fibrosis, suggesting a specificity of the pathway involved to idiopathic disease (14, 21).

Genetic factors may also affect response to treatment in IPF. A recent genome wide association study (GWAS) has reported the association between variants in the TOLLIP gene, encoding for a protein involved in modulating Toll-like receptors, and pulmonary fibrosis, implicating innate immunity processes in IPF pathogenesis (15). A variant within the *TOLLIP* gene was linked with a differential response to N-Acetylcysteine treatment in a retrospective analysis of subjects in the PANTHER trial. While NAC treatment was associated with a significant reduction in a composite endpoint (defined as death, transplant, hospitalization or ≥10% FVC decline) in patients with a rs3750920 TT genotype, a trend towards an increase in endpoint risk was seen in patients with a CC genotype (22). Although retrospective in design, this study is the first to suggest that response to treatment may differ according to genotype in patients with IPF, and strongly supports the need to stratify for all known key genetic risk variants in future IPF trials.

IPF is likely to result from the complex interaction of genes and environmental exposures. Epigenetic processes, defined as heritable modifications to gene expression which do not involve changes to the DNA sequence, are influenced by a number of factors, including age, environmental exposures and genetic variants. Epigenetic changes regulate transcription and include DNA methylation, histone acetylation/de-acetylation, and non-coding RNAs (23). Two highly significant risk factors for IPF, age and cigarette smoking, are themselves strongly associated with marked epigenetic changes (24).

Although the study of epigenetic regulation in IPF is relatively recent, analysis in lung tissue globally as well as cell specific gene expression regulation through methylation, acetylation, and regulatory microRNAs is providing crucial information on regulatory networks and potential therapeutic targets (reviewed in Helling and Yang) (25). For example, microRNAs each regulate large numbers of genes, and modulation of a single miRNA therefore allows regulation of multiple genes. Consistently downregulated miRNAs include miR-29 and let7-d, miRNAs that have a physiological anti-fibrotic role thorugh silencing of a number of profibrotic target genes (25). The downregulation of miR-29 induces a coordinate increase of many extracellular matrix genes in fibroblasts. Micro-RNA therapeutics are rapidly gaining momentum. As an example, Mimics of miR-29 are currently being considered as treatment of pulmonary fibrosis in the experimental setting (26).

In summary, one of the main challenges for the future will be the identification and use of molecular profiles to stratify patients with progressive fibrotic lung disease and identify genetic, epigenetic and protein markers to classify patients according to rate of progression and fundamental molecular pathways involved. It is clear that even in non IPF ILDs, phenotypes of relentlessly progressive disease exist, and molecular pathways may overlap. With the advent of anti-fibrotic treatments on the one hand, and the likelihood that targeted treatments may benefit some, but not all, patients with progressive lung fibrosis, molecular phenotyping is needed to allow a better classification of fibrotic lung diseases. Modern molecular tools are likely to be crucial in defining clusters of patients who share a specific molecular phenotype, therefore allowing better prognostication and institution of appropriate treatments.

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