**IDIOPATHIC PULMONARY FIBROSIS**

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**Summary**

Idiopathic pulmonary fibrosis (IPF) is the prototypic chronic progressive fibrotic lung disease. Healthy tissue is replaced by altered extracellular matrix and alveolar architecture destroyed, so leading to decreased lung compliance, disrupted gas-exchange, and ultimately respiratory failure and death. In less than a decade our understanding of the pathogenesis and management of this disease has been transformed, and two disease modifying therapies have now received worldwide approval. This Seminar summarises the presentation, pathophysiology, diagnosis, and treatment options now available to IPF patients. IPF has instructed our understanding of the mechanisms of lung fibrosis, and provides hope that similar approaches will transform our management of patients with other progressive fibrotic lung diseases.

**Epidemiology**

IPF is the most common of the idiopathic interstitial pneumonias. Whilst it has been considered to be a rare condition, it occurs with comparable frequency to that of stomach, brain, and testicular cancers.

1,2 Incidence has risen over time and is estimated to be between 2·8 and 18 cases per 100 000 persons per year in Europe and North America.2,3 Limited data are available on worldwide variation but incidence may be lower in Asia and South America where it is estimated to range from 0·5 to 4·2 per 100 000 per year.

IPF occurs more commonly in men and is rare in people less than 50 years of age (median age at diagnosis is about 65).4-6 While disease course is variable and somewhat unpredictable, the median survival from the time of diagnosis is thought to be 2 to 4 years.7

**Pathophysiology**

Historically IPF was considered a chronic inflammatory disorder, which gradually progressed to established fibrosis. However, at the turn of the century, following recognition that anti-inflammatory therapy did not improve outcome, this was reassessed, and subsequently an immunosuppressive therapeutic strategy incorporating prednisolone and azathioprine was demonstrated to actually increase mortality.8,9 It is now generally believed that IPF is a consequence of multiple interacting genetic and environmental risk factors, with repetitive local micro-injuries to an ageing alveolar epithelium playing a central role. This initiates aberrant epithelial-fibroblast communication, induction of matrix-producing myofibroblasts, and overwhelming extracellular matrix (ECM) accumulation and remodelling of lung interstitium **(Figure 1)**.

**Environmental exposures**

Particulate inhalation is implicated in IPF pathogenesis and progression. A history of cigarette smoking is associated with IPF development in the majority of patients.10 Multiple other environmental exposures have been associated with IPF including metal and wood dusts, agriculture and farming, viruses, and stone and silica.4,11,12

**Genetic factors**

There is increasing evidence of the role of genetic susceptibility in IPF development. Studies of familial interstitial pneumonia (FIP) (those cases affecting two or more members of the same biological family) have identified rare genetic variants including genes relating to surfactant dysfunction (*SFTPC*, *SFTPA2*) and telomere biology (*TERT*, *TERC*, *PARN*, *RTEL*).

4,13-19 Genome-wide association studies have identified common genetic variants which account for about one third of the risk of disease development.20-22 Whilst not demonstrating a direct causal link, these studies have identified the potential importance of alterations in host defence (*MUC5B*, *ATP11A*, *TOLLIP*), telomere maintenance (*TERT*, *TERC*, *OBFC1*) and epithelial barrier function (*DSP*, *DPP9*).

A common gain of function variant in the gene *MUC5B* promoter region is the risk variant with the largest genetic effect on development of both familial and sporadic IPF (odds ratio 4 to 8 per allele).20,21,23-27 The *MUC5B* variant has low penetrance and in isolation does not appear causative of IPF. *MUC5B* encodes a mucin-5B precursor protein that contributes to airway mucous production and may have an important lung host defense role.28,29 The site of altered *MUC5B* production has been localised to bronchiolar epithelium where it is proposed increased protein levels may either enhance injury due to reduced mucociliary clearance or impede normal lung repair.22,30

Intriguingly, IPF patients with the *MUC5B* gain of function variant may have a higher rate of survival.31 This finding requires external validation although in UK patients with IPF this variant was associated with a slower decline in lung function.26

**A maladaptive repair process**

Identification of pathologic mechanisms of fibrogenesis in IPF has been extremely challenging, however chronic dysregulation of Type 2 alveolar epithelial cells (AEC2s) is thought to be central. AEC2s are stem cells within the lung which contribute to renewal of Type 1 alveolar epithelial cells (AEC1s) during homeostasis or following lung injury.32,33 Loss of AEC1s and abnormal AEC2s are identified in IPF tissue, with fibroblastic foci typically located adjacent to hyperplastic or apoptotic AEC.8 In IPF tissue there is premature shortening of AEC2 telomeres, and within a mouse model shortening of AEC2 telomeres leads to lung remodelling and fibrosis.

34-36 Recent work has identified that AEC2s from IPF tissue have impaired renewal capacity, consistent with AEC2 stem cell failure.

37 Abnormal behaviour of AECs is associated with epithelial recapitulation of developmental pathways including Wnt/β-catenin and Sonic hedgehog pathways.38,39 Activated AECs secrete numerous fibrogenic growth factors and cytokines including transforming growth factor β (TGF-β) and platelet derived growth factor, with aberrant epithelial mesenchymal cross-talk driving recruitment and activation of highly synthetic and contractile myofibroblasts.

40 These activated myofibroblasts deposit increased and altered ECM components, destroying normal alveolar architecture and disrupting gas-exchange. Multiple sources of myofibroblasts are proposed including resident mesenchymal cell proliferation, lung interstitium pericytes, circulating fibrocytes, epithelial mesenchymal transition (EMT), and endothelial mesenchymal transition (EndMT).33,41

Progression from a normal to an abnormal ECM in IPF is poorly understood, although there is evidence that abnormal ECM deposition contributes to disease pathogenesis.42,43 Changes in ECM composition significantly alter cell behaviour, and a positive feedback loop between fibroblasts and aberrant ECM promotes fibrosis.44 Both altered ECM composition and stiffness may contribute to this process. The precise mechanisms by which matrix stiffness is transduced by fibroblasts remains unclear, but integrins, the predominant receptors for cell adhesion to ECM proteins, have a central role, with mechanosensitive protein-protein interactions occurring within adhesion complexes.

45,46 Downstream of this cell force-mediated activation of latent TGF-β , and intrinsic mechanotransduction via the Rho/Rho kinase pathway promotes myofibroblast differentation.47-49

In parallel with abnormal ECM production is the observation of aberrant lung remodelling with ‘bronchiolisation’ of alveolar tissue. At sites of damaged alveolar epithelium a regenerative response associated with developmental pathway activation occurs.

50 Abnormal activation of airway basal cells (which reside in the conducting airways down to the respiratory bronchioles and function as stem cells) is identified and may contribute to re-epithelisation of damaged alveolar epithelium and resulting ‘bronchiolisation’ of alveolar spaces.

51-54 In a subset of patients with IPF, higher cilium gene expression was associated with increased microscopic honeycombing although whether the bronchiolar abnormalities arise from *de novo* bronchiolisation or from adjacent normal bronchiolar structures remains uncertain.55

**Clinical presentations, signs, & symptoms**

Patients typically present with non-specific symptoms of exertional dyspnoea with or without dry cough **(Figure 2)**. This may initially be attributed to aging, deconditioning, or other comorbidities (e.g. smoking history, emphysema, cardiovascular disease, obesity), and so clinical suspicion of IPF by primary care physicians is required to limit diagnostic delays. Occasionally, patients will present acutely, with days to weeks of respiratory worsening, often accompanied by fever and flu-like symptoms. These acute exacerbations are discussed below and require careful diagnostic distinction from other forms of acute interstitial lung disease.

On physical examination, fine, high-pitched bibasilar inspiratory crackles are generally heard **(Audio 1)** and in approximately 30% of patients digital clubbing is present.56 Careful attention to signs of connective tissue disease is essential in ruling out connective tissue disease-associated disease. In established disease, pulmonary function tests identify restrictive disease (reduced total lung capacity) and abnormal gas exchange (reduced diffusing capacity for carbon monoxide).4 Early disease (or disease coexisting with emphysema which pseudo-normalizes volumes) may demonstrate normal spirometry and plethysmography, with only an isolated reduction in diffusion.

**Diagnosis**

IPF is diagnosed by identification of a pattern of usual interstitial pneumonia (UIP) on radiological or histological criteria in patients without evidence of an alternative aetiology.4,57,58 This approach is endorsed in consensus guidelines worldwide and has helped to standardise IPF diagnosis. A major challenge to clinicians is exclusion of other forms of idiopathic interstitial pneumonias and of known causes of interstitial lung disease such as domestic and occupational exposures, connective tissue disease, and drug toxicity. This is of particular importance as the UIP pattern is not exclusive of IPF and may also be associated with other conditions, including chronic hypersensitivity pneumonitis, asbestosis, connective tissue diseases, and drug toxicity. Many patients have histories of environmental exposures, medications, and symptoms that require clinicians to make judgements regarding aetiological significance.

Chest high-resolution computed tomography (HRCT) enables detailed evaluation of lung parenchyma and has revolutionized evaluation of suspected IPF. Reticular opacities, associated with traction bronchiectasis and clusters of subpleural, cystic airspaces of comparable diameters (typically 3-10 mm in diameter) with well-defined walls (often called honeycombing), in a predominantly bilateral, peripheral and basal distribution are typical of the UIP pattern **(Figure 3, and online Movie)**, while features such as mosaic attenuation, ground glass abnormality, and nodules suggest an alternative diagnosis.4,59-61 Patients with reticular abnormality in a subpleural, basal predominance but without honeycombing are considered to have a “possible” UIP pattern.

Where HRCT features are non-diagnostic, surgical lung biopsy (SLB) is advised. In-hospital mortality after elective biopsy in patients under the age of 65 and with limited co-morbidities is less than 2% but every patient still requires careful consideration as to whether SLB risks outweigh the potential diagnostic information.62 In older patients, those with co-morbidities (Updated Charlson score >1), significant physiological impairment, or for non-elective procedures, the risk is greater and SLB should generally be avoided. When considering undertaking SLB the pre-test probability of a subsequent histopathological UIP diagnosis in patients with possible UIP on HRCT is increased with older age, male sex, and the presence of traction bronchiectasis.63,64

On histopathology, the UIP pattern is characterised by interstitial fibrosis showing spatial heterogeneity with patchy involvement of lung parenchyma, areas of marked fibrosis, architectural distortion and microscopic honeycombing (cystic airspaces lined by bronchiolar epithelium and typically filled by mucin) **(Figure 3)**.4 At the interface between fibrotic and normal appearing lung tissue are aggregates of proliferating fibroblasts and myofibroblasts within a myxoid appearing matrix termed fibroblast foci. Fibroblast foci are a key histopathological feature of UIP pattern, believed to represent areas of active disease, and their absence excludes a definite histopathological UIP diagnosis. While in 2D they have been considered small, distinct lesions, it has been identified that in 3D they form heterogeneous structures with large variations in shape and volume.65,66

Clinical features, imaging, and histopathology may all play important roles in diagnosing IPF. A patient may receive an IPF diagnosis with varying degrees of diagnostic certainty. A dynamic multidisciplinary discussion between physicians, radiologists, and pathologists experienced in diagnosis of interstitial lung disease is recommended as this increases diagnostic agreement and so is considered the diagnostic“gold standard” although a small minority of patients remain unclassifiable.67,68

Accurate prognostication is difficult as the natural history of IPF appears highly variable. Some patients progress rapidly, others quite slowly, and others experience sudden worsening after periods of stability.4 Shortened survival time is associated with factors including older age, severe physiologic impairment, lower body mass index, greater radiologic disease extent, and presence of pulmonary hypertension, emphysema, and bronchogenic cancer.7

To predict individual patient prognosis, risk models incorporating demographic, clinical, and physiological parameters have been developed including the du Bois model and the gender, age, physiology (GAP) index.69-71 The GAP index incorporates gender, age, and lung physiology variables to identify three disease stages with a 1-year mortality risk of 6%, 16%, and 39% respectively.70 The calculation of such an index at diagnosis may aid the clinician to refine prognosis, help to guide management decisions such as lung transplantation timing, and allow appropriate life planning.

**Clinical genetic testing**

In those with a family history of interstitial lung disease suggestive of FIP, genetic testing may be appropriate following counselling as it can aid disease course prognostication and lung transplant risk stratification. FIP transmission is thought to be autosomal dominant with reduced penetrance, however disease penetrance of individual disease-associated genes remains unclear and so family member risk may be difficult to quantify.

72,73

Genetic testing in sporadic IPF is not recommended unless a personal or family history of extrapulmonary features associated with a telomeropathy such as aplastic anaemia, cryptogenic cirrhosis, or premature greying is identified.74 If present, clinical peripheral blood mononuclear cell telomere length testing may be considered , and if very short (<10% for age), investigation for telomerase-related gene mutations performed.73

**Clinical management**

Prompt referral of patients with known or suspected IPF to a centre with expertise in IPF care is advised, as delayed access is independently associated with increased risk of death.75 This provides access to expertise in diagnosis and management including disease modifying therapy initiation, monitoring, side effect control and non-pharmacological support **(Figure 4).**4,76 In addition to IPF focussed management, a number of co-morbidities commonly associated with IPF may be present including emphysema, pulmonary hypertension, gastro-oesophageal reflux disease (GORD), and obstructive sleep apnoea.77-80

**Disease modifying therapy**

Standardisation of IPF diagnostic criteria has enabled large, multi-centre, randomised, placebo-controlled trials (RCTs) of proposed disease modifying agents. RCTs identified that a number of putative therapies (e.g. prednisolone and azathioprine, acetylcysteine, warfarin) were ineffective or harmful; a landmark contribution to IPF patient care **(Figure 5)**.9,81 Also through these RCTs, two large phase 3 development programs identified the first effective disease modifying therapies for IPF, nintedanib and pirfenidone. Both drugs are now approved worldwide for IPF treatment, forever transforming patient management.82,83

Nintedanib is a tyrosine kinase inhibitor that suppresses multiple signalling receptors implicated in fibrosis pathogenesis including fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR).84,85 A phase 2 study identified a dose-dependent trend toward reduced lung function decline and reduction in acute exacerbation incidence.86 Two subsequent phase 3 trials were performed comparing nintedanib with placebo.82 Inclusion required a forced vital capacity (FVC) of greater than or equal to 50% of predicted and a diffusing capacity of the lung for carbon monoxide (DLCO) of between 30% and 79% predicted. Over 52 weeks, relative decline in FVC was significantly less in the active treatment arm in both trials (47·9% and 55·1%) when compared to placebo.82 In one of the two trials a significant difference in time to first acute exacerbation identified, and a pre-specified sensitivity analysis based on pooled data of confirmed or suspected acute exacerbations adjudicated centrally blinded to treatment arm identified a benefit of nintedanib (hazard ratio, 0.32, 95% confidence interval 0.16-0.65, p=0.001). Post hoc analyses segregating patients by age, smoking history, and FVC identified a consistent effect of nintedanib across subgroups.87

Pirfenidone is an orally administered pyridine with combined anti-inflammatory, anti-oxidant, and anti-fibrotic actions, although the precise mechanism of action is unknown.88,89 Regulation of TGF-β *in vitro*, and inhibition of fibroblast and collagen synthesis in animal models of lung fibrosis has been demonstrated. There have been four phase 3 trials of pirfenidone performed over the last decade. The first study demonstrated a significant reduction of 56·3% in relative decline in vital capacity (VC) in patients treated with pirfenidone.90 Two subsequent phase 3 trials then compared pirfenidone with placebo over 72 weeks.91 The effect of pirfenidone on FVC decline was discordant in these two trials, with one trial confirming the initial phase 3 results and the other demonstrating no significant difference. The fourth and final phase 3 study was conducted over 52 weeks in patients with an FVC between 50 to 90% predicted and a DLCO of between 30% and 90% predicted.83 As compared with the placebo group, the relative decline in FVC was significantly less in the active treatment arm (54·9%). Pooled analyses of 1247 patients from phase 3 trials have identified fewer deaths in the pirfenidone arms compared with placebo arms (hazard ratio, 0.52; 95% confidence interval 0.31 to 0.87, p=0.01) and that fewer patients experience a decrement in 6 minute walk distance. 83,92

The impact of nintedanib and pirfenidone on rate of FVC decline over one year appears similar **(Figure 5)**.82,83,91 Neither drug has prospectively demonstrated a survival benefit in these trials, although both show a trend in favour of reduction in mortality. It is therefore the safety profile and tolerability that will influence patient and provider choice. The drugs have good safety profiles within clinical trials, with acceptable tolerability in most patients although approximately 1/5 of patients may discontinue treatment as a consequence of side effects or disease progression. For both drugs, the primary safety concern is transaminitis, and both require regular monitoring for liver function. Pirfenidone may cause gastrointestinal (dyspepsia and anorexia) and dermatological (photosensitivity) side effects.93 Nintedanib may cause gastrointestinal (diarrhoea and nausea) side effects.94 Treatment with nintedanib in combination with full dose anticoagulants or in those who have had a major bleeding event should be considered if the anticipated benefit outweighs the potential risk, given a theoretical increased bleeding risk from the anti-VEGFR activity of the drug.95 Side effects are minimized with food, and in the case of nintedanib with the use of loperamide. Persistent side effects are typically responsive to temporary dose reduction or cessation.

As a chronic, invariably progressive disease we believe it is essential the majority of patients begin therapy with one of these two drugs at time of diagnosis, with exceptions for severe and, perhaps, asymptomatic disease. This is based on the belief that the earlier irreversible destruction of lung can be slowed, the more potential benefit there is to patients. Balancing the known effects on disease progression against the safety and tolerability profile in individual patients is critically important in determining the value of continued treatment.

**Lung Transplantation**

In selected patients with IPF, lung transplantation may improve quality of life and prolong survival, with a 5yr survival rate post transplantation of approximately 50%.4,96 However, only a minority of patients receive this intervention due to the medical complexity of the surgery and post-surgical treatment, and limited supply of donor organs. Given the heterogeneity of IPF disease course the optimum timing of referral for lung transplantation evaluation is unclear, but many patients are referred too late in their disease course. We believe the topic should be discussed with individual patients early in their disease course and referral for evaluation should be made if there is objective evidence of disease progression.

**Acute respiratory deterioration**

Patients with IPF may experience acute respiratory deteriorations, with development of new or worsening dyspnoea and increased oxygen requirements. These events are highly significant, with median survival of only 3-4 months post-event. Acute respiratory deterioration can occur from a number of known causes (e.g. infection); when idiopathic they are commonly referred to as acute exacerbations of IPF.97 Acute exacerbation of IPF is thought to occur in approximately 5-15% of patients with IPF per year and is more common in patients with physiologically and functionally advanced disease.98 By definition, acute exacerbation is characterized by new bilateral diffuse ground-glass opacities and/or consolidation on HRCT scan **(Figure 6)**. Whilst surgical lung biopsy should generally not be considered due to high non-elective morbidity rates, histologically diffuse alveolar damage is superimposed upon a UIP pattern.62,99 A recent working group report on acute exacerbation has suggested broadening the definition to include any acute respiratory deterioration with new widespread alveolar abnormality on chest HRCT not fully explained by cardiac failure or fluid overload.98

In patients undergoing acute respiratory deterioration, a priority is to identify any potentially treatable causes. Extraparenchymal causes such as pulmonary embolism, pneumothorax, and pleural effusion should be excluded. If safe to perform, CT angiography with HRCT cuts is the diagnostic test of choice. Infection should be suspected in consistent clinical cases and managed appropriately. In cases of acute exacerbation, high-dose glucocorticoids are conditionally recommended by international guidelines, however there are no controlled trial data demonstrating efficacy or safety.4,100 Guidelines make a conditional recommendation against mechanical ventilation in acute exacerbation, but this may be appropriate in selected cases such as the bridging of a patient to lung transplantation.

**Symptom-focused therapy**

Adjunctive symptom-based management is important given the high symptom burden of IPF including dyspnoea and cough.101 In patients with chronic cough possible contributing comorbidities including GORD should be considered. Opiates may reduce anxiety, dyspnoea, and cough.102 There is limited evidence suggesting corticosteroids may be effective in the treatment of chronic cough.103

Symptoms are often refractory to standard pharmacological intervention. Pulmonary rehabilitation improves dyspnoea and quality of life, and may improve function status.

104-106 Education programmes, and patient support groups may help to minimise the impact of dyspnoea upon activities of daily living and to reduce the psychological burden of IPF. Supplemental oxygen therapy should be considered to treat hypoxemia. With advancing disease, the involvement of palliative care physicians and end-of life planning should be discussed in the outpatient setting.

**Controversies & Uncertainties**

**Diagnosing IPF**

Approval of disease modifying therapies for IPF has increased the focus on early and accurate diagnosis with the aim of improving long term treatment outcome. Currently, the diagnostic certainty of IPF is based upon the presence or absence of specific morphological criteria; the approval of safe and effective therapies provides a timely opportunity to review this approach as only patients with IPF may receive these therapies.4

There is significant interest in broadening the radiological diagnostic criteria of IPF. Currently the presence of honeycomb lung destruction is required for a definite radiological diagnosis of IPF. While this criterion was applied in pirfenidone trials, it was not in nintedanib trials, where IPF was diagnosed radiologically if either honeycomb lung destruction or traction bronchiectasis and a reticular abnormality consistent with fibrosis were present in a basal and peripheral predominance.82,83 Post hoc subgroup analysis of these patients identifies the rate of decline in FVC to be identical in both groups.107

Multidisciplinary team (MDT) discussion was endorsed by guidelines as the “gold standard” for IPF diagnosis following the identification that there may be substantial differences in the diagnosis reached by individuals working in isolation compared to a dynamic face-to-face interaction between clinicians, radiologists, and pathologists where inter-observer agreement and diagnostic confidence is increased.67 More recent work has identified that agreement between MDTs in academic institutions is good for a diagnosis of IPF, with MDTs making the diagnosis of IPF with higher confidence and more frequently than clinicians or radiologists independently.108,109 However, there remains limited evidence for how the MDT approach is implemented in routine clinical care, and whether this impacts upon diagnostic accuracy and treatment decisions. To standardise individual patient diagnosis increased understanding of this process is required.

HRCT interpretation has become increasingly important in the diagnosis of IPF and only a minority of patients now undergo surgical lung biopsy. Transbronchial lung cryobiopsy using a flexible bronchoscope is an alternative method for sampling lung parenchyma proposed to have lower complication and mortality rates, although large multicentre prospective studies are required to confirm safety and diagnostic accuracy in IPF before introducing it in clinical practice.110,111

**Using modifying therapies in patients outside of clinical trial criteria**

The phase 3 studies of nintedanib and pirfenidone were designed to select a relatively homogenous population of patients considered to have mild to moderate IPF. Patients with severe functional impairment (FVC less than 50% predicted or DLCO less than 30% predicted) or major co-morbidities such as severe pulmonary hypertension were excluded. In many countries use of nintedanib or pirfenidone is limited by drug regulatory agency approval and reimbursement rules. Both drugs received regulatory approval in the USA without any severity threshold.112 While it is possible that the tolerability of disease modifying therapy in patients with more severe physiological impairment will be reduced, in post hoc analyses of phase 3 clinical trials there is no evidence to suggest that therapeutic efficacy varies with disease severity, and so informed discussion with individual patients outside of clinical trial criteria would seem reasonable before commencing treatment. 87,113

**Identification and management of non-responding patients**

Lung function will decline in patients with IPF despite treatment, however clinical assessment for disease progression and therapeutic response is extremely challenging. For an individual patient it is unclear how to define failure to respond to treatment, and whether to consider ceasing or altering therapy in patients with objective disease progression. Rate of change in FVC for an individual patient is variable over time, and so it is not possible to evaluate therapeutic response through comparison of FVC trends preceding and following disease modifying therapy commencement. Post hoc analysis of patients receiving pirfenidone identifies that patients experiencing a 10% or greater FVC decline or hospitalisation in the first 6 months of treatment still have a lower risk of FVC decline or death in the subsequent 6 months than those receiving placebo.114

In the United Kingdom, the National Institute for Clinical Excellence (NICE) recommend that nintedanib or pirfenidone is discontinued if over 12 months there is evidence of disease progression (defined as a decrease in predicted FVC of 10% or more), however it is uncertain if this does represent treatment failure.

115 As it is not possible to predict an individual’s disease course we do not know what the rate of decline may have been without treatment nor whether withdrawal of treatment might provoke a precipitous decline. Currently in patients with objective evidence of substantial physiological and/or radiological disease progression a change of disease modifying therapy might be considered, whilst in patients with advanced disease where the treatment burden is impacting upon quality of life then discontinuation may be appropriate.

**Incorporating genetics into routine clinical management**

There have been dramatic advances in understanding the influence of genetics upon the risk of developing sporadic IPF and possibly disease behaviour. Persons with the *MUC5B* variant in the general population have increased prevalence of sub-clinical interstitial lung abnormalities, and *MUC5B* is most consistently associated with the risk of developing IPF.24 Genotype might also influence response to pharmacologic therapy, with a recent post hoc analysis identifying that *TOLLIP* genotype might determine a beneficial or harmful effect of N-acetylcysteine therapy.116 While intriguing, translating these findings to routine clinical practice will require robust prospective studies to define the role for genetics in diagnosis and treatment of IPF.

**The role of gastro-oesophageal reflux**

GORD is common in patients with IPF, and chronic silent microaspiration, as a source of repetitive lung injury, has been proposed as a risk factor for IPF development and progression.

117,118 However, there are no prospective data supporting a causative or prognostic relationship. GORD therapy was associated with less radiological fibrosis and was an independent predictor of increased survival time in a retrospective analysis of patients with IPF.119 Post hoc analysis of three RCTs identified that patients taking anti-acid treatment had a smaller decrease in FVC.120 In contrast, post hoc analysis of three phase 3 trials of pirfenidone in IPF found that antacid therapy did not improve outcomes and might be associated within increased risk of infection in patients with an FVC of less than 70% predicted.121

Non-acid components of gastric juice are present in the bronchoalveolar lavage fluid of patients with IPF and so surgical management may prove more effective than medical anti-acid therapy.122 In a single centre retrospective trial of laparoscopic anti-reflux surgery (LARS) a non-significant trend towards decreased FVC decline was identified.122 Prospective studies of GORD therapies are required for patients with IPF before the routine commencement of medical or surgical therapies for asymptomatic reflux can be considered.

**The microbiome and antimicrobial treatments**

A potential role for infection influencing fibrosis initiation and progression has been proposed.29,123 Whether alterations in the microbiome represent an aetiological factor or a determinant of disease behaviour possibly influenced by genetic polymorphisms such as *MUC5B* or *TOLLIP*, a surrogate finding of another disease process such as microaspiration, or a marker of lung structure derangement in IPF remains uncertain.

Studies are ongoing into whether anti-microbials may influence IPF disease course. A phase 2 study of co-trimoxazole (trimethoprim/sulphamethoxazole) was performed in patients with fibrotic idiopathic interstitial pneumonia following the observation of a clinical improvement in patients with advanced fibrotic lung disease treated with long term oral co-trimoxazole.124,125 This was a negative study identifying no difference in the primary end point of FVC change over 12 months, however a possible reduction in mortality was observed in patients adhering to treatment. A phase 3 study is further investigating the significance of this.

**The role of biomarkers**

Biomarkers for diagnosis, prognosis, and response to therapy prediction may help to address controversies discussed above. Whilst numerous potential biomarkers have been studied including genetic polymorphisms, gene expression profiles, CCL18, collagen neo-epitopes, MMP7, and SPD, as yet none is prospectively validated for clinical practice.31,126-130 Major research efforts are ongoing towards biomarker validation through collaborative multicentre, prospective cohorts with longitudinal data collection and biobanking.

**Combination therapies**

Current monotherapies only slow disease progression and so a clear priority is developing approaches to halt, or ultimately even reverse IPF. An initial step will be to study novel therapies combined with currently approved therapies. In a recent clinical trial, the addition of the glutathione precursor n-acetylcysteine to pirfenidone unexpectedly increased rate of FVC decline, demonstrating the importance of RCT studies.131 Studies of the drug-drug interaction of pirfenidone and nintedanib are in progress, although pharmacokinetic interactions between them, in particular cumulative gastrointestinal effects, may preclude this, with some limited evidence of a lower exposure of nintedanib when added to pirfenidone.132

Clinical trial design in IPF has been altered by the approval of nintedanib and pirfenidone which are now the standard of care. Demonstrating superiority to them will likely require innovative trial design such as the use of composite endpoints. As our understanding of IPF continues to increase it is likely that novel molecular classification approaches will support the addition of targeted therapies to the pleiotropic mechanisms of action of the approved drugs.

**Conclusions & Future Directions**

In less than 10 years, the landscape of IPF has been transformed. Many no longer consider IPF ‘idiopathic’, with interacting aetiological factors including genetic polymorphisms, ageing, and environmental exposures culminating in a maladaptive repair process of injured lung. Advances in understanding disease pathogenesis integrated with establishment of methodologies to conduct large multicentre RCTs have resulted in approval of the first drugs to modify the disease course of IPF. Despite these achievements, a number of problems remain. Firstly, diagnosis of IPF can be challenging, and may vary between clinicians as it is solely based around morphologic criteria. Secondly, it is not possible to predict disease behaviour for individual patients, with significant inter-patient heterogeneity. Thirdly, quantification and management of response to disease modifying therapy is uncertain. Finally, although common pathogenic pathways of fibrosis have been proposed, it is unclear whether anti-fibrotic agents with proven efficacy in IPF will translate to other fibrotic diseases with extremely limited treatment options.133 The challenge of the next decade will be to address these questions whilst developing targeted therapies for use in combination with current treatments with the goals of halting fibrosis progression and maintaining quality of life of patients with IPF.

**Contributors**

All authors contributed to the design, figures, and writing of this manuscript.

**Conflicts of interest**

LR reports grants and personal fees from InterMune, and personal fees from Biogen, Sanofi-Aventis, Roche, ImmuneWorks, Boehringer Ingelheim, Celgene, FibroGen, Promedior, Bayer, Asahi-Kasei, and Pliant Therapeutics. HC reports personal fees from Medimmune, Bayer, Boehringer Ingelheim, Xfibra, Genoa, Gilead, Moerae Matrix, PharmAkea, Prometic, the Pulmonary Fibrosis Foundation, aTyr pharmaceuticals, GBT, Veracyte, Patara, Alkermes, Takeda, Pharma Capital Partners, and Bristol-Myers Squibb outside the submitted work.

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**Search strategy and selection criteria**

We searched PubMed from January 1996 to October 2016, using the search terms “pulmonary fibrosis”, “fibrosing alveolitis”, “usual interstitial pneumonia”, and “nonspecific interstitial pneumonia”. We mostly selected publications from the past 5 years although we also included highly regarded older publications. Reviews are cited to provide the reader additional detail and references. The search was limited to reports published in English.

**Figure Legends**

**Figure 1**. **Proposed mechanisms contributing to the pathogenesis of idiopathic pulmonary fibrosis.** Repetitive microinjuries to ageing alveolar epithelium activates alveolar epithelial cells to secrete multiple fibrogenic growth factors, cytokines, and coagulants. This promotes myofibroblast recruitment and activation from multiple sources including resident mesenchymal cell proliferation, pericytes of the lung interstitium, circulating fibrocytes, epithelial mesenchymal transition, and endothelial mesenchymal transition. These myofibroblasts deposit increased and altered extracellular matrix, with altered biomechanical stiffness further contributing to myofibroblast activation in a positive feedback loop. In parallel there is dysregulated repair of this injured lung parenchyma with abnormal activation of developmental pathways and ‘bronchiolisation’ of the lung.

**Figure 2.** **A conceptual model of idiopathic pulmonary fibrosis across an individual’s life course.**

**Figure 3. The radiological and histological patterns of usual interstitial pneumonia (UIP).** In (A) a coronal reconstruction of chest high resolution CT (HRCT) depicting the basal predominance of subpleural honeycombing which is typical of a UIP pattern In (B) an axial HRCT image taken at the level of the lower lobes depicting multi-layered subpleural honeycombing without evidence of features inconsistent with a pattern of usual interstitial pneumonia (UIP).In (C) a histological pattern of UIP at low power. The typical spatial and temporal heterogeneity can be observed with subpleural fibrosis and microscopic honeycombing, less-fibrotic central lung tissue, and fibroblast foci. On higher power (D), a fibroblast focus (\*) is noted at the interface between fibrotic and less-involved lung tissue.

**Figure 4.** **A step-wise approach to the comprehensive management of patients with idiopathic pulmonary fibrosis**.

**Figure 5.** **Therapies identified in recent clinical trials as harmful, ineffective, or effective in the treatment of idiopathic pulmonary fibrosis.** In the lower part of the figure the influence of disease modifying therapy on lung function decline is illustrated. The disease modifying therapies nintedanib and pirfenidone approximately halve the relative rate of decline of forced vital capacity (FVC) compared to placebo over 12 months in patients with IPF.82,83,91 Over 12 months the average decline in FVC in an untreated patient with IPF is approximately 200 ml.

**Figure 6.** **The radiological and histopathological changes of an acute exacerbation of idiopathic pulmonary fibrosis (IPF).** In (A) a patient with a diagnosis of idiopathic pulmonary fibrosis (IPF) with an axial chest high-resolution CT (HRCT) image taken at the level of the carina demonstrating subpleural reticulation with areas of traction bronchiectasis. In (B) the patient is hospitalised following the onset of worsening dyspnoea. An axial chest HRCT image taken at the level of the carina in the same patient now identifies that the predominant pattern is a diffuse ground glass abnormality becoming confluent with consolidation posteriorly (the so-called anterior-posterior density gradient) characteristic of an acute exacerbation of IPF. There is some minor respiratory motion artefact due to the patient’s dyspnoea during image acquisition. Although not obvious on this image, there is a tiny right pneumothorax and a chest drain has been positioned in the right pleural space (seen here, within the subcutaneous tissues of the anterior thoracic wall). A nasogastric tube is in the oesophagus. Surgical lung biopsy has no routine diagnostic role in cases of suspected acute exacerbation given high non-elective morbidity; when performed the histopathology slides identify that the alveolar septa are thickened by oedematous fibrosis and mild inflammation. The alveolar spaces show consolidation by fibrin and hyaline membranes, consistent with acute lung injury and diffuse alveolar damage.

**Movie 1.** An axial chest high-resolution CT (HRCT) scan of a patient with a diagnosis of idiopathic pulmonary fibrosis demonstrating the radiological pattern of usual interstitial pneumonia.

**Audio 1**. A recording of the breath sounds of a patient with idiopathic pulmonary fibrosis.

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