Idiopathic pulmonary fibrosis (IPF) is a progressive age-related lung disease, the cause of which is not been fully understood. IPF is a devastating disease with mortality worse than many cancers, and treatment options are limited. IPF is thought to occur after recurrent injury to the alveolar epithelium followed by abnormal repair characterized by the formation of fibroblast and myofibroblast foci and excessive deposition of extracellular matrix. An updated classification of the idiopathic interstitial pneumonias has encouraged a large number of clinical trials. On the whole, these have disappointed. Improvements in molecular techniques have developed our understanding of IPF and with it identified new pathways and potential targets for therapeutic intervention. These insights are leading to interest in biomarkers of disease progression and prognosis and to novel anti-fibrotic agents and a more targeted approach to the treatment of IPF.

Introduction

Over 100 years have passed since Osler described chronic interstitial pneumonia and over 40 years since Liebow and Carrington’s landmark histological classification of the interstitial pneumonias. While the intervening period has seen enormous developments in respirology and medicine as a whole, progress in our understanding and treatment of idiopathic pulmonary fibrosis (IPF) have been conspicuously slow.

IPF continues to exact a considerable toll. Estimating prevalence is fraught with uncertainty due to the wide variation in morphology, but recently published estimates from the USA suggest a prevalence of between 14 and 42.7 per 100 000 and annual incidence of 6.8–16.3 per 100 000. In the UK, it has been estimated at 4.6 per 100 000. IPF is a relentless disease and has a prognosis worse than many cancers with median survival of 2.9–5.0 years.

Despite this burden of disease, there have not been the equivalent level of research interest and clinical trials compared with diseases with a similar mortality. Accordingly, very few evidence-based treatments have made their way into clinical practice. Although palliative treatments can lessen the most disabling of symptoms, the therapeutic armamentarium has been despondently bare. This though may be about to change. Improvements of animal models, molecular techniques and genetic studies have helped our understanding of IPF. In 2002, a widely adopted update of the classification of the idiopathic interstitial pneumonias (IIPs) was particularly welcome. These events have contributed to more clinical trials in the last 5 years than in the history of IPF. A paradigm shift has occurred in our
understanding of the pathogenesis of IPF, and this model is driving forward the search for new therapeutic targets and setting the scene for a more targeted approach. Finally, with the emergence of interstitial lung disease (ILD) centres and the case made for a multi-disciplinary approach, the necessary ingredients are in place to encourage large multicentre clinical trials, which will be needed to test the latest agents. This review updates where we are with treatments currently used in clinical practice and highlights some future directions.

Case definition

IPF is the most common of the IIPs. It is characterized by the histological and radiological pattern of usual interstitial pneumonia (UIP). The typical patient with IPF presents between their 5th and 7th decades of life with a slight male preponderance.8,9 They have a gradual onset of symptoms with dyspnoea and cough, the most disabling. Digital clubbing occurs in 25–50%.8,9 Auscultation reveals fine end-inspiratory crackles, initially confined to the basal areas. They have restrictive lung physiology with impaired gas exchange and decreased PaO2 with rest or exercise. High-resolution computer tomography (HRCT) reveals bilateral predominantly basilar and sub-pleural reticular abnormalities, with honeycombing and minimal ground-glass opacities. The utility of bronchoalveolar lavage (BAL) as a diagnostic tool in IPF remains controversial but often shows an excess of neutrophils with or without eosinophils. Historical reports suggested that an increase in the BAL lymphocyte count may predict steroid responsiveness and therefore a more favourable outcome.10,11 It is likely though that some of these patients probably had other IIPs such as non-specific interstitial pneumonia (NSIP), which is characteristically a more indolent disease. More recent studies have discounted the role of BAL to prognosticate IPF,12 though it is still likely to be helpful in the diagnosis of alternative or co-existent conditions. Surgical lung biopsy reveals the key histological features of UIP, which are architectural destruction, fibrosis often with honeycombing and scattered fibroblastic foci in a sometimes patchy distribution.

The most recent national guidelines from the American and European thoracic societies have downgraded the role for histological confirmation.13 In the appropriate clinical setting, a HRCT pattern of UIP and the exclusion of other known causes of ILD are sufficient to diagnose IPF. When surgical biopsy is performed, specific combinations of HRCT and surgical lung biopsy can be used to correctly diagnose IPF and its probability. The firm diagnosis of IPF, therefore, rests on the consideration of all the available clinical, radiological and histopathological data. The guidelines strongly advocate the role of a multi-disciplinary discussion in the diagnosis of IPF. It is clear that not all practising clinicians will have direct access to these, but their role in indeterminate cases or where the data are not concordant is likely to be invaluable. Such ILD units are also likely to be able to take a leading role in translating developments in research into clinical trials.

Pathogenesis

The prevailing model of pathogenesis in IPF through the 1970s and 1980s had been of persistent inflammation, leading inexorably to pulmonary fibrosis. This model provided a rational basis for the role of anti-inflammatory agents such as corticosteroids and immunosuppressive agents such as azathioprine. However, the evident lack of efficacy of steroids in clinical practice and the failure of clinical trials to support a role for steroids has served to undermine the role of inflammation as the driving force in IPF. Over the last decade, a newer model of pathogenesis in IPF has gained ground. At its centre are epithelial injury and the loss of integrity of the alveolar–capillary basement membrane. This appears to have a pivotal role as to whether normal repair or fibrosis ensues. Strieter and Mehrad14 recently described how such a model could lead to pulmonary fibrosis.

In acute lung injury and normal repair, haemorrhage and extravasation of plasma occur in lung tissue. Platelets are activated, and degranulation occurs with coagulation. A number of mediators and cytokines are released. These activate leukocytes, endothelial cells, fibroblast/myofibroblasts and epithelial cells and lead to the deposition of extracellular matrix.14 Although the basement membrane is intact and the stimulus of the original injury has been removed, the deposition of extracellular matrix is remodelled and there is re-epithelization and re-endothelization of the alveolar–capillary barrier. The basement membrane is restored, and the normal process is complete.

In contrast, in fibrosis, the integrity of the basement membrane of the alveolar–capillary barrier is lost with the collapse of alveolar structures and fusion of their basement membranes. A switch from Type I to Type II epithelial cells occurs with establishment on an inappropriate extracellular matrix. Pro-fibrotic cytokines such as transforming growth factor beta-1 (TGF-β1), platelet-derived growth factor and tumour necrosis factor alpha (TNF-α) are released causing fibroblast transformation, proliferation and accumulation of an
extracellular matrix. Tissue destruction ensues with loss of alveolar structures and the hallmark histopathological features seen in UIP.

The importance of our improved understanding of the processes leading to fibrosis is underlined by the advent of new therapeutic agents that target the steps in the fibrotic pathway.

**Current therapies**

**Corticosteroids**

Some of the earlier promise of steroids stemmed from historic trials. It is likely that some of these patients would not meet our current criteria of IPF and instead had other more steroid responsive diseases such as ILD associated with collagen vascular disease and NSIP. Monotherapy with steroids is not a recommended maintenance treatment in most national guidelines. The role though of steroids as part of a ‘triple therapy’ of prednisolone, azathiaprine and N-acetylcysteine (NAC) was up and till recently less clear cut and had survived the guidelines albeit only for a minority of patients or as a weak recommendation (ATS/ERS 2010 and BTS 2008, respectively). The IFIGENIA trial (see later) appeared to support the use of triple therapy in IPF, but the trial design meant firm recommendations were not possible. An ongoing trial set out to verify the findings from IFIGENIA. The three-arm PANTHER–IPF study randomized patients to triple therapy, NAC or placebo. After recruiting 238 of a planned 390 patients, the trial sponsor, the National Heart Lung and Blood Institute, stopped the triple-therapy arm for safety concerns. Interim results have shown that the addition of NAC, added to prednisolone and azathiaprine, could attenuate the decline in forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) compared with patients on prednisolone and azathiaprine alone. All patients were maintained on prednisolone and azathiaprine but randomized to receive either NAC or placebo as well. In the placebo group, FVC and DLCO fell 6 and 8% of predicted but only 1.5 and 3% with the addition of NAC, respectively. As a recent editorial argues when put another way, anti-oxidant therapy reduced disease progression by ~70%.

Despite this striking figure, the study had important limitations. The study suffered a relatively high rate of dropout, ~30% lost to follow-up at 12 months due to death or patient withdrawal. The study was not powered or designed to detect an effect on mortality, ending after only 1 year. Above all, the biggest limitation to the study is the lack of a true placebo arm or a NAC-only arm. The remaining arms of the PANTHER-IPF trial should now address this. The full results, which are due out in 2013, should provide some of the clearest evidence yet for the use of NAC in IPF.

**Pirfenidone**

Pirfenidone is a relatively novel compound that has been tested in animal models and shown to have anti-fibrotic and anti-inflammatory properties. In vitro it inhibits the stimulatory effects of profibrotic cytokines on human lung fibroblasts.

In a phase II open-labelled study in 54 terminally ill patients with IPF, pirfenidone stabilized lung function in patients who were demonstrably deteriorating. Despite the design limitations and potential for survivorship bias, the results were the first use of pirfenidone in a clinical setting and paved the way for future clinical studies. In 2005, Azuma et al conducted a prospective double-blinded, multicentre placebo-controlled trial of pirfenidone in Japanese patients with IPF. They used a novel study design with change in the lowest oxygen saturation during exercise as a marker of severity in IPF and as predictor of survival.

In a pre-specified subset of patients who maintained an oxygen saturation (SpO2) >80% during a 6-min exercise test at baseline, the lowest SpO2 improved during a 6-min exercise test in the pirfenidone group at 6 and 9 months. Interestingly, acute exacerbations occurred in 5/35 of the placebo group...
and in none in the pirfenidone group. Based on the interim acute exacerbation rate at 6 months, the Data and Safety Management Board (DSMB) advised the study be aborted and pirfenidone administered to patients in the placebo group. This seems to have been premature. The study failed to demonstrate any significant difference in the primary end point, and although the changes in SpO2 measurements during the 6MET may be clinically relevant, the 6MET has not been validated in IPF.

Since this study, three phase-III randomized control trials have been published with primary end points of change in lung function. The first of these was a multicentre trial of 267 patients in Japan over 1 year, randomized to high-dose pirfenidone 1800 mg/day, low dose 1200 mg/day or placebo in the ratio of 2:1:2.27 Notably, the primary end point was changed from the lowest oxygen saturation during the 6MET to a decline in VC on the advice of the DSMB. Secondary end points were progression-free survival (PFS) as defined by death or \( \geq 10\% \) decline in VC from baseline and the change in the lowest SpO2 during a 6MET. In both pirfenidone groups, the mean decline in VC was attenuated when compared with placebo (−0.09L and −0.16L in the high dose and placebo groups, respectively). Although the distribution of the PFS was reportedly better, the exacerbation rate was not any better, and other secondary and tertiary end points were not met. Nevertheless, based on these results and the earlier phase II trial, pirfenidone has been given regulatory approval for the treatment of IPF in Japan.

Two further trials designed to confirm the effect of pirfenidone on lung function were published recently. The CAPACITY program28 (clinical studies assessing pirfenidone in IPF, research of efficacy and safety outcomes and studies 004 and 006) involved two concurrent trials held in 110 centres in Australia, Europe and North America. In study 004, 435 patients with IPF were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day or placebo. In study 006, 344 patients were assigned in a 1:1 ratio to pirfenidone 2403 mg/day or placebo. The primary end point was change in predicted FVC at 72 weeks. In study 004, pirfenidone reduced decline in FVC. Mean FVC at Week 72 was −8.0% in the pirfenidone 2403 mg/day group and −12.4% in the placebo group (relative difference of 35%). Treatment effect was evident at Week 24 and persisted until Week 72. Outcomes in the lower pirfenidone dose group (1197 mg/day) were intermediary. Study 006 failed to show significant difference between the pirfenidone and placebo groups at Week 72, though a significant treatment effect was evident at every time point from Week 12 to Week 48. In study 004, pirfenidone 2403 mg/day prolonged PFS—a secondary end point but failed to do so in study 006. On the whole, other secondary end points, including exercise testing and patient centred outcomes, failed to consistently demonstrate significant treatment effects with pirfenidone. Side effects were common with pirfenidone including photosensitivity and nausea, though this did not lead to high rates of treatment discontinuation.

The accumulative experience of the clinical trials in the use of pirfenidone appears to point towards a genuine treatment effect and that pirfenidone may attenuate the decline in FVC—an important and validated marker of IPF severity. However, the extents of this treatment effect, its reproducibility and when set against the potential toxicity of therapy, have meant that current guidelines have argued against its use in the majority of patients.

### Potential targets

**TGF-β**

A great deal of excitement surrounds the mediators involved in the dysregulation of tissue repair. TGF-β1 and platelet-derived growth factor are two of the most potent of these cytokines. TGF-β1 is up-regulated in the lung at sites of fibrogenesis.29 It is a powerful inducer of extracellular matrix synthesis and inhibits matrix degradation.30 It inhibits the proliferation of epithelial cells and thus could prevent the re-epithelization that is thought to play a pivotal role in lung injury and normal repair. TGF-β has numerous other effects including pro-fibrogenic, anti-inflammatory, immunoregulatory and modification of cell adhesion.29 Although targeting TGF-β1 may seem a worthwhile endeavour, doing so is likely to have widely undesirable and difficult to predict affects. Animal studies of TGF-β1 null mice showed no gross developmental abnormalities, but the animals did succumb to a mixed inflammatory response and multi-organ failure.31 Better candidate therapies will seek to target steps downstream of TGF-β1 activity. An example is c-Abelson (c-Abl), a proto-oncogene that is a downstream mediator of TGF-β1 signalling in fibroblasts.32 Imatinib, a tyrosine inhibitor and inhibitor of c-Abl, was found to prevent pulmonary fibrosis in a murine model of bleomycin-induced fibrosis.

Despite this promise, Imatinib failed to prevent progression of disease in a phase II/III study of 120 patients.33

**Galectin-3**

Recent studies identify Galectin-3 as a novel and exciting target in IPF.34 Galectin-3 is a
β-galactoside-binding animal lectin of ~30 kDa that is highly expressed in fibrotic tissue of diverse aetiologies. Mice deficient in galectin-3 develop reduced fibrosis in several models of organ fibrosis in vivo including liver and kidney, suggesting that galectin-3 may play a key role in organ fibrosis and may represent a fundamental novel target for intervention. Galectin-3 expression in tissue during organ fibrosis correlates both temporally and spatially with fibrosis. The role of galectin-3 in lung fibrosis and its effects on TGF-β function has recently been examined, using two well-characterized rodent models of lung fibrosis. Adeno-viral TGF-β1 and bleomycin-induced lung fibrosis are dramatically reduced in mice deficient in galectin-3. This was manifested by reduced TGF-β1-induced epithelial to mesenchymal transition (EMT) and myofibroblast activation and collagen production in vitro and in vivo. Galectin-3 deletion in lung epithelial cells resulted in reduced retention of TGF-bR1 at the cell surface and reduced serine/threonine phosphorylation and nuclear translocation of β-catenin but had no effect on Smad3 phosphorylation. A novel inhibitor of galectin-3, TD139, blocked TGF-β-induced β-catenin activation in vitro and in vivo and attenuated the late stage (Days 15–26) progression of lung fibrosis after bleomycin-induced lung injury. In patients with IPF, there is increased lung expression of galectin-3, and levels are elevated in BAL fluid and serum from patients with stable IPF compared with NSIP and controls. Moreover, serum galectin-3 rises sharply during an acute exacerbation, suggesting that galectin-3 may provide novel prognostic factor for IPF.

Thus, galectin-3 may be an important regulator of lung fibrosis and TGF-β function, and these studies provide a proof of principle for galectin-3 inhibition as a potential novel therapeutic strategy for IPF.

**Conclusion**

IPF is a devastating disease for which there have been limited effective therapeutic options. There is now hope on the horizon. Improvements of animal models, molecular techniques and genetic studies will continue to increase our understanding of the pathogenesis of IPF, which will drive the search for new therapeutic targets. Improvements in radiology and clinical imaging will continue to improve diagnosis and the assessment of disease activity. As there is greater understanding of the pathogenesis of IPF, there will be increased identification of novel targets, which can be exploited for therapeutic gain. This has now resulted in the development of new strategies and therapies for IPF. New drugs such as pirfenidone, targeted anti-TGF-β agents and strategies to block galectin-3 offer new hope for the future treatment and improve the prognosis of patients with IPF.

**Conflict of interest:** T.S. is a co-founder of Galecto Biotech, a company registered in Denmark in 2011, which is developing Galectin-3 inhibitors for clinical use.

**References**


