

## Review

QJM

# Idiopathic pulmonary fibrosis: an update

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## Summary

Idiopathic pulmonary fibrosis (IPF) is a chronic lung condition of uncertain aetiology that should be considered in the differential diagnosis of patients who experience breathlessness, cough and reduced exercise tolerance. IPF is characterized histologically by the presence of usual interstitial pneumonia, and often has typical radiological appearances. Long-term successful management options are limited and frequently unsuccessful;

as the disease progresses, palliation of symptoms becomes the mainstay of treatment. In a minority of patients, lung transplantation provides the only hope of long-term survival. The median survival of patients with IPF is approximately 3 years, which in turn emphasizes the need for further investigation into its pathogenesis and potential disease-modifying pharmacological therapies.

## Introduction

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis, is associated with considerable morbidity and mortality,<sup>1,2</sup> and has a survival rate comparable to many cancers. The presenting clinical features of IPF are non-specific and are shared with many other cardio-respiratory conditions. The aim of this evidence-based review is to provide clinicians with an update in its diagnosis and management. Future therapies, many of which are currently being assessed in clinical trials, will also be discussed. We performed a comprehensive literature search using Medline, Clinical Evidence, Cochrane library and EMBASE. The following key words or phrases were used in the search: idiopathic pulmonary fibrosis, cryptogenic fibrosing alveolitis, usual interstitial pneumonia, diagnosis, survival, treatment, corticosteroids, azathioprine, cyclophosphamide, fibroblast, lung transplantation, oxygen, warfarin, pirfenidone, interferon- $\gamma$ -1b, warfarin, bosentan, etanercept, imatinib,

pulmonary hypertension and immunosuppressives. Published articles up to March 2006 were then selected and extracted, along with articles which the authors felt to be topical and of interest to clinicians.

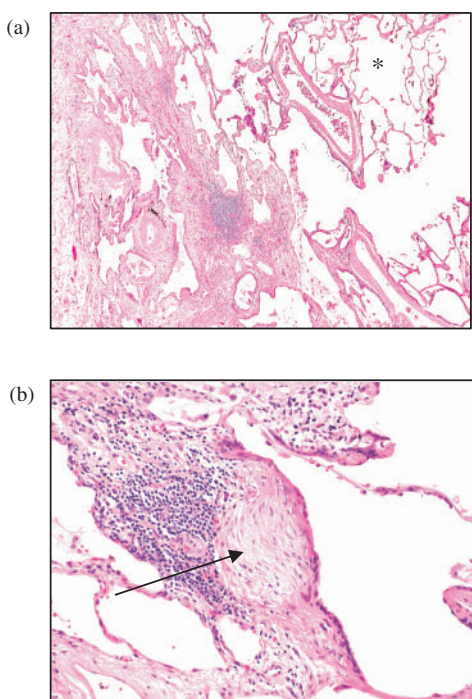
## Definition

The interstitium is the microscopic space between the alveolar epithelium and capillary endothelium which forms part of the blood–gas barrier. IPF affects not only the interstitium but also the alveolar spaces, and is associated with the light microscopy appearance of ‘usual interstitial pneumonia’ (UIP) (Figure 1, Box 1).<sup>3</sup> In UIP, ‘pneumonia’ is used to describe inflammation (rather than infection), while ‘usual’ indicates that the histological pattern is the most commonly observed.

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## Clinical features and natural history

Typical symptoms of IPF include chronic progressive exertional breathlessness, frequently accompanied by a non-productive cough. As IPF progresses, breathlessness impacts on activities of daily living, resulting in many patients becoming housebound, socially isolated and depressed.<sup>4</sup> Clinical examination usually reveals end inspiratory fine crackles, which are often 'high pitched' or 'Velcro-like' in character. Up to 50% of patients have finger clubbing, and those with more advanced disease may develop cor pulmonale. There is commonly a delay of several months before the diagnosis is made. Indeed, many



**Figure 1.** Typical histological features of usual interstitial pneumonia at **a** low and **b** high power. The 'patchy' nature of UIP is highlighted in **a**, with relatively normal alveoli (asterisk), contrasting with significant interstitial thickening on the left. A fibroblast focus (arrow) is seen in **b**, and represents a site of ongoing disease activity with acute fibroblastic proliferation and collagen deposition. Increased numbers of fibroblastic foci correlate with poorer survival.

### Box 1. Key histological features of IPF.

- Patchy fibrosis, often with intervening normal or mildly affected lung and pathological lesions of varying age.
- Predominantly subpleural or paraseptal changes
- Minimal or absent inflammation
- Fibroblastic foci (areas of acute fibroblast proliferation and collagen deposition)
- Honeycombing

patients are empirically treated with diuretics for 'left ventricular failure' or antibiotics for a 'lower respiratory tract infection' before the diagnosis becomes apparent.

Untreated IPF follows a relentlessly progressive course in most patients. Early studies generally overestimated survival rates, since patients with less aggressive interstitial pathology such as non-specific interstitial pneumonia (NSIP) were included in long-term follow-up. More recent studies have confirmed that median survival is approximately 3 years.<sup>5</sup> An acute clinical deterioration precedes death in up to half of patients, often with minimal preceding change in physiological variables such as lung function.<sup>6</sup> This in turn indicates that periods of relative stability can be punctuated by often rapid decline. Mortality is most frequently due to respiratory failure (39%), while other causes of death include heart failure (14%), lung cancer (10%), ischaemic heart disease (10%), infection (6%) and pulmonary embolism (3%).<sup>7</sup>

## Epidemiology

IPF is relatively uncommon, with a prevalence estimated at 7–20 individuals per 100 000 population.<sup>8</sup> It is a disease predominately of the elderly, with a mean age of onset of 67 years. It is slightly more common in males and in those with a history of smoking. The total number of deaths in England and Wales due to IPF has trebled over the past twenty years.<sup>9</sup>

## Pathology

Typical features are described in Box 1 and shown in Figure 1.<sup>10</sup> The terms IPF and UIP are frequently used interchangeably, although it should be noted that a pattern of interstitial inflammation and fibrosis sometimes indistinguishable from UIP may occur in other conditions, such as asbestosis, connective tissue diseases, chronic hypersensitivity pneumonitis, and certain drug-induced lung diseases.<sup>1</sup> In early IPF, there is evidence of patchy alveolar and capillary damage, presumed to

be secondary to an unknown insult. Alveolar epithelial injury consists of patchy necrosis, with loss of type I pneumocytes, and regenerative hyperplasia of type II pneumocytes. Alveolar capillary injury consists of cytoplasmic swelling and basement membrane thickening and reduplication.<sup>11</sup> As the disease progresses, fusion of adjacent alveolar structures by intraluminal connective tissue occurs, along with formation of characteristic fibroblastic foci and ultimately honeycomb fibrosis (Figure 2).<sup>12</sup>

## Pathogenesis

The cause of IPF is unknown. The original 'inflammation/alveolitis' hypothesis suggested that IPF was a chronic inflammatory disease, occurring in response to an unknown stimulus, and if left untreated, led to progressive lung injury and ultimately fibrosis.<sup>13</sup> As a consequence, there was initial enthusiasm for anti-inflammatory therapy, using oral corticosteroids and cytotoxic agents. However, it is now increasingly evident that inflammation does not play a pivotal role, which explains why these therapies have been largely ineffective.

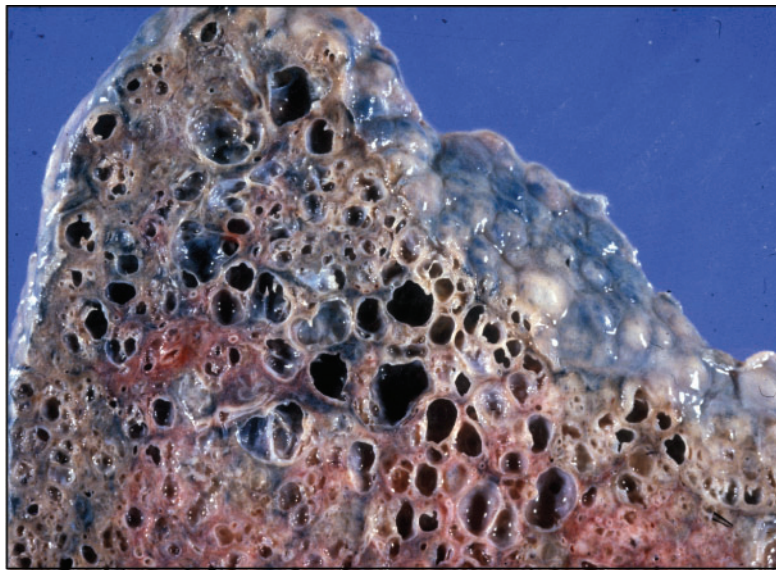
The current 'epithelial/mesenchymal' hypothesis suggests that IPF results from repeated, and unidentified, exogenous and endogenous stimuli leading to sequential microscopic lung injury, with disruption of the alveolar epithelium.<sup>13</sup> Failure of re-epithelialization occurs, which results in ongoing injury with unregulated proliferation of interstitial fibroblasts, and the formation of

fibroblast-myofibroblast foci and ultimately fibrosis. This complex process is well-described elsewhere and offers potential targets for therapeutic intervention.<sup>14</sup> Animal data suggest that systemic fibrocytes may localize to the lungs and may be important in the underlying pathogenesis of IPF, although evidence in human IPF is lacking.<sup>15,16</sup>

Aberrant angiogenesis occurs in IPF, and it has been suggested that an imbalance exists in the expression of angiogenic (IL-8) versus angiostatic (IFN- $\gamma$ -inducible protein, IP-10) CXC chemokines, favouring net angiogenesis in IPF.<sup>17,18</sup> This has led to interest in IFN- $\gamma$  as a potential therapy in IPF, since this might promote induction of angiostatic chemokines such as IP-10. Furthermore, administration of IFN- $\gamma$  to humans with IPF leads to a marked increase in a CXC chemokine (CXCL11) which is a potent inhibitor of angiogenesis.<sup>19</sup> In a mouse model of pulmonary fibrosis, CXCL11 attenuates bleomycin-induced pulmonary fibrosis via inhibition of vascular remodeling.<sup>20</sup>

Various environmental stimuli have been suggested as risk factors for developing IPF, including cigarette smoking, antidepressants, chronic aspiration, metal and wood dusts, and infectious agents, including Epstein Barr virus.<sup>1</sup>

Familial IPF is rare, although clustering within families has been well described.<sup>22</sup> In the UK, familial IPF has a prevalence of 1.34 cases per million and accounts for only 0.5–2.2% of all cases.<sup>23</sup> In Finland, familial IPF accounts for 3.3–3.7% of cases.<sup>24</sup> Patients with familial IPF tend to present at a younger age and some cases are associated with surfactant protein C genes, with two mutations resulting in protein misfolding,



**Figure 2.** Gross pathological specimen showing lung fibrosis and honeycombing in an individual who had advanced IPF.

causing type II epithelial cell injury.<sup>25</sup> Susceptibility to IPF probably involves a combination of genetic polymorphisms related to epithelial cell injury and abnormal wound healing.<sup>21</sup>

## Diagnosis

Distinguishing between IPF (as defined histologically by the presence of UIP) and 'non-IPF' is important in terms of prognosis and response to treatment. Patients with IPF have a median survival of approximately 3 years, and tend not to respond to corticosteroids. In contrast, more common 'non-IPF' pulmonary disorders such as NSIP confer a much more favourable prognosis.<sup>5</sup> A multi-disciplinary approach is likely to be more successful in achieving a confident diagnosis.<sup>26</sup>

## Blood markers

No blood marker has been identified in being helpful in the diagnosis of IPF. Nonetheless, a strongly positive rheumatoid factor or anti-nuclear antibody can raise the possibility of an associated connective tissue disease,<sup>27</sup> while a raised angiotensin-converting-enzyme level is associated with sarcoidosis, and c-ANCA with Wegener's granulomatosis.

## Pulmonary function testing

Spirometry can be normal in early disease, although as the disease progresses it becomes typically restrictive. More detailed pulmonary function testing often demonstrates reduced lung volumes, impaired gas transfer and oxygen desaturation during exercise. Desaturation during exercise can be easily assessed in a standard 6-min walk, and is highly reproducible.<sup>28–30</sup>

## Radiology

A chest radiograph may be normal in early IPF.<sup>31</sup> As the disease progresses, changes include progressive reduction in lung volumes, and predominantly peripheral and basal fibrotic changes (Figure 3a). High-resolution computerized tomographic scanning (HRCT) is a key investigation if IPF is suspected (Figure 3b) and allows a confident non-invasive diagnosis in some patients, estimation of disease severity, distribution and prognosis (Box 2).<sup>32</sup> A normal HRCT scan virtually excludes the diagnosis. Features such as mediastinal lymphadenopathy, ground-glass attenuation, cysts, upper-lobe predominance, pleural plaques and effusion, should raise the possibility of alternative diagnoses.

## Bronchoscopy

Fibreoptic bronchoscopy and transbronchial biopsy and lavage are of limited value in the diagnosis of IPF, but may be useful in identifying alternative or concomitant disorders such as opportunistic infection.<sup>2</sup>

## Lung biopsy

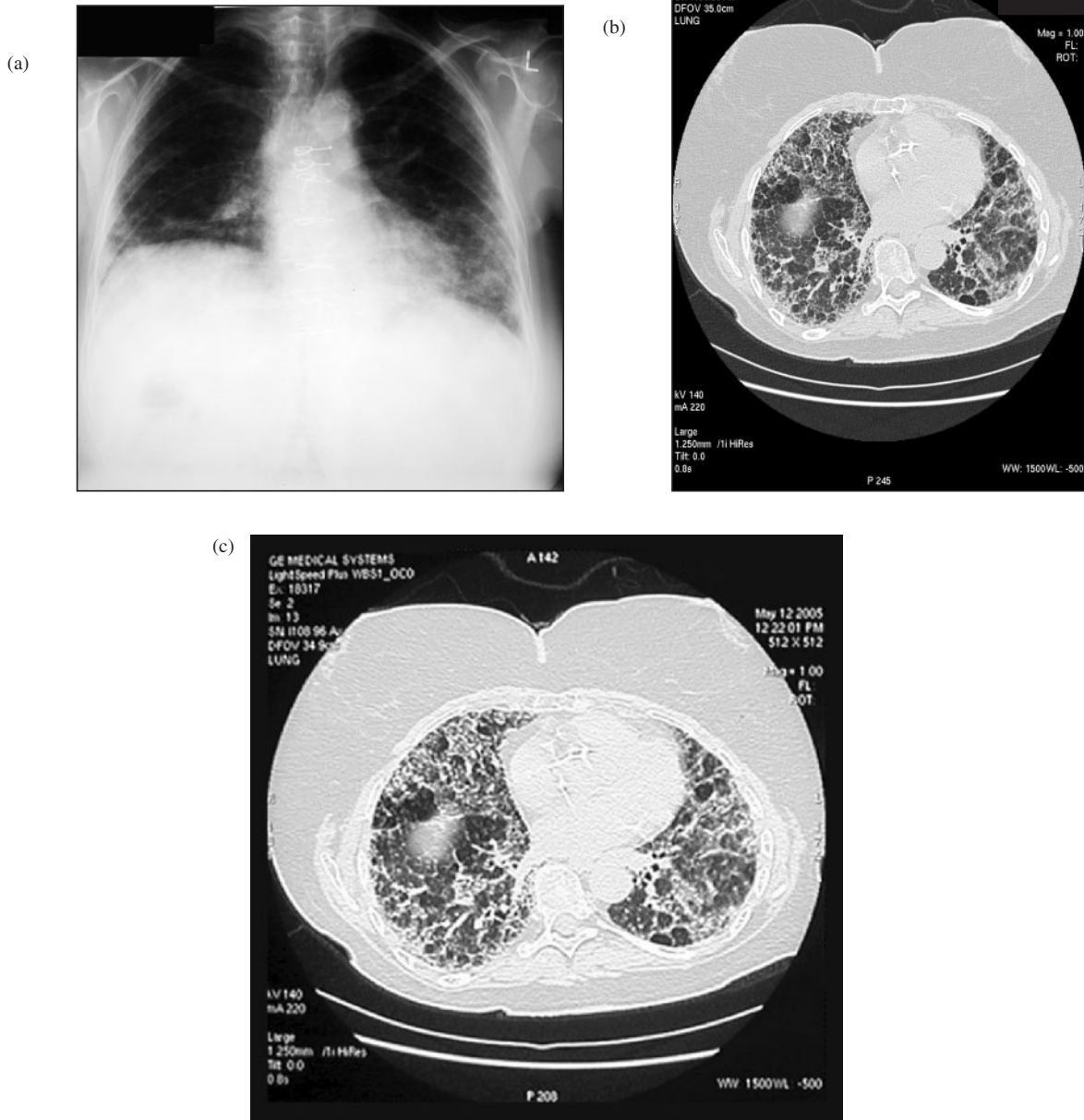
It is inappropriate to proceed to a surgical lung biopsy in some individuals because of frailty, advanced age or co-morbidities. Indeed, the diagnosis may be confidently made if specific clinical, radiological and physiological criteria are satisfied (Box 3).<sup>1</sup> If surgical lung biopsy is required, this is usually done using a video-assisted thoracoscopic (VATS), rather than the traditional 'open' approach. If multiple surgical lung biopsies are taken from different lobes, more than one interstitial disease may be identified. Such discordant pathology tends to involve both UIP and NSIP, with the natural history tending to follow that of the poorest prognosis (UIP).<sup>33</sup> This in turn suggests that multiple rather than single surgical lung biopsies should be taken from several lobes.

## Prognosis

Definitive information regarding prognosis and response is important, in order to allow patients with a poorer prognosis to be referred earlier for lung transplantation. A number of prognostic physiological markers have been suggested, either alone or in combination, although no simple classification currently exists.<sup>34,35</sup> Longitudinal changes in pulmonary function tests (e.g. forced vital capacity (FVC) and gas transfer over 6–12 months) appear promising, and have been shown to be predictive of mortality.<sup>36</sup> Falls in FVC and gas transfer are regarded as clinically significant at  $\geq 10\%$  and  $\geq 15\%$ , respectively,<sup>37</sup> while a fall in oxygen saturation to  $< 88\%$  during a 6-min walk is associated with higher mortality.<sup>28,30</sup>

Features observed on HRCT also add prognostic information to the histological diagnosis of UIP. For instance, survival is worse if patients with histologically-proven UIP have HRCT changes considered to be 'definite' or 'probable' UIP, compared with those with histological UIP but an 'atypical' HRCT picture for UIP.<sup>38</sup>

In advanced IPF, destruction of the pulmonary vasculature and honeycomb fibrosis often leads to pulmonary hypertension. A systolic pulmonary artery pressure on cardiac echocardiogram



**Figure 3.** **a** Chest radiograph from a patient with biopsy-proven IPF, showing bibasal pulmonary reticulonodular shadowing with volume loss. **b** High-resolution CT scan from the same patient showing characteristic interlobular and intralobular septal thickening, ground glass attenuation, loss of volume, traction bronchiectasis and honeycombing with a subpleural bibasal predominance.

**Box 2.** Typical high resolution CT scan features in patients with idiopathic pulmonary fibrosis.

- Bilateral (rarely unilateral)
- Lower lobe predominance
- Subpleural reticular abnormalities
- Minimal or no ground-glass changes
- Honeycombing
- Traction bronchiectasis

**Box 3.** Diagnostic criteria for IPF in absence of surgical lung biopsy.**Major criteria (all 4 features must be present)**

- Exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental exposures, and collagen vascular diseases.
- Abnormal pulmonary function studies that include evidence of restriction with or without impaired gas exchange.
- Bibasal reticular abnormalities with minimal ground glass opacities on high resolution computed tomographic scan
- Transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis

**Minor criteria (3 out of 4 features must be present)**

- Age >50 years
- Insidious onset of otherwise unexplained dyspnoea on exertion
- Duration of illness 3 months
- Bibasal inspiratory crackles (dry or “Velcro” type in quality)

**Box 4.** Current recommendations for treatment of IPF.\***Prednisolone**

- 0.5 mg/kg/day orally for 4 weeks then,
- 0.25 mg/kg/day for 8 weeks, then
- 0.125 mg/kg/day

**Azathioprine**

- 2–3 mg/kg/day to maximum dose of 150 mg/day.
- Dosing should begin at 25–50 mg/day and increase gradually by 25 mg increments every 7–14 days until the maximum dose is reached

**N-acetyl cysteine**

- Not currently recommended in guidelines, although a recently published study demonstrated that a dose of 600 mg tid, in addition to prednisolone plus azathioprine, slows down deterioration in lung function over 1 year. However, no effect on mortality was demonstrated.<sup>60</sup>

**Notes**

- \*Convincing evidence to support the use of prednisolone plus azathioprine does not exist, although treatment with both agents is often tried empirically.
- Doses should be based on lean body weight (ideal weight expected for a patient according to age, sex and height).
- Azathioprine may be substituted by cyclophosphamide.
- Consider prophylaxis of *Pneumocystis jiroveci*.
- Treatment response should be evaluated at 6 months. If objective evidence of improvement occurs, treatment can be continued.

of >50 mmHg is associated with a 1-year survival rate of 45%, compared to a pulmonary artery pressure of <50 mmHg, which has a 1-year survival rate of 83%.<sup>39,40</sup>

## Management

Many hospitals now have dedicated interstitial lung disease clinics, with evidence supporting a multidisciplinary approach to both diagnosis and management.<sup>26</sup> Many of the treatments advocated in current guidelines are largely ineffective, with limited evidence to support their continued

use. In particular, convincing evidence to support using conventional ‘anti-inflammatory’ therapy (oral corticosteroids and azathioprine) does not exist, and treatment-related toxicity is common.<sup>41,42</sup>

Once the diagnosis of IPF has been established, it is reasonable to wait for 6 months and decide whether clinical, radiological or physiological deterioration has occurred over this time. If so, empirical conventional treatment can be considered (Box 4), and where appropriate, the patient considered for lung transplantation. Ideally, patients should be offered participation in a large placebo-controlled clinical trial, although this is often not practical.

## Assessing response to treatment

Initial hospital clinic review is often 1–2-monthly. However, a more formal assessment of response should be made at 6 months, since some treatment effects are not observed until this time. Clinical response at this stage can be broadly classified as 'improvement', 'stability' or 'failure'.<sup>1</sup> Such responses can be assessed in terms of symptoms, changes in chest radiograph appearances and physiology (spirometry, gas transfer and 6-min walk). If clinical deterioration occurs at 6 months, drug therapy should be stopped or altered. Conversely, if stability or improvement occurs, existing therapy should be continued. Hospital follow-up subsequently should be individualized on the basis of clinical response.

## Other management issues

### Oxygen

A comprehensive review of home oxygen provision has been published elsewhere.<sup>43</sup> Long-term and ambulatory oxygen therapy should only be prescribed after appropriate assessment by a hospital specialist. Patients with chronic hypoxaemia ( $pO_2 \leq 7.3$  kPa) or hypoxaemia ( $pO_2$  7.3–8 kPa) plus evidence of secondary polycythaemia or pulmonary hypertension require long-term oxygen therapy for a minimum of 15 h daily. Ambulatory oxygen, in the form of light-weight oxygen cylinders, facilitates the provision of oxygen therapy during activities of daily living. It can also be prescribed to patients with a  $pO_2$  above the limit for long-term oxygen therapy but who demonstrate evidence of exercise arterial oxygen desaturation (defined as fall in saturation of 4% to a value <90%), and it improves maximal exercise performance in patients with interstitial lung disease.<sup>44</sup> There is no adequate evidence available to make firm recommendations regarding short-burst oxygen therapy, despite its use in many patients, and it should only be prescribed if an improvement in breathlessness and/or exercise tolerance is documented.<sup>43</sup>

### Osteoporosis

Risk factors particularly implicated in the development of osteoporosis include advanced age, reduced physical activity, poor nutritional status, cigarette smoking and long-term corticosteroid use. In 86 patients referred for lung transplantation, 55 of whom had UIP-pattern disease, osteopenia and osteoporosis were found in 57% and 13% of

patients respectively.<sup>45</sup> The majority of patients in the study were using oral corticosteroids (74%), with half already receiving preventive therapy for osteoporosis. Given the increased risk of bone loss and multiplicity of risk factors, patients with IPF should undergo bone densitometry and receive prophylaxis (bisphosphonate and supplemental calcium/vitamin D) and other advice according to published guidelines.<sup>46</sup>

### Pulmonary rehabilitation

This should be introduced when patients become aware of their disability, typically Medical Research Council dyspnoea grade 3 (the patient needs to walk slower than individuals of similar age on the level or to stop for breath when walking at their own pace on the level).<sup>47</sup> Supplementary oxygen during training may be necessary when clinically important desaturation (<90%) has been found at training load in the preliminary test.<sup>43</sup>

### Palliative care

In advanced IPF, there should be a low threshold for starting opioids and benzodiazepines for symptomatic relief of breathlessness.

### Lung transplantation

Lung transplantation has been comprehensively reviewed elsewhere.<sup>48</sup> However, single-lung transplantation is generally the procedure of choice, although as in most transplant procedures, the availability of donor organs is the limiting factor. The International Society of Heart and Lung Transplantation have suggested an upper age limit of 65 years for single-lung transplantation, which is relevant given that the mean age of onset of IPF is 67 years. Other factors that determine surgical feasibility include other major organ dysfunction, nutritional state, previous thoracic surgery, presence of osteoporosis, and psychological and social factors. Given the poor prognosis associated with IPF, some advocate referral of suitable patients at the time of diagnosis, although local guidelines should be followed.<sup>48</sup> In terms of referral for transplantation, it is important to identify those with severe disease (gas transfer <39% predicted) or who have limited disease with gas transfer >40% predicted but evidence of progression such as FVC fall >10% over 6 months and/or desaturation <88% during a 6-min walk. An international database of lung transplant patients has reported survival of 69% at 1 year, 42% at 5 years, and 15% at 10 years.<sup>49</sup>

## Acute exacerbations of IPF

Acute exacerbations, or 'accelerated IPF', are common, and preceded death in 47% of patients in a recent study.<sup>50</sup> Defining features include worsening dyspnoea over a month, new diffuse pulmonary opacities on chest radiography, worsening hypoxaemia, and rapid development of respiratory failure in the absence of infection or alternative diagnoses.<sup>51</sup> The pathology underlying the acute deterioration is usually that of diffuse alveolar damage (adult respiratory distress syndrome). Patients require high concentrations of oxygen, and are usually too unfit to undergo aggressive investigations. Empirical high-dose intravenous corticosteroids (for example once-daily methylprednisolone 500–1000 mg for 3 days), can be tried, although evidence suggesting any benefit is limited to case reports.<sup>52,53</sup> Several studies have shown that patients admitted to intensive care units have poor short- and long-term prognosis; in one study, 92% of hospital survivors died a median of 2 months after discharge.<sup>54</sup>

## Future therapies

### Pirfenidone

Pirfenidone (5-methyl-1-phenyl-2(1H)-pyridone) is an oral anti-fibrotic agent assessed recently in a double-blind, placebo-controlled, multi-centre study of 107 Japanese patients with IPF.<sup>55,56</sup> Although there was no significant change in the primary endpoint (6-min walk oxygen saturation at 6 months), there was a trend favouring active treatment in those with milder disease. Positive treatment effects were observed in secondary endpoints, including change in vital capacity measurements at 9 months and episodes of acute exacerbations of IPF. The latter occurred exclusively in the placebo group during the 9 months, leading to the Data Safety Monitoring Board advising early cessation of the study.<sup>56</sup> Further phase II and III studies evaluating pirfenidone are ongoing.

### Interferon- $\gamma$ -1b

Interferon  $\gamma$  is an endogenously-produced cytokine, with a wide variety of anti-fibrotic, anti-inflammatory and anti-infective effects. In a recent large randomized placebo-controlled study, the effects of subcutaneous interferon  $\gamma$ -1b were assessed in 330 patients with IPF.<sup>57</sup> The primary endpoint was disease-progression-free survival.

However, in this well-designed landmark study, no difference was seen between the two groups. Nonetheless, subgroup analyses suggested a potential mortality benefit with interferon  $\gamma$ -1b in patients with milder disease. A further larger study (600 patients) is currently in progress, to determine whether clinically worthwhile benefits can be achieved with active treatment.

### N-acetylcysteine

Oxidant/anti-oxidant imbalance occurs in the lungs of patients with IPF.<sup>58</sup> Glutathione functions as an anti-oxidant, and reduced levels are found in the lungs of patients with IPF.<sup>59</sup> N-acetylcysteine (NAC) is a precursor for glutathione synthesis. A recently completed double-blind, randomized, placebo-controlled study suggested that NAC supplementation, 600 mg three times daily, for 1 year, added to prednisolone and azathioprine, preserved vital capacity and gas transfer in patients with IPF to a greater extent than standard therapy alone (relative difference of 9% for FVC and 24% for gas transfer).<sup>60</sup> FVC and gas transfer declined in both groups. The difference in the extent of the decline reached statistical significance, but no significant difference in mortality between the two groups was identified.<sup>60</sup>

### Warfarin

Pulmonary embolism is commonly implicated as a common cause of death in patients with IPF.<sup>7</sup> Furthermore, microvascular injury is evident, with abnormal vascular phenotypes identified in patients with idiopathic pulmonary fibrosis and secondary pulmonary hypertension.<sup>61,62</sup> The effects of anticoagulant therapy for IPF have recently been described in a prospective Japanese study in which 56 patients with IPF (mean age 69 years, mean FVC 70% predicted) were randomized to receive either prednisone alone, or prednisolone plus anticoagulant therapy (warfarin as an outpatient and intravenous dalteparin if admitted to hospital).<sup>63</sup> Survival was significantly better in the anti-coagulant group (87% at 1 year, 63% at 3 years) vs. the non-anticoagulant group (58% at 1 year, 35% at 3 years). Overall, 5/23 patients died in the anti-coagulant group compared to 20/33 in the non-anticoagulant group. There was no significant difference in the probability of a hospitalization-free period between the two groups, and the major cause of clinical deterioration was acute exacerbation during follow-up. The mortality associated with acute exacerbations of IPF in the anti-coagulant group was significantly reduced, compared to that in the non-anticoagulant group



(18% vs. 71%,  $p=0.008$ ). Plasma D-dimer levels in patients who had an acute exacerbation of IPF and died were also significantly higher.<sup>63</sup> Other than the prevention of venous thromboemboli, it is uncertain whether anti-coagulants confer other benefits. However, it has been suggested that corticosteroids may induce a hypofibrinolytic effect, with anti-coagulants cancelling out the adverse effect of corticosteroids on the intravascular coagulation balance. In the same study, it is acknowledged that the effects of anticoagulation alone were not studied, in turn indicating that it is unclear whether the superior prognosis relates to the effects of anticoagulation alone.<sup>63</sup>

### Endothelin-1 antagonism (bosentan)

The endothelins are a family of 21-amino-acid peptides, with a variety of pro-fibrotic effects. Endothelin-1 (ET-1) is expressed in a variety of pulmonary diseases, including pulmonary vascular disease and pulmonary fibrosis.<sup>64</sup> In animal models, oral administration of bosentan (a dual ET-1 antagonist) protects against fibrosis in bleomycin-injured rats.<sup>65</sup> Bosentan is licensed for use in the treatment of patients with pulmonary arterial hypertension, and is currently being evaluated in IPF (the BUILD 1 trial: bosentan use in interstitial lung disease) and patients with interstitial lung disease associated with systemic disease (BUILD 2).<sup>66</sup> In both studies, the primary endpoint is the effect of randomized treatment upon a 6-min walk.

### Tumour necrosis factor $\alpha$ antagonism (etanercept)

Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a pro-inflammatory cytokine, and a critical mediator in the pathogenesis of pulmonary fibrosis.<sup>67</sup> It has a variety of pro-fibrotic effects, such as stimulation of fibroblast proliferation and collagen gene upregulation.<sup>68</sup> Mice missing TNF- $\alpha$  receptors or treated with soluble TNF- $\alpha$  receptors are relatively resistant to bleomycin/silica-induced fibrosis.<sup>69,70</sup> In humans with IPF, alveolar macrophages release increased amounts of TNF- $\alpha$ ,<sup>71</sup> and this has been localized particularly to hyperplastic type II alveolar epithelial cells. A number of cytokine gene polymorphisms have been described within the TNF- $\alpha$  gene on chromosome 6, and one of these has been associated with an increased risk of developing IPF.<sup>72</sup>

Etanercept is a recombinant soluble TNF- $\alpha$  receptor blocker. An open-label pilot study prospectively assessed the effects of etanercept in

nine patients with advanced IPF (mean FVC 46% predicted).<sup>73</sup> After an average of 9 months of treatment (twice-weekly etanercept and 10 mg prednisolone), one patient died, while improvement (>15% increase from baseline) in FVC was noted in three, with improvements in gas transfer in four. The study also suggested stabilization of lung function over a mean follow-up of 19 months.<sup>73</sup> Results of a recently completed Phase II, multi-centre, randomized, double-blind, placebo-controlled study are awaited.

### Imatinib

Imatinib mesylate, a phenylaminopyrimidine derivative and signal transduction inhibitor, is a potent and specific tyrosine kinase inhibitor that is already used in patients with chronic myeloid leukaemia and gastrointestinal tumours.<sup>74</sup> It also specifically inhibits platelet-derived growth factor (PDGF) receptor tyrosine kinase. PDGF is one of the key growth factors that play a role in the pathogenesis of pulmonary fibrosis. Imatinib has been shown to inhibit proliferation of mesenchymal cells in a bleomycin-induced pulmonary fibrosis model and a double-blind, placebo-controlled Phase II–III trial assessing the safety and efficacy of imatinib in patients with idiopathic pulmonary fibrosis has recently been completed, although not yet published.<sup>75</sup>

### Conclusion

Until recently, many clinicians have viewed the treatment of IPF with a sense of therapeutic nihilism. Hopefully in the future this can be replaced with some optimism, given greater understanding of the pathogenesis of IPF. In particular, the shift from considering IPF as a disease characterized by inflammation, to one of a disease characterized by aberrant wound healing, has led to the development of 'designer' anti-fibrotic therapies.<sup>14,56</sup> Large multicentre trials evaluating new drugs are urgently required, in order to provide clinicians and patients alike with a firm evidence-based platform from which to try to reverse the dismal outcomes of this devastating disease.

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