Research Review™
EDUCATIONAL SERIES

Idiopathic Pulmonary Fibrosis

About the Expert

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Professor Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a respiratory physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary artery hypertension, respiratory physiology, and venous thromboembolic disease. Lutz is happy to be contacted to discuss research ideas either as a sounding board or for consideration of future collaborations.

Abbreviations used in this issue

6MWT = 6-minute walk test (or distance)
AE = adverse event
AEC = alveolar epithelial cell
CI = confidence interval
CTGF = connective tissue growth factor
DLCO = diffusing capacity for carbon monoxide
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
GAP = gender, age and physiology
HR = hazard ratio
HRCT = high-resolution computed tomography
IIP = idiopathic interstitial pneumonia
IL = interleukin
ILD = interstitial lung disease
IPF = interstitial pulmonary fibrosis
LOXL2 = lysyl oxidase-like 2
PDGF = platelet-derived growth factor
PEY = person-exposure year
PFS = progression-free survival
QoL = quality of life
SGRQ = St George's Respiratory Questionnaire
TGF-β = transforming growth factor-β
TKI = tyrosine kinase inhibitor

This Educational Series provides detailed insight into disease-background and disease-management issues in idiopathic pulmonary fibrosis (IPF), a devastating disorder for which no cure is currently available. However, exciting new treatments and possible combination schedules are emerging with the potential to slow disease progression and/or reduce mortality, thereby substantially shifting the management paradigm for IPF. Several such treatments are discussed in this review, which is intended for use by respiratory physicians and specialists. Expert commentary is provided by Professor Lutz Beckert.

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Introduction

IPF is one of the most aggressive and frequent forms of idiopathic interstitial lung disease (ILD).[1] In individuals aged ≥75 years, the prevalence of IPF is estimated at >200 cases per 100,000 population, and mean survival is approximately 3 years. Traditionally, IPF was considered an inflammatory disorder, and treatment centred on anti-inflammatory or immunosuppressant medications such as azathioprine, cyclophosphamide and prednisone. However, IPF is now regarded as a fibrotic condition that results from abnormal wound healing after repeated pulmonary damage. A lung injury (the exact cause of which is unknown) affects alveolar epithelial cells (AECs), whose apoptosis or 'reprogramming' causes a cascade of events: vascular leak; extravascular coagulation; innate immune activation; fibroblast recruitment, proliferation and activation; and extracellular matrix synthesis and cross-linking. Several causes of alveolar injury have been suggested. These include cigarette smoke, environmental exposure to toxins (e.g. asbestos, avian toxins), gastro-oesophageal reflux, viral infection, and internal mechanisms such as autoimmunity, genomic instability or telomerase length.[1,2]

Potentially, we are witnessing a 'sea-change' in IPF management, with increased pathophysiological understanding of the disorder. Landmark studies in IPF management have also been published, such as ASCEND[3] and INPULSIS,[4] and several new compounds are currently being investigated in phase II trials.[2] Among the latter categories are agents that reduce AEC injury or reduce abnormal repair processes induced by AEC injury. These agents include monoclonal antibodies thought to target interleukin (IL)-13, integrin αvβ6, or the cross-linking enzyme lysyl oxidase-like 2 (LOXL2); inhibitors of connective tissue growth factor (CTGF); and antagonists of lysophosphatidic acid type 1 receptors. Lysophosphatidic acid is thought to have a fundamental role in promoting wound-healing responses that contribute to pulmonary fibrosis. Overall, there are now *'… strong grounds for optimism that new IPF therapies will improve the outlook for patients with this devastating disease.'*[2]

Disease classifications

Clinical distinction between IPF, the most common of the idiopathic interstitial pneumonias (IIPs), and other IIPs is particularly important because of the divergent management implications (**Figure 1**).[5,6] Other IIPs are thought to be primarily inflammatory conditions, whereas IPF is primarily a fibrotic disorder. The prognosis for other IIPs is generally much better than that for IPF. In IIPs other than IPF, the key intervention continues to be anti-inflammatory therapy, with the aim being to preserve functional status.[6]

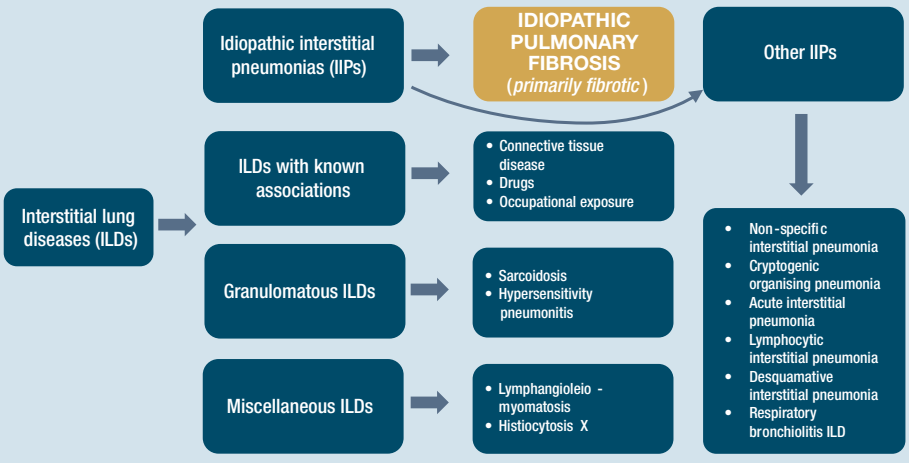

Figure 1. **Classification of interstitial lung diseases (ILDs).[6]**

Pathophysiology

IPF occurs mainly in middle-aged and elderly individuals and constitutes 20–30% of all ILD.[7] The clinical course of IPF may take several forms (**Figure 2**):[8]

- Subclinical — It is widely acknowledged that symptoms typically occur a median of 1–2 years before diagnosis, but 'subclinical', radiographic evidence of IPF may occur even before symptoms appear.
- Rapidly progressive — This primarily affects males who are heavy cigarette smokers. Symptoms are usually evident for <6 months before the first clinical presentation, and patients with rapidly progressive disease have reduced survival relative to those with a slowly progressive clinical course.
- Acute exacerbations — These are classed as the rapid worsening (within a few days to a few weeks) of symptoms, pulmonary function, and radiographic evidence (e.g. high-resolution computed tomography [HRCT] showing bilateral 'ground-glass' opacities and consolidation against a background reticular pattern); this is in the absence of discernible causes such as heart failure, infection, or pulmonary embolism. The prognosis for patients with acute exacerbations is poor.
- Slowly progressive — This is the traditional IPF phenotype and is characterised by slow deterioration of pulmonary function (forced vital capacity [FVC] decreases by a mean of 0.13–0.21 L each year), worsening dyspnoea, and death within a few years of diagnosis.

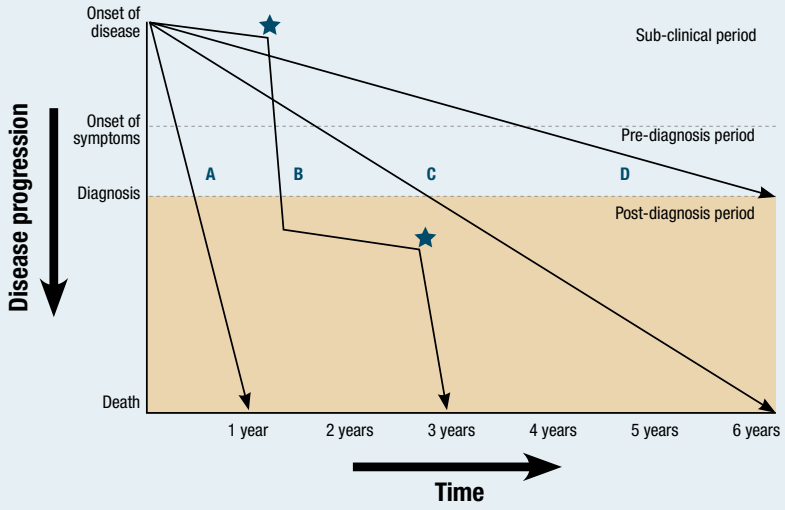

Figure 2. **Diagrammatic representation of possible clinical courses of IPF** (adapted from Ley et al.[8]). A subclinical period of disease progression exists during which only radiographic evidence of disease may be noted. This is followed by a symptomatic phase comprising clinical stages both pre- and post-diagnosis. The rate of deterioration and progression to death may be fast (*line A*), mixed (*line B*), or slow (*lines C and D*), with phases of relative disease stability interspersed with acute decline (*asterisks*).

IPF has considerably detrimental effects on quality of life (QoL).[9,10] It is characterised by gradual replacement of pulmonary parenchyma with fibrotic tissue, with consequences of cough, dyspnoea, impaired pulmonary function, and death.[2]

The cause of IPF remains unknown; however, besides 'triggers' such as cigarette smoke, environmental toxins, gastro-oesophageal reflux, and infections, various fibrogenic cytokines and growth factors released by AECs, and several genetic factors may also be involved in the pathogenesis of IPF. For instance, tumour necrosis factor-α, platelet-derived growth factor (PDGF), insulin-like growth factor-1, endothelin-1, and transforming growth factor-β (TGF-β) are all thought to be involved in fibrogenesis.[11,12] Furthermore, genetic mutations may lead to misfolding and accumulation of surfactant proteins C and A2, which in turn may lead to stress on the endoplasmic reticulum in AECs. The 'stressed' AECs may then have increased susceptibility to apoptosis when specific injuries (e.g. from bacterial or viral infection) occur. Mutations may also manifest in genes encoding the two main components of telomerase: the telomerase RNA component (*TERC*); and telomerase reverse transcriptase (*TERT*). Reduced telomerase function may then accelerate telomere shortening associated with aging, and telomere erosion may cause DNA damage, AEC aging and apoptosis.[2] Furthermore, a single-nucleotide polymorphism in the promoter region for the airway mucin gene (*MUC5B*) increases alveolar and airway mucus production. This genetic mutation has been associated with an increased likelihood (up to 14-fold greater) that individuals will develop IPF.[13–16]

Prevalence

The incidence and prevalence of IPF are greater than generally recognised in the middle-aged (>50 years) and elderly population and appear to be increasing over time.[17] For example, Raghu et al.[18] reported an incidence of 93 per 100,000 people aged ≥65 years, and a prevalence of 494 per 100,000. Earlier estimates in the US reported an incidence of 6.8–16.3 cases per 100,000 people.[2] In the UK, the incidence of IPF clinical syndrome in primary care reportedly increased by 35% from 2000 to 2008, with an overall incidence of 7.44 per 100,000 person-years.[19] Lung Foundation Australia has established the Australian IPF Registry and is currently recruiting. Release of comprehensive data from this registry is eagerly anticipated.

Prognosis

Currently, the best-validated prediction model in IPF is the so-called GAP score, which uses three readily available physiological parameters: gender, age, and physiology.[20] Each patient gains points according to gender (male, 1 point), age (>60 years, 1 point; or >65 years, 2 points), FVC (<75%, 1 point; <50%, 2 points), diffusing capacity for carbon monoxide (DLCO <55%, 1 point; <36%, 2 points), and inability to perform physiological tests (3 points). Thus, GAP score translates into survival prediction (**Table 1**).

Table 1. **GAP staging for IPF[20]**

Points	Stage	Mortality rate (% of pts)		
		At 1 year	At 2 years	At 3 years
0–3	I	5.6	11.0	16.0
4–5	II	16.0	30.0	42.0
6–8	III	39.0	62.0	77.0

GAP, gender, age and physiology; IPF, idiopathic pulmonary fibrosis; pts, patients.

An online version of the GAP score calculator (from the American College of Physicians) is available here.

Research advances continue to improve prognostic indicators in IPF. The presence of fibroblastic foci in histological specimens may be useful for predicting prognosis in ILD, and may also become a therapeutic target.[21] Serial measurement of extracellular matrix breakdown products (neoepitopes) may also predict survival in IPF.[22] In addition, measurement of telomere length in peripheral blood leucocytes led to discovery that short telomeres identify more aggressive disease and may become a pointer for treatment.[23]

Regarding recent, definitive, phase III clinical trials, significantly improved progression-free survival (PFS; p<0.001) was evident, as was significantly reduced all-cause mortality (p=0.01) and mortality from IPF (p=0.006).[3] Nonetheless, the prognosis for patients with IPF remains poor, with median survival reported as 2–5 years;[24] the 5-year mortality rate for IPF has been documented as approximately 70–80%. Most deaths are due to IPF progression rather than frequently occurring comorbidities, although significant causes of death in IPF can include bronchogenic carcinoma, heart failure, infection, and pulmonary embolism.[8]

Diagnosis and testing

Most patients with IPF present with at least a 6-month history of slow onset exertional dyspnoea, with or without a nonproductive cough. Some patients have no presenting symptoms, and IPF is identified by chance. However, accompanying symptoms may include arthralgia, chest pain, clubbing of finger and toenails, fatigue, low-grade fever, myalgia, and weight loss; these symptoms are sometimes uncommon.[25]

Accurate diagnosis of IPF, and distinction from other IIPs, is particularly important now that new treatments for IPF are becoming available.[5,6] A detailed patient history should be taken, and physicians should

carefully evaluate clinicopathological, physiological and radiographic findings. Physical examination may identify the following features:[25]

- 'Velcro' crackles — fine, bibasilar crackles noted in most patients on inspiration.
- Digital clubbing — this is typically present in about one-quarter to one-half of cases.
- Pulmonary hypertension at rest — this may present in about one-third to one-half of patients.[2]

Pulmonary function tests are useful for identifying a reduced DLCO or limiting ventilatory defects. Some physicians use a 6-minute walk test (6MWT) at the first clinical evaluation of patients with suspected IPF. If patients desaturate to <88% during a 6MWT, gradual deterioration of DLCO (>15% over 6 months) is a strong prognostic indicator of increased mortality.[8,25]

HRCT is a sensitive, specific and pivotal tool for diagnosing IPF.[25] Such scanning reveals bilateral, subpleural, reticular opacities or honeycomb changes in IPF patients; these changes are most marked in basal regions.[6] Although some abnormalities may be evident on chest X-ray, none of these has diagnostic specificity for IPF.[25]

Surgical lung biopsies are not routinely required to confirm a diagnosis of IPF and should be reserved for when differentiation between usual interstitial pneumonia and other IIPs is needed.[25] Only about 8–12% of patients may undergo a surgical lung biopsy because of the attendant risks of mortality (3–4%), infection, prolonged air leak (6–12%), or pain at the biopsy site (57%). Recent encouraging data suggest that transbronchial cryobiopsy may find a role as a diagnostic procedure instead of surgical lung biopsy.[26]

Burden of disease

Common comorbidities in IPF include: chronic obstructive airway disease; coronary artery disease; emphysema; obesity; gastro-oesophageal reflux disease and obstructive sleep apnoea (each present in up to approximately 90% of patients with IPF); and pulmonary hypertension (present in up to one-third to one-half of patients with IPF).[2,27] A specific focus in the future treatment of IPF may be on profibrotic pathogenic mediators (e.g. angiotensin II, fibroblast growth factor, PDGF, TGF-β) involved in both IPF and pulmonary hypertension.[2]

Another indication of the major disease burden posed by IPF can be gleaned from mortality data for the condition. Annualised mortality rates in the US have been estimated at 64.3 deaths per million (men) and 58.4 deaths per million (women).[25] However, mortality from the condition appears to be increasing steadily worldwide. Depending on the disease-classification codes used, Hutchinson et al.[28] reported an overall 2–3% annual increase in mortality in a diverse range of countries. In Australia, age-standardised mortality for 'other interstitial pulmonary diseases with fibrosis' (*International Classification of Diseases* code J84.1) increased from 4.23 per 100,000 population in 2000 to 5.08 per 100,000 in 2011.[28] In the UK, it is estimated that annual mortality from IPF clinical syndrome is greater than that from leukaemia, lymphoma, mesothelioma, ovarian cancer, and renal cancer.[19]

In patients with IPF, mortality rates increase with increasing age, and are greater in men than women. The rates vary seasonally and are greatest during the winter months, even after exclusion of infectious causes.[8] It is estimated that approximately 60% of patients with IPF die from, rather than with, the disorder. Among patients who die with IPF, death typically occurs after an acute exacerbation. Conversely, if an acute exacerbation is not the cause of death, increased risks of cardiovascular or venous thromboembolic events usually contribute to mortality.[25] Overall, the principal causes of death in patients with IPF are acute exacerbations, acute coronary syndrome, congestive heart failure, infections, lung cancer, and venous thromboembolism.[29]

Unmet patient needs

Many IPF patients are diagnosed late and have many unmet healthcare needs in the interval between symptom onset and time of diagnosis.[30] A German IPF registry, for example, reported that the time from first symptoms to diagnosis was approximately 2 years.[31]

Arguably, unmet healthcare needs are also a major issue in the New Zealand clinical setting, as has been suggested by various patient advocacy groups. Recently, in Europe, patient advocacy groups were interviewed and directed development of an IPF Patient Charter, which highlights unmet healthcare needs and serves as a 'call to action' for healthcare policy makers.[32] Principal components of the IPF Patient Charter comprise the needs to:[33]

1. Improve diagnosis — i.e. methods for teaching ILD diagnosis should be improved, as should current diagnostic tools (e.g. auscultation via electronic stethoscope, HRCT).
2. Improve access to treatment — especially regarding pulmonary rehabilitation, enhanced use of pirfenidone and nintedanib, and lung transplantation.
3. Fully utilise multidisciplinary healthcare teams consisting of specialists and allied healthcare professionals, such as physiotherapists, nurse specialists, and psychologists.
4. Enhance dissemination, at diagnosis and during follow-up, of detailed patient information about IPF, treatment (including palliative care), and comorbidities.
5. Improve communication about, and coordination of, palliative care and end-of-life preferences.
6. Increase research funding, with the specific goals of enhanced investigation and prevention of fibrotic lung disease.

Towards the end of 2015, almost 10,000 people had signed the IPF Patient Charter, but to ensure timely regulatory changes, more signatures are needed.[33]

Treatment of IPF

As there is no known cure for IPF, the basis of management has traditionally been to provide symptomatic relief and effective management of comorbidities.[6,25] Smokers should be advised to stop, and smoking cessation therapy should be offered if necessary. Domiciliary oxygen support may be needed and, specifically, all patients with hypoxaemia (partial pressure of oxygen <55 mmHg [<60 mmHg for patients with concurrent pulmonary hypertension], or oxygen saturation by pulse oximetry <88%) at rest or during exercise should receive oxygen; the principal aim is to maintain oxygen saturation ≥90% at rest, during sleep, and during exertion.[6,25] Pulmonary rehabilitation may be appropriate for increasing exercise capacity in some patients,[34] and all patients should be vaccinated against pneumococcal and influenza infections.[6,25] Comorbidities, such as chronic obstructive pulmonary disease, coronary artery disease, gastro-oesophageal reflux disease, and obstructive sleep apnoea, should be managed according to best-practice guidelines,[25] and patient referral for lung transplantation should be considered when DLCO is <40%, or when disease progression is significant over 6 months (≥10% decrease in FVC and/or ≥15% decrease in DLCO).[6] It remains unclear whether unilateral or bilateral lung transplantation provides the best long-term outcomes.[27]

'Patient-centredness' is now an important consideration in IPF management.[10,35] That is, increasing interest is focusing on patients' perspectives and how these can be used to improve clinical care.[10] Patient-centredness refers to *'… a partnership among practitioners, patients, and their families … to ensure that decisions respect patients' wants, needs, and preferences.'*[35] In other words, patient-reported outcomes such as health-related QoL, and the effects of novel drugs on QoL, will now likely have far greater bearing on clinical decision-making processes. Important issues to consider are that fatigue may be more troublesome than dyspnoea for many patients with IPF. A productive cough may also be more problematic than a dry cough, and many patients may have difficulties with phlegm clearance.[35]

In addition, a significant aspect of recent American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines for IPF management is that strong and conditional treatment recommendations are based on the perspectives of patients, clinicians and policy makers.[27] From the patients' viewpoint, a strong recommendation dictates that *'… most individuals in this situation would want the recommended course of action, and only a small proportion would not.'* Such a recommendation includes that against the use of combination prednisone, azathioprine, and *N*-acetylcysteine therapy (see *Pharmacotherapy*). A conditional recommendation dictates that *'… the majority of individuals in this situation would want the suggested course of action, but many would not.'* Conditional recommendations in these definitive guidelines comprise those for the use of pirfenidone and nintedanib.[27]

Because of the unpredictable clinical course of IPF, which is rapidly progressive in some cases, and because of significant patient suffering, many patients require early referral to palliative care.[36]

Pharmacotherapy

The PANTHER-IPF trial[37] informs recent guidelines[27] that immunomodulatory therapy with prednisone and azathioprine is not appropriate in patients with IPF.[5] Specifically, the combination of prednisone, azathioprine and *N*-acetylcysteine should be avoided in IPF, as also should treatment with warfarin, certain selective tyrosine kinase inhibitors (TKIs), and some selective endothelin receptor antagonists and phosphodiesterase-5 inhibitors (e.g. sildenafil).[4]

Recent research into the management of IPF has focused on the novel agents pirfenidone (Esbriet®) and nintedanib (Ofev®), both of which are registered by Medsafe in New Zealand. Although the precise mechanism of pirfenidone action is unclear, the compound has antifibrotic, anti-inflammatory, antioxidant and pleiotropic effects. Pirfenidone reduces loss in forced expiratory volume in 1 second (FEV_1) and improves survival; however, it does not improve dyspnoea. Nintedanib is a TKI that possesses antifibrotic and anti-inflammatory activity, and which reduces the loss of pulmonary function and may improve dyspnoea; however, it does not improve survival.[1,5]

Importantly, definitive, large-scale, phase III studies such as ASCEND (pirfenidone)[3] and INPULSIS (nintedanib)[4] demonstrated slowed progression of the decline in pulmonary function in IPF patients. Pooled phase III data from more than 1,200 patients involved in the ASCEND and two CAPACITY trials revealed a 48% reduction in 1-year mortality for pirfenidone relative to placebo (hazard ratio [HR] 0.52; 95% confidence interval [CI]: 0.31, 0.87; p=0.01). Moreover, the relative risk reduction for treatment-emergent 1-year mortality due to IPF was 68% (HR 0.32; 95% CI: 0.14, 0.76; p=0.006). The size of the treatment effect on mortality was large and internally robust across various analyses and subgroups.[3,24] Besides mortality, a comprehensive analysis of pooled data from the ASCEND and CAPACITY studies revealed major, statistically significant improvements in a diverse range of primary and secondary outcome measures of IPF disease progression.[38]

The onus is now shifting towards 'real-world' studies and registries, which in some ways provide clinically more meaningful data than that from rigidly controlled clinical trials. Indeed, clinical trials often have a study bias towards inclusion of patients with more moderate disease, fewer comorbid conditions, ideal follow-up, and typical IPF presentations. Generally, recent clinical trials in IPF have included only limited numbers of patients with severe disease or with combined pulmonary fibrosis and emphysema syndrome.[17]

In the real-world setting, the INSIGHTS-IPF German registry is continuing to evaluate disease-management trends in IPF.[17,31] Data for the first 502 patients included in the registry revealed: greater disease severity at diagnosis than in various recent randomised controlled studies; high rates of previous exposure to avian factors and asbestos; corticosteroid use in approximately one-quarter of patients, despite this being discouraged by recent guidelines; and pirfenidone use in fewer than 50% of patients.[31] These issues suggest that increased educational efforts are required to ensure broader dissemination of optimum, evidence-based practice methods for IPF management.[17] Meanwhile, long-term, observational studies in the real-world setting — RECAP[39] (which is an open-label extension of the phase III trials) and PASSPORT[40] — are ongoing with pirfenidone. An interim analysis of RECAP data revealed 69% survival after 4.4 years. Interim results from PASSPORT indicate that only 16% of patients discontinued treatment because of adverse events (AEs); serious AEs were rare.[24]

Several phase II studies of novel compounds (e.g. IL-13 antagonists, integrin αvβ6 antagonists, inhibitors of LOXL2 or CTGF, and antagonists of lysophosphatidic acid type 1 receptors) are ongoing in IPF;[2] some of these studies are being conducted in New Zealand. If a patient is interested in participating in a research trial, contact your nearest specialist service.

Progression of research is now also moving towards evaluation of combination pirfenidone-plus-nintedanib therapy for cumulative benefit or potential synergy. Already, a phase II Japanese trial has identified that this combination has an acceptable safety and tolerability profile.[41] Other studies are currently recruiting participants: for example, a US study in 80 patients that is due for completion in April 2017 (NCT02598193); and an international study in 100 patients that is due for completion in January 2017 (NCT02579603).

A major pharmacotherapeutic challenge in the future management of IPF will be the successful development of appropriate combination schedules.[5] Also warranted are future detailed investigations of the potential roles of cotrimoxazole and thalidomide, since recent studies suggest that cotrimoxazole may have an important anti-infective role in IPF,[42] and that thalidomide may become useful in improving QoL in patients with IPF.[43] In addition, relevant pharmacogenomic, pharmacoeconomic and biomarker studies will provide valuable disease-management information.[27] *'With new therapies becoming available, the challenge now is how to personalize the approach to management using the biomarkers and genetic markers available or, alternatively, to devise strategies for the development of combination regimens.'*[5]

CLINICAL STUDIES

A phase III trial of pirfenidone in patients with idiopathic pulmonary fibrosis

Authors: King TE Jr, et al.

Background: Two phase III studies (a Japanese trial and CAPACITY 004) confirmed that pirfenidone reduced disease progression in IPF by reducing the decline in vital capacity or FVC. However, a third phase III trial (CAPACITY 006) failed to meet this endpoint. The **AS**sessment of pirfenidone to **C**onfirm **E**fficacy a**ND** safety in IPF (ASCEND) trial was therefore conducted to further evaluate the beneficial effects of pirfenidone on disease progression.

Methods: This randomised, double-blind study was conducted at 127 sites in 9 countries, including Australia and New Zealand. A total of 555 patients with IPF were randomised to receive pirfenidone 2,403 mg/day or placebo for 1 year. The primary study outcome was change in FVC or mortality at 1 year. Secondary study endpoints comprised 6-minute walk distance, PFS, dyspnoea, and total mortality and mortality due to IPF.

Results: At 1 year, a 47.9% reduction was evident in the proportion of pirfenidone versus placebo recipients who had a decline of ≥10% in predicted FVC or who died (16.5% vs 31.8% of patients; p<0.001; **Figure 3**). Moreover, the relative proportion of pirfenidone-treated patients versus placebo recipients without a decline in FVC was increased by 132.5% (22.7% vs 9.7% of patients; p<0.001). Pirfenidone significantly reduced the endpoints of decline in 6-minute walk distance or death (p=0.04); and the relative risk of death or disease progression (–43%; HR 0.57; 95% CI: 0.43, 0.77; p<0.001). In ASCEND alone, no significant pirfenidone–placebo differences were

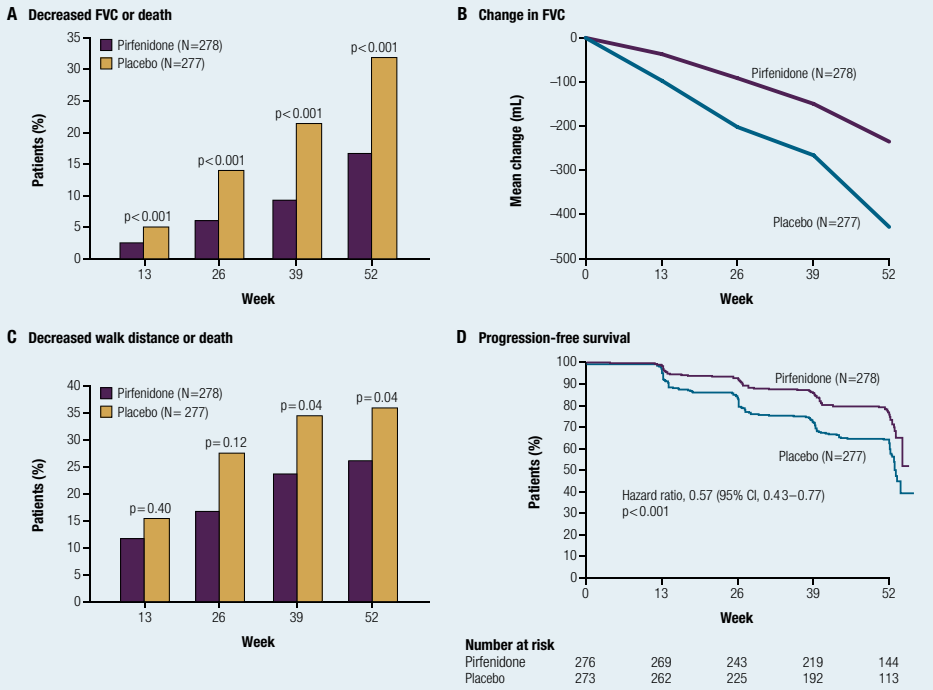

Figure 3. **Primary and secondary outcome data from the ASCEND trial** (adapted from King Jr et al.[3]). A, Patients with a ≥10% decrease in predicted FVC or death; B, Mean decrease from baseline in FVC; C, Patients with a ≥50 m decrease in 6-minute walk distance or death; D, Kaplan-Meier estimate of PFS.

noted in dyspnoea scores, all-cause mortality, or mortality from IPF. Nonetheless, in a prespecified pooled analysis of data from the ASCEND and CAPACITY trials, pirfenidone versus placebo was shown to significantly reduce all-cause mortality (HR 0.52; 95% CI: 0.31, 0.87; p=0.01) and mortality due to IPF (HR 0.32; 95% CI: 0.14, 0.76; p=0.006). AEs rarely led to treatment cessation. Skin-related and gastrointestinal AEs were more frequent in the pirfenidone than placebo group.

Conclusion: In summary, pirfenidone administration for 1 year led to significant slowing of IPF disease progression. The effect of pirfenidone to slow the decline in FVC was evident as early as week 13 and continued throughout treatment. Pooled phase III data revealed that pirfenidone significantly reduced all-cause mortality and that due to IPF.

Comment: Pirfenidone is an orally available antifibrotic agent. The above ASCEND trial is the fourth randomised, double-blind, placebo-controlled trial. The CAPACITY studies in September had been interpreted by European countries and Canada as positive, but in the United States, Australia and New Zealand as negative. The ASCEND study slowed the decline in lung volumes and 6-minute walk distance, and may also indicate reduced mortality in patients with IPF. **Bottom line: The results of this landmark study give us hope that we have the first treatments available for this progressive lung disease.**

Reference: N Engl J Med 2014;30:2083–92.
Full article.

Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis

Authors: Richeldi L, et al.

Background: Nintedanib, an inhibitor of multiple TKIs, was shown in the phase II TOMORROW study to be associated with a reduced decline in FVC, fewer acute exacerbations, and preserved QoL in patients with IPF. The next step in nintedanib development was the conduct of two duplicate phase III studies — INPULSIS-1 and INPULSIS-2 — to assess the efficacy and safety of nintedanib 150 mg twice daily in patients with IPF.

Methods: The INPULSIS studies were randomised, double-blind, placebo-controlled trials conducted at 205 sites in 24 countries, including Australia. A total of 1,066 patients received nintedanib or placebo for 1 year. The primary study outcome was the annual rate of FVC decline. Principal secondary study outcomes comprised time to first acute exacerbation, and change from baseline in St George's Respiratory Questionnaire (SGRQ) score.

Results: In INPULSIS-1, the adjusted annual decline in FVC was significantly less in the nintedanib than placebo group (–114.7 vs –239.9 mL; p<0.001); the same was true in INPULSIS-2 (–113.6 vs –207.3 mL; p<0.001; **Figure 4**). No significant nintedanib–placebo difference was noted in time to first acute exacerbation in INPULSIS-1 (HR 1.15); however, the converse was true in INPULSIS-2 (HR 0.38; 95% CI: 0.19, 0.77; p=0.005). Regarding change in SGRQ score over 1 year, no significant difference manifested between the nintedanib and placebo groups in INPULSIS-1; conversely, in INPULSIS-2, a significantly smaller SGRQ score increase (i.e. greater preservation of QoL) was noted in the nintedanib than placebo group (2.80 vs 5.48 points; p=0.02). A prespecified pooled analysis of data from INPULSIS-1 and INPULSIS-2 revealed no significant differences between nintedanib and placebo in terms of all-cause mortality, death from a respiratory cause, or mortality between randomisation and 1 month after the last dose of study drug. The most frequent AE in nintedanib-treated patients was diarrhoea (61.5–63.2% of patients vs 18.3–18.6% of placebo recipients).

Conclusion: Nintedanib significantly slowed IPF disease progression, and had a variable effect on QoL preservation. Pooled INPULSIS data revealed no significant survival benefit for nintedanib.

Comment: Nintedanib is an orally available TKI that has been shown in previous studies to reduce the decline in FVC in IPF. These international authors report on the INPULSIS trial with more than 1,000 patients with IPF. Like pirfenidone, nintedanib has gastrointestinal side effects, with 60% of patients reporting diarrhoea; corresponding proportions for pirfenidone and placebo are 28% and 20%, respectively. However, the trial demonstrated reduced loss of FVC, and also improved QoL and time to first exacerbation. **Bottom line: This landmark study gives us hope that we have the first treatments available for IPF.**

Reference: N Engl J Med 2014;370:2071–82.
Full article.

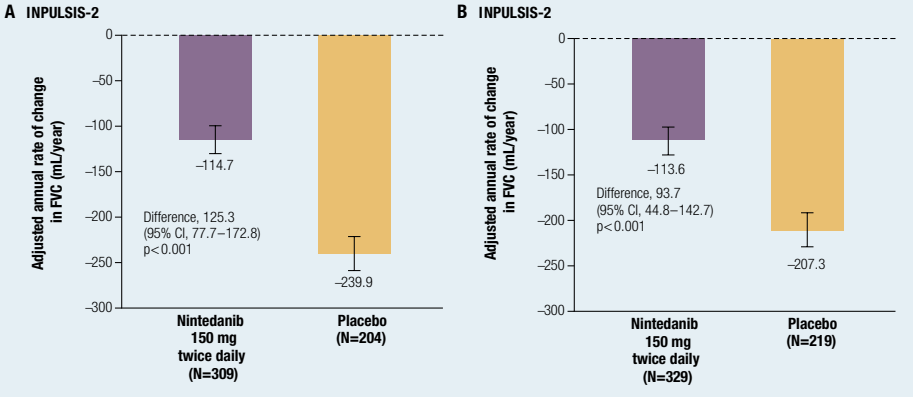

Figure 4. **Primary study outcome data from INPULSIS-1 and INPULSIS-2** (adapted from Richeldi et al.[4]).

Safety of pirfenidone in patients with idiopathic pulmonary fibrosis: integrated analysis of cumulative data from 5 clinical trials

Authors: Lancaster, et al.

Background: A detailed analysis of long-term safety and tolerability data was conducted for the integrated population involved in five clinical studies assessing pirfenidone in IPF.

Methods: Data were pooled from three phase III trials (ASCEND, CAPACITY 004 and CAPACITY 006) and two ongoing observational studies, one of which was RECAP. Safety outcomes were evaluated from the first study dose until 1 month after the last dose of study drug.

Results: Overall, 1,299 patients were included in the analysis, with a total exposure to pirfenidone of 3,160 person-exposure years (PEYs). The median duration of exposure was 1.7 years (range 1 week to 9.9 years), and the mean daily dose of pirfenidone was 2,054 mg. Among the most frequent AEs in the integrated population were gastrointestinal events (nausea 37.6% of patients; diarrhoea 28.1%; dyspepsia 18.4%; vomiting 15.9%) and rash (25.0%). Most of these AEs were of mild-to-moderate severity, and rarely required treatment cessation. Hepatic transaminase levels were raised to more than 3 times the upper limit of normal in 3.1% of patients (adjusted incidence 2.3 per 100 PEYs). However, these increases were typically transient, reversible with dosage adjustment, and without major clinical sequelae.

Conclusion: Over a long-term treatment period of up to 9.9 years in almost 1,300 patients with IPF, pirfenidone proved to be safe and generally well tolerated.

Comment: Thirteen of the authors of this review were on the steering committee of the ASCEND or CAPACITY studies. They report on 1,299 participants who had been taking pirfenidone for a mean of 1.7 years, amounting to 3,160 PEYs. Almost all participants reported some AEs. However, the most common AE leading to discontinuation was progression of IPF. Gastrointestinal events, dyspepsia, vomiting and rash were mild to moderate and rarely caused treatment cessation. **Bottom line: Treatment with pirfenidone appears effective and safe. It is associated with predictable and manageable gastrointestinal and skin side effects.**

Reference: BMJ Open Resp Res 2016;3:e000105.
Full article.

EXPERT'S COMMENTS

Expert summary comment: We are witnessing a watershed moment in the management of IPF. About 15 years ago we agreed on a new nomenclature for IIP, including HRCT-based criteria for IPF. The last decade has also seen several, essentially negative, randomised controlled trials in the treatment of IPF. The most important of these was the PANTHER trial, which demonstrated that prednisone, azathioprine and *N*-acetylcysteine increase mortality in IPF. Current international guidelines advise against the use of prednisone/azathioprine in stable IPF.

The prognosis in IPF remains poor and many healthcare needs remain unaddressed. Nonetheless, two new antifibrotic agents — pirfenidone and nintedanib — have been shown to improve outcomes in the management of IPF. Both agents have limitations and come with considerable side effects; however, both also have a good evidence-base and are awaiting funding. As we gain clinical experience with these novel agents, we are entering a new era of treatment possibilities for IPF.

TAKE-HOME MESSAGES:

- Traditionally, IPF was considered an inflammatory disorder. It is now regarded as a fibrotic condition resulting from abnormal wound healing.
- Steroids and azathioprine have been shown to increase mortality and should not be used in the treatment of stable IPF.
- The incidence and prevalence of IPF are increasing in line with increasing longevity in the general population.
- The prognosis for patients with IPF remains poor. Median survival has been reported as 2–5 years, and the 5-year survival rate as approximately 20–30%.
- IPF management has traditionally been based on providing symptomatic relief; many patients require early referral to palliative care.
- Exciting new treatments are emerging with the potential to slow disease progression and/or reduce mortality.
- Pirfenidone reduces loss in FEV_1, and improves survival but not dyspnoea. Nintedanib reduces loss of pulmonary function and may improve dyspnoea; however, it does not improve survival.

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