



POSITION STATEMENT

Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia*

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a fibrosing interstitial lung disease (ILD) of unknown aetiology with a median survival of only 2–5 years. It is characterized by progressive dyspnoea and worsening lung function, ultimately resulting in death.

Until recently, there were no effective therapies for IPF; however, with the publication of two landmark clinical trials in 2014, the anti-fibrotic therapies, nintedanib and pirfenidone, have gained widespread approval.

This position paper aims to highlight the current evidence for the treatment of IPF, with particular application to the Australian and New Zealand population. We also consider areas in which evidence is currently lacking, especially with regard to the broader IPF severity spectrum and treatment of co-morbid conditions. The utility of non-pharmacological therapies including pulmonary rehabilitation, oxygen as well as symptom management thought to be important in the holistic care of IPF patients are also discussed.

Key words: idiopathic pulmonary fibrosis, interstitial lung disease, nintedanib, pirfenidone, treatment.

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*This document has been peer reviewed by independent experts and subsequently endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) in July 2017.

Received 27 July 2017; accepted 31 July 2017.

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Abbreviations: 6MWD, 6-min walk distance; 6MWT, 6-min walk test; ACE, AntiCoagulant Effectiveness; AE, acute exacerbation; AE-IPF, AE of IPF; AZA, azathioprine; cHP, chronic hypersensitivity pneumonitis; CPAP, continuous positive airway pressure; CPFE, combined pulmonary fibrosis and emphysema; CTD, connective tissue disease; CTD-ILD, CTD-related ILD; CTGF, connective tissue growth factor; DL_{CO}, diffusing capacity of lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; f-ILD, fibrotic ILD; FVC, forced vital capacity; GAP, gender, age and physiology; GORD, gastro-oesophageal reflux disease; IFN- γ , Interferon gamma; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LTOT, long-term oxygen therapy; MDM, multidisciplinary meeting; MMP, matrix metalloproteinase; MUC5B, mucin 5B; NAC, N-acetylcysteine; NZ, New Zealand; OSA, obstructive sleep apnoea; PH, pulmonary hypertension; PRED, prednisolone; SDB, sleep-disordered breathing; TOLLIP, toll-interacting protein; TSANZ, Thoracic Society of Australia and New Zealand; UIP, usual interstitial pneumonia.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a fibrosing interstitial lung disease (ILD) of unknown aetiology. IPF is characterized by progressive dyspnoea and worsening of lung function, ultimately resulting in death, with a median survival of only 2–5 years.¹ While the pathogenesis remains unclear, it is likely multifactorial, with both a genetic predisposition, as well as environmental factors including smoking and industrial dust exposures thought to contribute. While the exact incidence of IPF in Australia is unknown, recent studies indicate that the prevalence of IPF is increasing globally and is estimated to be between 1.25 and 63 patients per 100 000.²

The hallmark of IPF is the presence of a usual interstitial pneumonia (UIP) pattern on imaging and/or histopathology.¹ The diagnosis of IPF can be difficult as clinical and radiological features often overlap with other ILD including chronic hypersensitivity pneumonitis (CHP), connective tissue disease-related ILD (CTD-ILD) and fibrotic nonspecific interstitial pneumonia (fNSIP). There is also significant phenotypic heterogeneity within IPF, with some patients having rapidly progressive disease, and others having a more stable disease course.³ This complexity is acknowledged within the most recent 2011 ATS/ERS/JRS/ALAT guidelines which call for a multidisciplinary discussion to exclude other known causes of ILD and to assess for a UIP pattern on radiology and/or histology. According to these guidelines, IPF diagnosis can be categorized as 'definite', 'probable', 'possible' or 'inconsistent with' IPF, according to the presence of UIP features. The diagnosis of IPF by multidisciplinary evaluation is further discussed in detail in an accompanying position paper in this edition of the journal.

This position paper aims to highlight the current evidence for the treatment of IPF, adopted from the international guidelines on IPF treatment published in 2015,⁴ with particular application to the Australian and New Zealand (NZ) population. We also consider areas in which evidence is currently lacking, especially with regard to the broader IPF severity spectrum, as well as non-pharmacological therapies thought to be important in the holistic care of IPF patients. A suggested treatment algorithm based upon current evidence and expert opinion is also presented.

METHODS

This position paper highlights important aspects of the treatment of IPF as it pertains to Australia and NZ, and do not represent treatment guidelines *per se*. T.J.C. was appointed to chair a panel of 18 members, who were selected for their expertise in various aspects of IPF diagnosis and management. The expert panel was comprised of 15 respiratory physicians, 1 physiotherapist, 1 respiratory nurse as well as a patient representative (D.B.) who had opportunity to contribute to all stages of the writing process. There was widespread representation from both Australia and NZ. After an initial discussion with all authors, authors were

assigned specific sections for completion. Comprehensive literature review was performed and articles for inclusion were determined by each writing group for their assigned sections and were not systematically evaluated. Where evidence was lacking, expert opinion was provided on how to address these areas. All sections, including referenced articles, were then reviewed and discussed at subsequent meetings where all authors had the opportunity to contribute to all sections.

After the completion of specific sections by assigned authors, three authors compiled and edited the complete manuscript (H.E.-A.J., P.H. and T.J.C.). All authors reviewed and approved the final manuscript. The committee did not receive any commercial sponsorship and all panel members worked on an honorary basis. This position paper is endorsed by the Thoracic Society of Australia and New Zealand (TSANZ) and will be disseminated by publication in *Respirology*, and via the TSANZ and Lung Foundation Australia in a collaborative pre-specified translation plan. The clinical relevance of the document will be reviewed after a maximum of 5 years.

GENERAL MEASURES

It is important to discuss general health measures with all patients with IPF, as well as their families, to ensure active engagement. The management of IPF patients involves many health professionals including the respiratory physician, IPF nurses, pharmacists, physiotherapists and other allied health professionals, as well as palliative care and transplant teams. As such, the patient's local general practitioner plays a vital role in the coordination of care of these patients and should be involved at all stages.

The comprehensive management of patients with IPF not only involves the consideration of IPF-specific pharmacological therapies for disease management but also the management of other co-morbidities, disease-related symptoms, overall general health as well as patient education. While specific evidence for the management of general health measures is lacking in IPF, these global health factors can have implications beyond IPF disease. For example, it is important for patients to maintain good nutrition and a healthy body weight as this is often a consideration for transplant eligibility. Smoking cessation is also important in that regard and also has implications regarding the use of long-term oxygen therapy (LTOT). Smoking has also been shown to decrease systemic exposure to both nintedanib and pirfenidone and smoking cessation should be strongly advised when initiating either of these medications.⁵

Depression and anxiety are other common but often overlooked co-morbidities in IPF patients, associated with a poorer quality of life and poorer outcomes.⁶ Underlying depression and anxiety are often correlated with the presence of debilitating symptoms such as dyspnoea, a symptom affecting up to 90% of patients at diagnosis.⁷ Depression and anxiety may also be exacerbated by medication side effects, acute exacerbations

(AE) and deterioration requiring hospital admission, as well as fear associated with the overall poor prognosis in IPF. There are no controlled studies addressing the management of depression and/or anxiety in IPF patients.

PHARMACOLOGICAL THERAPY

Anti-fibrotic therapy

Until recently, no effective therapies were available for IPF. However, following a number of landmark clinical trials (Table 1), nintedanib and pirfenidone are now recommended for the treatment of IPF in the updated multinational clinical practice guidelines,¹ and are licensed for the treatment of IPF in an increasing number of countries. Figure 1 suggests an algorithm for the management of patients with IPF.

Pirfenidone

Pirfenidone is a novel anti-fibrotic agent, and while its precise molecular target remains unknown, it exhibits pleiotropic anti-fibrotic actions via several pathways. The first human clinical trial of pirfenidone in IPF was reported in 1999,³⁰ and since that time, it has been evaluated in four phase 3 randomized controlled trials. Taniguchi *et al.* initially reported reduced decline in vital capacity and improved progression-free survival in 275 Japanese patients,⁹ and this was followed by two concurrent multinational studies (CAPACITY[®] 004 and 006) involving 779 patients in the USA, Europe and Australia.¹⁰ In the positive 004 study, high-dose pirfenidone (2403 mg/day) was associated with a significantly reduced mean decline in percentage predicted forced vital capacity (FVC) compared with placebo at week 72 ($-8.0 \pm 16.5\%$ and $-12.4 \pm 18.5\%$, respectively; $P = 0.001$). While the 006 study was negative (with a decline in mean FVC of $-9.0 \pm 19.6\%$ and $-9.6 \pm 19.0\%$ in the pirfenidone and placebo arms, respectively; $P = 0.5$), the pre-specified pooling of the study data demonstrated a significant effect of pirfenidone (2403 mg/day) in reducing the rate of decline in FVC.

While the European Medicines Agency approved pirfenidone for use in IPF in 2011, regulatory authorities in the US requested additional trial data. The ASCEND[®] study¹³ confirmed the positive effect of pirfenidone, with a relative reduction of 47.9% in the proportion of patients who had an absolute decline of FVC $\geq 10\%$ predicted, or who died, at week 52. A pre-specified survival analysis (including data from the CAPACITY[®] and ASCEND[®] studies), demonstrated a reduction in all-cause and IPF-related mortality (hazard ratio: 0.35; $P = 0.03$). Subgroup analysis (using pooled data from both CAPACITY[®] and ASCEND[®] studies)³¹ demonstrated the treatment effect of pirfenidone to be generally consistent across all demographic variables and baseline measures of IPF disease severity. An analysis of safety outcomes for the CAPACITY[®] and ASCEND[®] studies, including 1299 patients with a median duration of pirfenidone exposure of 1.7 years (range: 1 week–9.9 years), reported nausea (37.6%), diarrhoea (28.1%), dyspepsia (18.4%),

vomiting (15.9%) and photosensitive rash (25%) as the most common adverse events, although these were generally mild and without significant clinical consequences.³² Nausea and rash were the adverse events most commonly associated with treatment discontinuation in 1.7% and 1.5% of patients, respectively. Particularly relevant to the Australian and NZ climate is the risk of photosensitivity, and patients should be counselled regarding the avoidance of direct sunlight exposure.

Nintedanib

Nintedanib (formally known as BIBF 1120), an intracellular inhibitor of tyrosine kinases, attenuates fibrosis via several mechanisms, including reduction in fibroblast proliferation and differentiation of fibroblasts to myofibroblasts.^{33,34} In a randomized, double-blind, placebo-controlled phase 2 dose finding study (TOMORROW[®]),¹¹ 431 patients were assigned to various nintedanib doses (50, 100 and 150 mg daily, and 150 mg twice daily (bd)) or placebo for 52 weeks. Compared with placebo, nintedanib 150 mg bd was associated with reduced decline in FVC, a reduction in investigator-reported AE of IPF (AE-IPF) and preservation of health-related quality of life.

Subsequently, in two replicate randomized, double-blind, placebo-controlled phase 3 studies (INPULSIS[®]-1 and INPULSIS[®]-2),¹² 1066 patients were assigned in a 3:2 ratio to receive nintedanib (150 mg bd) or placebo. Compared with placebo, nintedanib was associated with a reduced annual rate of FVC decline in both trials (with a difference of 125.3 mL/year; 95% CI: 77.7–172.8; $P < 0.001$ in INPULSIS[®]-1 and 93.7 mL/year; 95% CI: 44.8–142.7; $P < 0.001$ in INPULSIS[®]-2).¹² In a key secondary end point, there was a reduction favouring nintedanib in time to first investigator-reported AE-IPF in INPULSIS[®]-1 but not INPULSIS[®]-2, but when AE-IPF were centrally adjudicated, there was a significant reduction favouring nintedanib in the pooled data set. In a pre-specified analysis, the effect of nintedanib on annual rate of decline in FVC was similar across a range of subgroups, irrespective of age, gender, baseline FVC severity or smoking status.³⁵ Furthermore, in patients with a 'possible' pattern of UIP with traction bronchiectasis on HRCT (but without a surgical lung biopsy), the treatment effect of nintedanib was similar to patients with honeycombing on HRCT and/or confirmation of UIP on surgical lung biopsy.³⁶

The most frequent adverse event in the nintedanib groups was diarrhoea (with rates of approximately 60%), which resulted in cessation of the drug in <5% of patients. Other common adverse events included nausea, vomiting and decreased appetite, occurring in 8–25% of patients.

Clinical experience with anti-fibrotic medications

There is increasing data for the use of both pirfenidone and nintedanib emerging from single centres and larger IPF registries, with findings broadly consistent with

Table 1 Randomized controlled trials in idiopathic pulmonary fibrosis

Study	Year	Intervention	Mode of action	n	Duration (weeks)	Primary outcome	Result
Anti-fibrotic medications							
Azuma <i>et al.</i> ⁸	2005	Pirfenidone	Anti-fibrotic	107	63	SpO ₂ change on 6MWT	NEG
Taniguchi <i>et al.</i> ⁹	2010	Pirfenidone	Anti-fibrotic	275	52	VC change	POS
CAPACITY [®] 004 and 006 ¹⁰	2011	Pirfenidone	Anti-fibrotic	779	72	FVC change	POS [†]
TOMORROW [®] ¹¹	2011	Nintedanib	Anti-fibrotic	432	52	FVC change	POS
INPULSIS [®] -1 and -2 ¹²	2014	Nintedanib	Anti-fibrotic	1066	52	FVC change	POS
ASCEND [®] ¹³	2014	Pirfenidone	Anti-fibrotic	555	52	FVC change	POS
Pulmonary vasodilators							
BUILD [®] -1 ¹⁴	2008	Bosentan	Pulmonary vasodilator	158	52	6MWD change	NEG
STEP-IPF [®] ¹⁵	2010	Sildenafil	Pulmonary vasodilator	180	12	6MWD > 20% improvement	NEG
BUILD [®] -3 ¹⁶	2011	Bosentan	Pulmonary vasodilator	616	52	Disease progression	NEG
ARTEMIS-IPF [®] ¹⁷	2013	Ambrisentan	Pulmonary vasodilator	492	35	Death, hospitalization, disease progression	NEG
MUSIC [®] ¹⁸	2013	Macitentan	Pulmonary vasodilator	178	52	FVC change	NEG
Antioxidants							
IFIGENIA [®] ¹⁹	2005	NAC (background prednisone, AZA)	Antioxidant	182	52	FVC change, DL _{CO} change	POS
Homma <i>et al.</i> ²⁰	2012	Inhaled NAC	Antioxidant	76	48	FVC change	NEG
PANTHER [®] ²¹	2014	NAC	Antioxidant	264	60	FVC change	NEG
Immunomodulation							
Raghu <i>et al.</i> ²²	2004	IFN-γ	Immunomodulation	330	58	Disease progression	NEG
Raghu <i>et al.</i> ²³	2008	Etanercept	Immunomodulation	88	48	FVC DL _{CO} and P(A-a)O ₂ change	NEG
INSPIRE [®] ²⁴	2009	IFN-γ	Immunomodulation	826	64	Mortality	NEG
Daniels <i>et al.</i> ²⁵	2010	Imatanib	Immunomodulation	119	96	Disease progression	NEG
Combination treatments							
PANTHER [®] ²⁶	2012	Prednisone, AZA, NAC	Immunomodulation and antioxidant	155	32	FVC change	Harmful
PANORMA [®] ²⁷	2016	Pirfenidone and NAC	Anti-fibrotic and antioxidant	123	24	FVC, DL _{CO} and 6MWT change	NEG
Other							
Horton <i>et al.</i> ²⁸	2012	Thalidomide		24	12	Cough	POS
ACE-IPF [®] ²⁹	2012	Warfarin	Anticoagulant	145	28	Death, hospitalization, FVC 10%	NEG

[†]Overall pooled results were positive, although CAPACITY[®] 006 was negative for primary outcome.

6MWD, 6-min walk distance; 6MWT, 6-min walk test; ACE, AntiCoagulant Effectiveness; AZA, azathioprine; DL_{CO}, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; IFN-γ, Interferon gamma; IPF, idiopathic pulmonary fibrosis; NAC, N-acetylcysteine; NEG, negative; P(A-a)O₂, Alveolar-arterial gradient for oxygen; POS, positive; SpO₂, oxygen saturation; VC, vital capacity.

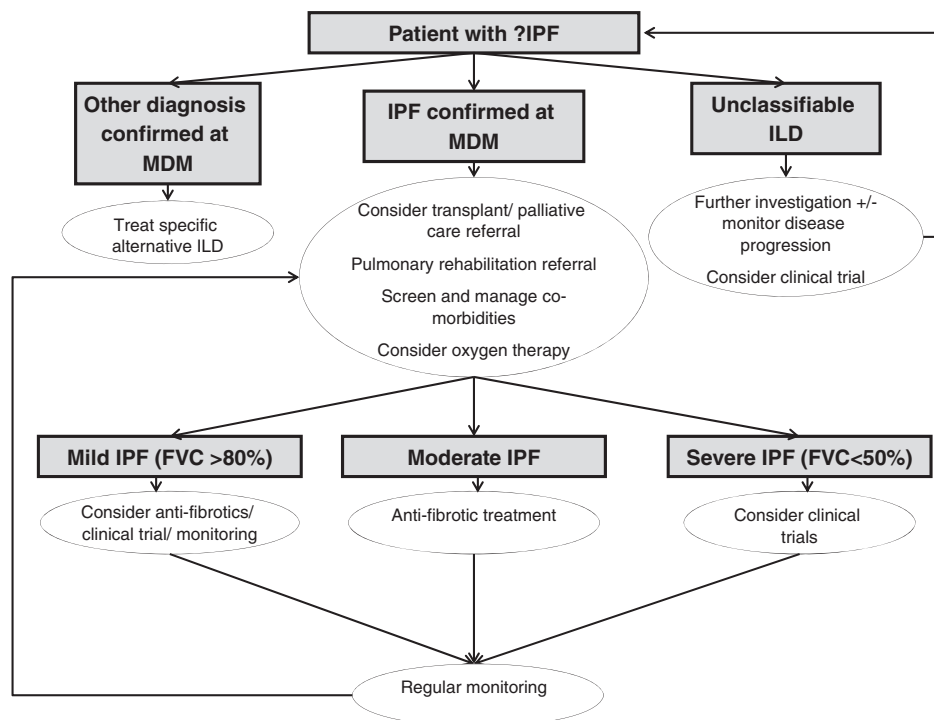


Figure 1 Suggested algorithm for the management of patients with IPF. FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MDM, multidisciplinary meeting.

clinical trial data. PASSPORT[®], a prospective, observational long-term registry, was established in 2011 following the approval of pirfenidone by the European Medicines Agency. Following interim analysis of the first 530 patients (who had received at least one dose of pirfenidone), the PASSPORT[®] investigators have concluded that the longer term safety profile of pirfenidone is consistent with that seen in clinical trials, and no new or unexpected safety signals have emerged.³⁷

INPULSIS[®]-ON is a single-arm extension study in which patients participating in the INPULSIS[®] studies then received open label treatment with nintedanib.³⁸ Interim analysis demonstrated that the beneficial effect of nintedanib in decreasing disease progression was maintained over 2 years, and long-term treatment with nintedanib had a manageable safety and tolerability profile similar to that seen in the initial INPULSIS[®] studies.

Numerous single centre experiences^{39–42} have reported similar findings with regard to treatment efficacy and safety profile, including successful management of side effects and acceptable but higher discontinuation rates in 'real-world' populations who were older with more severe lung function impairment and co-morbidities compared with clinical trial populations.⁴²

Combination therapy

There are little data on the combination of pirfenidone and nintedanib to date. Since they have different mechanisms of action, it has been postulated that combination may induce a greater reduction in FVC decline. In a small group of 50 patients, Ogura *et al.*⁴³ conducted a randomized, double-blind, phase 2, dose escalation trial to assess the safety, tolerability and

pharmacokinetics of nintedanib, alone and in combination with pirfenidone. Overall, while the patients on combination therapy reported slightly higher rates of nausea and vomiting, adverse events were mostly mild to moderate with the authors concluding that combination therapy had an acceptable safety and tolerability. There are two ongoing studies currently assessing combination treatment in IPF.⁴⁴

Practical questions with regard to anti-fibrotic therapy

While clinical trials (with clearly defined inclusion and exclusion criteria) provide broad guidelines as to who may benefit from anti-fibrotic therapy, in real-world clinical practice, deciding which drug to use, when and in whom is not often as straightforward. Both pirfenidone and nintedanib appear to have similar efficacy in reducing FVC decline, and while a mortality benefit has been demonstrated with pirfenidone, nintedanib has been shown to reduce adjudicated AE-IPF. The substantially different side effect profile for each drug, compliance with tablet medications, medication interactions and patient preference are likely to be key factors in deciding which agent to use.

Evidence supporting early initiation of treatment has recently been published, with both nintedanib and pirfenidone demonstrating similar treatment efficacy irrespective of baseline lung function severity, suggesting a beneficial effect of anti-fibrotic therapy even in patients with well-preserved physiology.^{45,46} There is also evidence from small studies to suggest that patients with a more rapid decline in the months prior to therapy with pirfenidone may have better attenuation of FVC decline.^{47–49}

While IPF disease heterogeneity is increasingly recognized, tools for predicting disease behaviour in individual patients (in particular, identifying those at risk of progressive disease) remain frustratingly imprecise. A focus on 'personalized medicine' and predictive biomarkers in IPF may provide vital information in identifying patients at risk for progressive disease in the future, although such information is not currently routinely available.^{45,46}

Despite therapeutic intervention with anti-fibrotic agents, it is likely that patients with IPF will continue to experience disease progression. Pooled data from the CAPACITY[®] and ASCEND[®] studies suggest that in patients who progress on pirfenidone (defined as a decline in FVC of $\geq 10\%$ during a 6-month period), continued treatment with pirfenidone resulted in a lower risk of subsequent FVC decline or death.⁵⁰ Similar data are available for nintedanib.⁵¹ With the availability of two proven therapies, some patients and clinicians will opt for switching treatment in the event of disease progression, although little evidence exists to support or refute this approach.

Summary

- **In the 2015 multinational IPF treatment guidelines,⁴ both nintedanib and pirfenidone received positive treatment recommendations for IPF. Consistent with these recommendations, in patients with a multidisciplinary confirmed diagnosis of IPF of mild to moderate severity, monotherapy with either pirfenidone or nintedanib should be considered as first-line therapy.**
- **The choice of anti-fibrotic agent should be individualized to the patient according to their co-morbidities and likely tolerability of either medication.**

Treatment of IPF patients with varying disease severity

There is no universal consensus on how to define disease severity of IPF patients, with several different methods including baseline FVC, diffusing capacity of lung for carbon monoxide (DL_{CO}), GAP (gender, age and physiology) index,⁵² composite physiological index (CPI)⁵³ and Japanese disease severity classification (JSC)⁵⁴ described. Whilst there is some difficulty using a single measure of FVC to judge severity of impairment in the clinical setting where a premorbid value is often unknown, it has been widely accepted as a measure of disease progression and despite its failings, has been repeatedly used as a primary outcome measure for clinical trials.⁵⁵

Very mild asymptomatic disease. It is currently unclear whether patients with very mild, asymptomatic disease would benefit from anti-fibrotic treatment as there are no specific randomized controlled trials in this group. In a post hoc analysis of the pooled INPULSIS[®] data, patients with FVC $> 90\%$ predicted were found to have the same rate of FVC decline as those with FVC $\leq 90\%$,⁴⁶ as did the patients stratified by FVC $> 80\%$ or GAP stage I disease in the pooled

ASCEND[®]/CAPACITY[®] cohorts.⁴⁵ Treatment with anti-fibrotic medications appeared to attenuate progression of IPF to the same degree in these mild cohorts as they did in the more severe groups. While these data appear to support the use of anti-fibrotic medications in this cohort, these are post hoc analyses and it is yet to be determined whether these results translate into meaningful clinical benefit, especially in patients who have preserved and stable lung function. In this cohort with mild, asymptomatic disease, the decision to treat should be individualized, taking into consideration the patient's age, co-morbidities and potential side effects of treatment.

Mild to moderate disease. In this population with mild-to-moderate IPF, there is currently the most data for treatment with anti-fibrotic medications. All major anti-fibrotic clinical trials have required an FVC $\geq 50\%$ for inclusion, with the ASCEND[®] trial alone stipulating an upper limit of $\leq 90\%$. The mean FVC was higher in the nintedanib (78.1–80.5%) than the pirfenidone trials (ASCEND[®] mean FVC: 67.8%, CAPACITY[®] mean FVC: 74.4–76%). In the recent international consensus guidelines, treatment of this group with anti-fibrotic medications was given a conditional positive recommendation.⁴ This mild-to-moderate IPF cohort is also the group that funding bodies in some countries have chosen for government-funded anti-fibrotic therapy.

Severe disease. There is very little evidence to guide clinicians with regard to treatment of patients with severe IPF, as this cohort of patients was systematically excluded from all large controlled trials. There have been a number of small real-world cohort studies suggesting that those with more severe disease may actually have greater benefit from pirfenidone with a similar rate of adverse events.^{47–49,56} A controlled study using nintedanib in severe IPF is currently recruiting patients globally (NCT02802345). Further data are required before any suggested management recommendations can be made with regard to anti-fibrotic agents in severe IPF. Local prescribing restrictions have prohibited the use of anti-fibrotic agents in severe disease in many countries until more data are available.

Definite versus probable and possible IPF

In clinical practice, there are often patients in whom a definite IPF diagnosis cannot be secured, usually due to atypical imaging and lack of a surgical lung biopsy. Surgical lung biopsy is not without risk and many patients with IPF have co-morbidities precluding a biopsy or elect not to consent to the procedure.⁵⁷ In such patients, a definite diagnosis of IPF cannot be confirmed and are given a pragmatic diagnosis of probable or possible IPF without lung biopsy. There has been growing support for this pragmatic approach with several studies showing that a UIP pattern on histopathology is often confirmed at surgical lung biopsy in patients with possible IPF.^{58–61}

It is likely those with possible IPF have the potential to benefit from treatment with anti-fibrotic therapy, 31.9% of the patients enrolled in the INPULSIS[®] trials

had possible UIP with traction bronchiectasis on HRCT, without a surgical lung biopsy. A post hoc analysis of data from these studies demonstrated that these patients have disease progression and treatment response no different from those with definite UIP.³⁶ Small retrospective cohort studies of pirfenidone also suggest treatment equivalence.^{49,62}

UIP pattern in non-IPF disease and unclassifiable ILD

While IPF frequently presents with a UIP pattern on HRCT, a UIP pattern does not exclusively represent a diagnosis of IPF. Other fibrosing ILD including CTD-ILD, CHP and asbestosis can also present with a UIP pattern on HRCT and/or histopathology and thus may incorrectly be diagnosed as IPF. Given that treatment of these conditions differs considerably from IPF, it is crucial that any patient with a fibrosing ILD undergo a thorough assessment including a detailed history of environmental exposures as well as specific questioning for subtle symptoms and signs of a CTD.⁶³ Evaluation of autoantibodies as well as serum precipitins should also be considered in a compatible clinical context.⁶⁴ The use of bronchoscopy and bronchoalveolar lavage is debated and should be considered on an individual basis.¹ All patients should undergo an ILD multidisciplinary meeting (MDM) with physicians, radiologists and histopathologists specialized in ILD present, as subtle features that may help differentiate these conditions may be present. Despite the biological plausibility for the use of anti-fibrotic agents in patients with non-IPF UIP, there are no current data to support this practice.

However, despite thorough investigation and discussion at an ILD MDM, a significant minority of patients with ILD remain unclassifiable.^{65,66} This is often due to the absence of, or inadequate histopathology, as well as conflicting clinical, radiological and histopathological data. While there is no consensus definition of 'unclassifiable ILD', this group is likely to be heterogeneous, reflected by their overall prognosis which lies between IPF and non-IPF ILD.⁶⁵ While there may be biological plausibility for efficacy of anti-fibrotic therapy in these 'unclassifiable' fibrosing ILD there is no current evidence to support their use. There are ongoing clinical studies with both pirfenidone and nintedanib recruiting unclassifiable ILD and progressive fibrosing ILD patients, respectively.

Summary

- **Anti-fibrotic therapy appears to have similar efficacy in decreasing disease progression in patients with both mild and moderate disease severity.**
- **The overall treatment benefit in very mild, asymptomatic disease is unknown and treatment should be considered on an individual basis.**
- **Despite biological plausibility, there is no controlled evidence to support the use of anti-fibrotic therapy for IPF patients with severe disease or those with non-IPF UIP or unclassifiable ILD. Such patients should be encouraged to enrol in clinical trials.**

Therapies proven not to have effect in IPF

IPF clinical trials have historically suffered from two major problems: first, older studies included patients who would now not be considered to have true IPF; and second, small initial investigations reported positive outcomes, but these findings were not replicated in larger, appropriately powered studies. The randomized controlled trials that have been performed, as well as their overall outcomes, are summarized in Table 1. As demonstrated by this table, there have been a number of trials, particularly with the use of immunomodulation, pulmonary vasodilators and N-acetylcysteine (NAC) which have had disappointing results.

The use of combination prednisolone (PRED), azathioprine (AZA) and NAC in IPF, as well as anticoagulation, offer useful lessons regarding interpretation of data on which clinical 'best practice' is based. Although the small initial trials of these therapies were promising, larger, appropriately powered trials demonstrated not only lack of efficacy, but also increased harm.

Combination PRED, AZA and NAC

For many years, the standard of care for IPF was immunosuppression with a variety of agents, with or without the addition of the oral antioxidant, NAC. In the late 2000s, most respiratory physicians used either PRED plus AZA with or without NAC for their patients,⁶⁷ in keeping with consensus guidelines at the time.⁶⁸ The data supporting triple therapy (PRED/AZA/NAC) was obtained from a study examining PRED/AZA versus PRED/AZA/NAC, suggesting the addition of NAC improved outcomes.¹⁹ The use of PRED/AZA in IPF was based on a single study in the early 1990s using small numbers (27 patients) with no statistically significant outcomes,⁶⁹ and whilst there had been observational studies regarding PRED in pulmonary fibrosis in the early 1980s,⁷⁰ there had never been a randomized trial examining the use of PRED alone.

In order to address these knowledge gaps, the PANTHER IPF trial was established examining the effect of NAC alone (plus matched placebos for AZA and PRED), PRED/AZA/NAC triple therapy and triple placebo.²⁶ The study was stopped early as the death rate in the triple therapy arm was 10% versus 1% in the triple placebo group, with a concomitant increased rate of hospitalization and AE. As such, triple therapy of IPF halted worldwide. The question of whether NAC alone was beneficial in IPF was addressed by a later publication that showed no benefit of NAC versus placebo in any outcome measure.²¹

In Europe, oral NAC has been used in combination with pirfenidone, despite an absence of data. This approach has now been assessed in a randomized clinical trial, which has demonstrated that the addition of NAC therapy increases the risk of photosensitivity, and an exploratory analysis of change in FVC suggests that NAC plus pirfenidone may worsen lung function decline.²⁷ As such, the use of pirfenidone with oral NAC cannot be recommended.

Summary

- **Consistent with the international guidelines, the combination of PRED, AZA and NAC should not be used in the treatment of IPF.**
- **The current evidence does not support the use of NAC alone or in combination with pirfenidone for the treatment of IPF.**

Anticoagulation: warfarin

In IPF, a systemic procoagulant state is present, with an increase in both circulating factor VIII and platelet activation. An initial small and poorly controlled clinical trial of warfarin in IPF demonstrated a survival benefit⁷¹; however, a larger, definitive study (ACE-IPF) was stopped early due to an increased risk of death in the warfarin group.²⁹ The increased mortality was not due to excess bleeding, but rather from disease progression, suggesting that warfarin worsens the fibrotic process.

Following this study, primary treatment of IPF using warfarin was abandoned, but the question remained, what should be done in patients who need anticoagulation for other clinical indications? This has been controversial, but there is growing evidence, although often retrospective and uncontrolled, that patients with confirmed IPF who are anticoagulated with warfarin for appropriate indications have an increased mortality.^{72,73} The most recent data,⁷⁴ using a post hoc analysis of patients in the placebo arms of IPF trials analysed by warfarin use, has demonstrated a significant increase in mortality, with a hazard ratio of nearly five. At present, it is unclear if this risk is related only to warfarin or if it also applies to direct oral anticoagulants.

Summary

- **Current evidence does not support the use of anticoagulation for the treatment of IPF.**
- **For patients on anticoagulation for other indications, careful consultation with appropriate specialists regarding the indications, risks and benefits of anticoagulation is suggested before any alterations are made.**

Anti-reflux therapy

Patients with IPF have a high prevalence of gastro-oesophageal reflux disease (GORD), although the reported prevalence varies widely depending at least in part on how GORD is ascertained,⁷⁵⁻⁷⁷ and in half it is asymptomatic. Patients with IPF are also more likely to have a hiatus hernia.⁷⁸ This strong and long-recognized association suggests either that GORD contributes to IPF pathogenesis (for instance through microaspiration with subsequent alveolar epithelial injury), and/or that IPF predisposes to GORD (for instance via changes in intrathoracic pressures during respiration) or that the two diseases share a common cause, and has further led to the idea that antacid therapy or even surgical fundoplication may be an effective therapeutic strategy for IPF.

Unfortunately, there are no randomized-controlled studies to address this hypothesis; however, in 2006, two relatively small retrospective studies were published suggesting a possible therapeutic benefit of antacid therapy⁷⁹ and surgery,⁸⁰ leading the ATS/ERS to cautiously recommend treatment of asymptomatic gastro-oesophageal reflux in the 2011 guidelines.¹ A more recent, larger, but again post hoc analysis of the patients enrolled in the placebo arms of the three IPFnet randomized trials provided further support for this position⁸¹ leading the ATS/ERS in the 2015 guideline update to again cautiously suggest that antacid treatment should be prescribed for patients with IPF,⁴ although the confidence of this recommendation was low. Most recently, two large post hoc analyses of the pooled data from the pirfenidone⁸² and nintedanib⁸³ studies found no benefit of antacid therapy. Concerningly, in the pirfenidone studies, use of antacid therapy was associated with an increased risk of generalized and respiratory infections in patients with more severe (FVC < 70%) IPF.⁸² There are no suitably controlled data to define the effect of fundoplication on the natural history of IPF, but an NHLBI (National Heart, Lung, and Blood Institute)-sponsored randomized controlled trial of laparoscopic fundoplication in IPF (NCT01982968) is ongoing and is expected to report results in 2017.

Summary

- **There is conflicting evidence regarding the role of antacid therapy in IPF. Only observational data exist, with some studies suggesting benefit, some suggesting no benefit and one suggesting potential for harm. Since appropriately designed studies assessing the roles of medical or surgical treatment of gastro-oesophageal reflux in IPF are awaited, it remains unclear whether these treatment strategies confer benefit.**

Current and future trials

While the discovery of anti-fibrotic therapy has been the recent focus of IPF management, it is important to highlight that there has also been significant progress in the understanding of IPF pathobiology. Preclinical trials have resulted in the discovery of several pathways thought to contribute to inflammation and fibrosis in IPF and are now the subject of targeted therapy. Despite recent advances in IPF treatment, anti-fibrotic medications only decrease the disease progression by approximately 50% at 12 months, still leaving a large unmet clinical need for further therapies. Table 2 describes a comprehensive list of novel therapies currently undergoing study from clinical trials database including NIH (National Institutes of Health),⁸⁴ European Union clinical trials register and 'IPF watch'. These trials are at various stages of recruitment and completion.

In addition to pharmacological interventions, cell therapy is at an early stage of development. A seminal phase 1 study establishing the safety of mesenchymal stromal cell infusion in IPF⁸⁵ has been completed. There are further studies underway and the 'Study of Autologous Mesenchymal Stem Cells to Treat IPF' (NCT01919827) is a phase 1, open, multicentre, non-

randomized, study with escalating doses, which will evaluate the safety and efficacy of mesenchymal stem cells in IPF.

Treatment of AE

AE-IPF has been defined by an international task force as an acute, clinically significant respiratory deterioration characterized by evidence of new, widespread alveolar abnormality, in a patient with a previous or concurrent diagnosis of IPF, where the deterioration is not fully explained by cardiac failure or fluid overload.⁸⁶ This definition has recently been modified to include exacerbations with a known cause (e.g. infection), as well as those of unknown aetiology. The rationale behind this change is that although the aetiology of AE-IPF remains uncertain, it appears likely that many exacerbations may be triggered by an external insult such as infection or microaspiration,⁸⁷ and there are little data to suggest that there is a meaningful distinction between these two. Identification of a cause for an AE-IPF does not appear to alter prognosis, although this is an area of ongoing research interest.

AE-IPF are more common in patients with physiologically advanced lung disease, with low FVC being the most consistent risk factor^{87–89}; other physiological parameters have also been associated with increased risk, including low DL_{CO} and reduced 6-min walk distance (6MWD).

The prognosis of AE-IPF is poor. The median survival of patients who have AE-IPF is approximately 3–4 months,^{87,88} and up to 46% of deaths in IPF are preceded by an AE.⁸⁹ Respiratory failure from AE-IPF is associated with high in-hospital mortality (>50% in most series).^{87,90}

There remain no proven effective therapies for AE-IPF. Management includes supportive care including supplemental oxygen to correct hypoxaemia, palliation of symptoms, consideration of broad spectrum antibiotics to cover the possibility of infection and consideration of mechanical ventilation. The decision to undertake mechanical ventilation in this setting needs to be carefully considered, as the in-hospital mortality is as high as 90% in this population.⁸⁶ In individual situations (e.g. following identification of a specific treatable cause for the exacerbation such as infection or pulmonary embolism, or as a bridge to lung transplant), such a decision may be considered appropriate. The ATS/ERS guidelines recommend against mechanical ventilation, stating that ‘the majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, but mechanical ventilation may be a reasonable intervention in a minority’ (weak recommendation, low-quality evidence).¹

Corticosteroids are often used in AE-IPF, although there is no controlled evidence to support this. Although there are only anecdotal reports of benefit, in the absence of other therapies, and in view of the poor prognosis of AE-IPF, corticosteroids are often given in this situation. The ATS/ERS guidelines include a weak recommendation that the majority of patients with AE-IPF should be treated with corticosteroids.¹ Other treatments may be considered for AE-IPF. Observational

cohort studies of a number of therapies (cyclophosphamide, cyclosporine, rituximab combined with plasma exchange and intravenous (i.v.) immunoglobulin, tacrolimus, i.v. thrombomodulin, polymyxin-B-immobilized fibre column haemoperfusion) have suggested benefit; however, there are no randomized controlled trials and the routine use of these agents outside a clinical trial setting is not supported by the current evidence.⁸⁶

In the absence of effective treatment for AE-IPF, prevention of such events becomes important. There are some data to support the use of nintedanib to prevent the development of AE-IPF.^{9,11,12} Additionally, a cohort study using subjects from placebo arms of clinical trials showed a reduction in AE in those on anti-acid therapy.⁸¹ Further studies are required before recommendations can be made for prevention of AE-IPF.

Summary

- **The prognosis of AE-IPF is poor. Available treatment options are limited, and not supported by controlled trial data. Further studies of prevention and treatment strategies for AE-IPF are needed.**

Treatment of co-morbidities

Optimization of co-morbidities in IPF patients can enhance quality of life and in some patients longevity. Early recognition and treatment of infections, regular vaccinations and routine health screening are also important preventative strategies in this population. Prevalent co-morbid diseases in IPF patients include cardiovascular disease, GORD, pulmonary embolism, lung cancer, pulmonary hypertension (PH), emphysema/airway disease and obstructive sleep apnoea (OSA).^{91–94} Whilst there is limited specific evidence for treatment of these conditions in IPF patients, targeted therapy may be considered where benefits are likely to outweigh potential harm.^{1,4}

Pulmonary hypertension

PH is reported to occur in 3–86% of IPF patients, resulting in poorer survival.^{95–97} Variations in the severity of fibrotic lung disease across study populations, as well as differences in PH diagnostic methodology account for this wide range, and thus the true prevalence is uncertain. Most IPF patients with PH will have only mild or moderate severity pulmonary vascular disease; however, a subset of approximately 10% will develop severe PH, with associated right heart failure.⁹⁷

The majority of patients fall within Group 3 of the classification scheme set out by the European Society of Cardiology/European Respiratory Society (ESC/ERS), that is ‘PH associated with lung diseases and/or hypoxia’, although some patients may also have elevated pulmonary pressures from concomitant left heart disease (Group 2 PH).⁹⁸ There are currently no specific vasodilator therapies indicated for Group 3 PH. Trials in sildenafil, bosentan, ambrisentan and macitentan have been disappointing, with all failing to demonstrate efficacy in the IPF population (Table 1).^{14,15,17,18,99} A recent placebo-controlled trial using riociguat in the

Table 2 Current trials for the treatment of idiopathic pulmonary fibrosis

Study	Intervention	Mode of action	Phase	Primary outcome	Company/ countries
Mechanism: blockade of inflammation and fibrosis					
NCT01766817	BMS-986020	Lysophosphatidic acid (LPA) antagonist	2	Safety and efficacy	Bristol Myers Squibb, NY, USA
NCT02257177	TD 139	Galactin-3 inhibitor	2	Safety and tolerability	Galecto Bitotec, Scotland
NCT02688647	KD025	ROCK2 inhibitor	2	Safety, tolerability and activity	Kadmon Corporation, NY, USA
NCT02036580	Tralokinumab	IL-13 blocker	2	Safety, tolerability and dose finding	AstraZeneca, Japan
NCT02874989	Dasatinib + Quercetin	Tyrosine kinase inhibitor + anti-inflammatory	1	Safety	Wake Forest School of Medicine
Mechanism: blockade of inflammation (NHLBI)					
NCT02315586	Apolipoprotein A1 mimetics	Anti-inflammatory	1	Safety	
NCT02397005	ZL2102	Anti-inflammatory	1	Safety	Perth
NCT02173145	Azithromycin	Immunomodulation/anti-inflammatory	2	Efficacy against cough	Berne
NCT00262405	Zileuton	Anti-inflammatory	2	Compared with azathioprine/prednisolone	University of Michigan
NCT00786201	CNTO 888 Carlumab	Immunomodulation	2	Evaluate the safety and effectiveness	Centocor Inc, PA, USA
NCT02345070	SAR156597	Immunomodulation	2	Safety and efficacy	Sanofi, France
NCT02085018	Omeprazole	Attenuate acid reflux	2	Efficacy	Newcastle-upon-Tyne hospitals
NCT02759120	Doxycycline or co-trimoxazole	Immunomodulation	3	Efficacy	Weill-Cornell
EUDRACT 2014-004058-32	Co-trimoxazole	Immunomodulation	2	Efficacy	Norfolk and Norwich University
Mechanism: blockade of fibrosis					
NCT01890265	FG-3019	Antibody against CTGF	2	Safety and efficacy	Fibrogen, San Francisco, CA, USA
NCT00463983	SOM230	Octreotide	1	safety	France
NCT00189176	Tetrathiomolybdate	Copper chelator reduces collagen-1	2	Safety and efficacy in patients who failed previous treatment	University of Michigan
NCT01872689	Lebrikizumab	Inhibits (IL-13), periostin	2	Safety and efficacy	Hoffman La Roche
NCT02648048	Vismodegib	Antagonist of hedgehog signalling	P1b	Safety and tolerability in combination with pirfenidone	Hoffman La Roche, Switzerland
NCT01619085	BIBF 1120	Tyrosine kinase inhibitor	2	Long-term safety	Boehringer Ingelheim, Germany
NCT02538536	PBI-4050	Reduces TGF, CTGF		Safety and tolerability	Prometic Biosciences, Isle of Man
NCT01462006	Sirolimus	mTOR inhibitor	2	Test if drug reduces circulating fibrocytes	University of Virginia
NCT02738801	GLPG1690	Autotaxin inhibitor	2	Exploratory phase 2a study	Galapagos

Table 2 Continued

Study	Intervention	Mode of action	Phase	Primary outcome	Company/ countries
NCT01254409	PRM-151	Pentraxin-2 Serum amyloid P, monocyte and macrophage differentiation	2	Efficacy	Promedior MA, USA
NCT02612051	GSK3008348	Integrin avb6 antagonist	1	Safety	GlaxoSmithKline (GSK), UK
NCT00203697	Minocycline	Inhibits angiogenesis and fibrosis	3	Safety and efficacy	University of California, Los Angeles, CA, USA
NCT01371305	STX100	Antibody to integrin avb6	2	Efficacy	Biogen, MA, USA

CTGF, connective tissue growth factor; mTOR, mammalian target of rapamycin; NHLBI, National Heart, Lung, and Blood Institute; TGF, transforming growth factor.

idiopathic interstitial pneumonias, including IPF (the RISE-IIP study), was discontinued prematurely due to an increased risk of death and serious adverse events in the treatment arm.

The STEP-IPF trial using sildenafil versus placebo in patients with advanced IPF (but not necessarily with PH) provides some indirect support for vasodilator therapy in selected patients. Whilst the primary outcome measure of $\geq 20\%$ improvement in 6MWD was not met, secondary outcomes of gas transfer, oxygenation, breathlessness and quality of life were significantly improved with the intervention.¹⁵ Patients with suspected moderate-to-severe PH may be referred to specialist centres for consideration of right heart catheterization and a trial of sildenafil, with ongoing close surveillance.¹⁰⁰ Supplemental oxygen and diuretics may also improve symptom burden and haemodynamics in severe patients with associated right heart failure.

Summary

- **All trials of specific vasodilator therapy for PH in IPF have been negative in terms of their primary end point.**

Sleep-disordered breathing

Sleep-disordered breathing (SDB) is reportedly common in IPF cohorts, with observed frequency ranging between 59% and 90%.^{93,101–103} Nocturnal hypoxaemia is also prevalent, occurring both with and without associated apnoeas, due to ventilation/perfusion inequality, alveolar hypoventilation and their position on the steep portion of the oxy-haemoglobin dissociation curve. Two studies have linked increased mortality risk with the number of nocturnal desaturation events and nadir sleep oxygen saturation in ILD patients.^{103,104} Justifications for investigation and treatment of SDB in this population include the association between OSA and the development of PH, as well as the impact of sleep fragmentation on daytime functional status and quality of life.^{104–108} Standard screening questionnaires for the

presence of SDB (such as the Epworth Sleepiness Scale) are poorly sensitive in IPF patients and thus identifying those at risk can be challenging.^{93,103,109,110}

In-laboratory polysomnography or home-based sleep studies may be considered in IPF patients for the detection of OSA and/or significant nocturnal hypoxaemia; however, the optimal timing of these investigations is unclear.

A non-randomized study of IPF patients with moderate-to-severe OSA suggested improved daytime functioning and sleep quality at 12 months along with improved survival at 2 years, in those compliant with continuous positive airway pressure (CPAP) versus those who were non-compliant.¹¹¹ Although potentially subject to confounding bias, this study provides supportive evidence for a proactive approach to SDB in this patient group. Thus, when moderate-to-severe OSA is identified in IPF patients, a trial of CPAP therapy may be appropriate. Specialist sleep clinic input is recommended, given the difficulties that many fibrotic lung disease patients have with tolerating positive pressure ventilation during sleep. Supplemental nocturnal oxygen therapy is recommended for IPF patients with significant nocturnal hypoxia (as described in further detail in *Non-pharmacological therapy: Oxygen*). This may also be a reasonable strategy for patients poorly tolerant of CPAP; however, there is limited published evidence to support this.

Summary

- **OSA and nocturnal hypoxia occur frequently in IPF patients.**
- **Sleep studies could be considered when sleep apnoea or nocturnal hypoxia is suspected.**

Combined pulmonary fibrosis and emphysema

Combined pulmonary fibrosis and emphysema (CPFE) is a recently defined syndrome describing the coexistence of pulmonary fibrosis and radiological emphysema in individuals with significant tobacco exposure.¹¹² It is

presently unclear whether this entity represents a distinct disease phenotype or is simply the coincidence of two processes with a common aetiology. The majority of patients with CPFE have the UIP pattern of IPF on HRCT, although other ILD patterns can be seen, including desquamative interstitial pneumonia.^{112,113} Patients with CPFE typically have preserved spirometry and lung volumes despite extensive disease. Airflow obstruction is present in some, but not in all CPFE patients.¹¹⁴ Both DL_{CO} and K_{CO} (transfer co-efficient of the lung (i.e. DL_{CO}/VA)) are usually severely reduced. Profound oxygen desaturation is common and the majority will progress to develop resting hypoxaemia.¹¹⁵ PH is present in up to 50% of CPFE patients at diagnosis, with an associated increased mortality risk beyond that of CPFE patients without PH and of IPF patients without emphysema.^{116,117} The risk of lung cancer is also higher for CPFE than for either IPF or chronic obstructive pulmonary disease (COPD) alone.¹¹⁸

Therapeutic options for CPFE are currently very limited, with a paucity of clinical trials in this disease subset. Patients with emphysema greater than the extent of pulmonary fibrosis were specifically excluded from the trials of pirfenidone and nintedanib.^{12,13} Patients who had emphysema extent less than fibrosis on HRCT with a forced expiratory volume in 1 s (FEV₁)/FVC ratio of >80% were, however, included in the ASCEND[®] and INPLUSIS studies, suggesting that the presence of emphysema may not necessarily preclude response to treatment. A post hoc analysis from the INPLUSIS[®] studies of patients with emphysema on HRCT compared with those without emphysema demonstrated similar efficacy for nintedanib in patients with CPFE.¹¹⁹

Vasodilator agents have not been trialed in CPFE patients with associated PH. Such therapies should be administered with caution, given the potential for worsening hypoxaemia due to increased ventilation/perfusion mismatch.¹²⁰ As with IPF-related PH, CPFE-PH requires specialist centre management. Standard bronchodilator therapy may benefit those with airflow limitation. Supplemental oxygen is suggested for patients with PH and developing right heart failure. CPFE patients should be referred to either lung transplantation or palliative care services where appropriate.

Summary

- **There is increased risk of both PH and lung malignancy in patients with CPFE.**
- **Supplemental oxygen and inhaled bronchodilator therapy may help relieve breathlessness in some patients with CPFE.**
- **In a subset of patients with fibrosis greater than emphysema and FEV₁/FVC > 80%, there is evidence to suggest a benefit from anti-fibrotic therapy.**

NON-PHARMACOLOGICAL THERAPY

Oxygen

Adverse outcomes are predicted by resting oxygen requirements as well as degree of exercise- and sleep-related hypoxaemia in IPF.^{103,104,121–123} At the present time, it is unknown whether prevention of hypoxaemia

with supplemental oxygen under these circumstances assuages the increased mortality risk. Surprisingly, there are very few studies investigating the use of oxygen in IPF populations.

Oxygen prescribing guidelines

Current recommendations for supplemental oxygen in IPF and other ILD patients are extrapolated from two landmark trials in COPD.^{1,124,125} Australian/NZ guidelines advise oxygen therapy for patients with chronic lung disease who have resting hypoxaemia (PaO₂ (arterial oxygen partial pressure) < 55 or < 60 mm Hg in the presence of hypoxic organ damage (including polycythaemia, PH or right heart failure)).^{126,127} Intermittent ambulatory oxygen may be considered for those with exercise-induced desaturation where an improvement is seen in exercise capacity or dyspnoea, as assessed with a blinded trial of oxygen versus air during the 6-min walk test (6MWT).¹²⁷ Guidelines also recommend nocturnal oxygen for respiratory patients who desaturate below 88% for at least one-third of total sleep time, in the absence of concomitant SDB. With largely equivocal evidence, an individualized approach for the latter two indications is advised.

Ambulatory oxygen during exercise

In many countries, oxygen is routinely provided during exercise training in ILD patients who are known to desaturate. Two small IPF study cohorts demonstrated improved endurance and maximal work rate whilst breathing FiO₂ (fraction of inspired oxygen) (60% versus 21%) during incremental cardiopulmonary exercise testing.^{128,129} Ambulatory oxygen during 6MWT was seen to improve walk distance, heart rate, SpO₂ (oxygen saturation) recovery and subjective dyspnoea scores in two retrospective studies of IPF subjects.^{130,131} The improvement in walk distance remained significant in the subgroup that carried their portable cylinders during the test, reflective of an encumbrance that could potentially limit the benefits of ambulatory oxygen in everyday practice.¹³⁰ However, in a more recent prospective trial, IPF patients did not improve their 6MWD using 4 L/min of oxygen compared with air.¹³² To date, there have been no published studies examining the longer term benefits of ambulatory oxygen for those who desaturate with exercise but are not hypoxic at rest. There are also no data on its impact on quality of life; however, a large randomized control trial addressing this question is currently underway (AmbOx study, NCT02286063).

Nocturnal oxygen

Guidelines advocate supplemental nocturnal oxygen for chronic lung disease patients with significant sleep desaturation, albeit with minimal supportive data. In the COPD literature, overnight oxygen therapy has not been demonstrated to improve survival in those patients with nocturnal hypoxia but daytime normoxia.^{124,125,133} Pulmonary haemodynamics may be improved in COPD patients receiving long-term nocturnal oxygen; however, this has not been investigated in IPF populations.¹³⁴ In two single-night studies in ILD

subjects, oxygen reduced breathing frequency and heart rate through elimination of sleep-associated desaturation; however, sleep quality and arousal index were not significantly altered.^{135,136}

Continuous oxygen therapy

The literature is equally sparse in the application of oxygen for IPF patients who are hypoxaemic at rest. A Cochrane review, updated in 2010, included only one unpublished reference.¹³⁷ This trial randomized 62 ILD patients to receive either LTOT or no oxygen (Braghiroli A, Donner CF, personal communication with permission). Mortality at 12, 24 and 36 months was the same in each group. Physiological and quality of life data were not reported. With ethical considerations of allocating placebo to hypoxaemic subjects, it is unlikely that such a study will be repeated. IPF-specific guidelines make a strong recommendation for LTOT in those with resting hypoxaemia, but acknowledge the lack of evidence specific to this disease group.^{1,124,125}

General considerations and summary

There are many practical issues to take into account when prescribing oxygen, particularly in the ambulatory setting. Important factors include the cost of portable concentrators, the physical challenges of carrying or pulling a delivery device and the limited duration of cylinder oxygen delivery and need for frequent refills. It is currently not known whether continuous versus pulse flow delivery meet patient needs equally, particularly in advancing disease. Local oxygen funding bodies vary in their equipment provision for those who fulfil criteria, and this will also influence choice of delivery modality.

Summary

- **Consistent with international guidelines, clinicians should offer LTOT for IPF patients with resting hypoxaemia, and consider supplemental oxygen for those with significant exercise- and sleep-related oxygen desaturation.**

Pulmonary rehabilitation

It is common for patients with IPF to experience dyspnoea on exertion, poor health-related quality of life and marked exercise intolerance. These impacts persist in patients using anti-fibrotic therapies^{12,13} and often worsen as the disease progresses. There is growing evidence that pulmonary rehabilitation has important effects on symptoms, functional capacity and well-being in patients with IPF. A Cochrane review examining randomized controlled trials of pulmonary rehabilitation in ILD¹³⁸ reported that in the subgroup with IPF, 8–12 weeks of supervised pulmonary rehabilitation produced improvements in 6MWD that exceed the minimal important difference (mean: 36, 95% CI: 16–55 m). There were also significant improvements in dyspnoea and health-related quality of life with moderate effect sizes. All pulmonary rehabilitation programmes included whole-body endurance training (walking or cycling), most included resistance

(strength) training and some also included education, nutrition counselling and psychosocial support.

The ATS/ERS guideline for IPF management makes a weak recommendation in favour of pulmonary rehabilitation for IPF, which indicates that pulmonary rehabilitation should be used in the majority of patients.¹ This recommendation recognizes the uncertainty regarding the duration of benefit; the only trials that have examined long-term outcomes have reported that gains in exercise capacity diminish in the 6–12 months following pulmonary rehabilitation, although health-related quality of life may be better preserved.^{139,140} Early referral to pulmonary rehabilitation should be considered as patients with milder disease appear to have more sustained benefit.¹⁴¹ The ATS/ERS pulmonary rehabilitation statement¹⁴² also reports that pulmonary rehabilitation delivers meaningful short-term benefits in patients with IPF, whilst acknowledging the challenges in providing rehabilitation for patients who may have progressive disease. Recently, the Australian and New Zealand Pulmonary Rehabilitation Guidelines have made a weak recommendation for pulmonary rehabilitation in patients with ILD, including those with IPF.¹⁴³ The guideline authors found no evidence that exercise prescription should differ from the standard protocols that have been used for many years in patients with COPD, suggesting that patients with IPF can be successfully treated in existing pulmonary rehabilitation services.

In Australia and NZ, most pulmonary rehabilitation programmes will accept referrals for patients with IPF. However, those with IPF experience similar barriers to pulmonary rehabilitation attendance as others with chronic lung disease, including fear of exercise and associated breathlessness, the burden of regular travel to attend the programme and a lack of perceived benefit. These barriers should be explicitly addressed at the time of referral, preferably by the treating medical team, as encouragement from the doctor is a key facilitator of pulmonary rehabilitation uptake.¹⁴⁴ Because patients with IPF frequently use supplemental oxygen or experienced marked exercise-induced desaturation, it is preferable for pulmonary rehabilitation to take place in programmes that have the capacity to deliver oxygen during training, consistent with exercise training protocols for patients with IPF of known effectiveness.¹³⁸ Although the educational curriculum for pulmonary rehabilitation was originally designed for COPD, patients with IPF would prefer that disease-specific information was delivered during the programme, including management of cough, how to handle IPF medications and their side effects and optimal disease management for IPF.¹⁴⁵

Summary

- **Pulmonary rehabilitation confers meaningful benefits in exercise capacity, symptoms and health-related quality of life, especially in patients with milder disease.**
- **Patients with IPF can be successfully managed in existing pulmonary rehabilitation programmes and early referral to pulmonary rehabilitation is encouraged.**

Lung transplant

Despite the recent advances in IPF therapy, there is still no cure for this relentlessly progressive disease. As a result, lung transplantation remains the only definitive treatment for selected patients with IPF.

The timing of referral for lung transplantation consideration is important and should be early in the course of the disease. Patients can wait a long period of time for suitable lungs, as the small chest cavity can limit the suitability of donor organs and thus prolong wait times. A recent consensus document for the selection of lung transplant candidates¹⁴⁶ recommends referral of appropriate candidates with a diagnosis of IPF at the time the diagnosis is made, regardless of the severity of their disease at lung function testing. This recommendation reflects the phenotypic heterogeneity of IPF, the difficulty in predicting disease course and overall poor prognosis of IPF patients compared with other indications for lung transplantation.

The heterogeneity of IPF is illustrated by the fact that although the median wait list time to transplant is lower in IPF than in other diagnoses, the mortality on the waiting list is higher.¹⁴⁷ A recent paper from a single centre in Italy also shows that the diagnosis of IPF was associated with the highest mortality on the lung transplant waiting list. Factors associated with greater mortality include higher levels of CO₂ and the need for higher flows of O₂.¹⁴⁸

Indications for listing for lung transplantation include: a decrease in FVC \geq 10% or DL_{CO} \geq 15% over 6 months, desaturation to \leq 88% on 6MWT, a decrease in 6MWD during follow-up, PH as well as hospitalization for respiratory decline, pneumothorax or AE.

The absolute and relative contraindications for lung transplantation are outlined in Table 3. Of note, age >65 years is no longer an absolute contraindication to lung transplantation. Rather than chronological age alone, the physiological reserve of the patient as assessed by a variety of frailty measures and the presence of co-morbidities with end organ damage are important contributing factors to the decision for lung transplant listing.¹⁴⁶

Outcomes after lung transplantation are less than ideal, with a median survival post lung transplantation for IPF of 4.5 years. This is well below that of lung transplantation for cystic fibrosis and COPD (7.8 and 5.4 years, respectively).¹⁴⁹ The reasons for this discrepancy are not clear, but include the age of the recipients and the presence of co-morbidities. This does not however explain all of the variances. However, recent attempts to further define the risks of early mortality post lung transplantation have not found IPF to be an independent risk factor.¹⁵⁰

Unlike suppurative lung diseases, IPF patients are eligible for single, as well as double lung transplants. The choice is dependent on a number of factors including:

1. The availability of suitable donor lungs: Two recipients can be transplanted from the same donor. This is particularly relevant for smaller, blood group O potential recipients.
2. The size of the chest cavity: It is possible to transplant a larger single lung as the mediastinum will move over to accommodate the lung. This is particularly important in small potential recipients as the disease inherently further reduces the size of the chest cavity.

Reported outcomes comparing single versus double lung in IPF are conflicting with previous data suggesting no difference,¹⁵¹ with one recent publication reporting better outcomes for double lungs.¹⁵²

Summary

- Lung transplantation is a viable option for selected patients with IPF and confers a survival benefit.
- Consistent with the international lung transplantation consensus document, early referral to a transplant centre is essential, as it is difficult to accurately predict disease trajectory in IPF.

Palliative care

Despite advances in pharmacotherapy, dyspnoea, cough and fatigue remain debilitating symptoms¹⁵³ and

Table 3 Contraindications to lung transplantation

Absolute contraindications	Relative contraindications
Malignancy within the last 2–5 years	Age >65 with low physiological reserve
Other untreatable major organ dysfunction	Mechanical ventilation and/or extracorporeal life support
Uncorrectable atherosclerotic disease with end organ dysfunction	Progressive or severe malnutrition
Acute medical instability or bleeding diathesis	Severe, symptomatic osteoporosis
Chronic infection with highly virulent and/or resistant microbes including active <i>Mycobacterium tuberculosis</i> infection	Colonization or infection with highly resistant or virulent microbes
BMI > 35.0 kg/m ²	BMI > 30 kg/m ²
Non-adherence to medical therapy	Extensive prior chest surgery with lung resection
Psychiatric or psychological conditions associated with inability to cooperate with healthcare team	Hepatitis B and/or C
Absence of social support system	HIV infection
Severely limited functional status with poor rehabilitation potential	Suboptimal treatment of diseases with potential for end organ damage
Substance abuse/dependence	

are often difficult to manage. It is important to recognize that these symptoms can affect patient's quality of life and sense of well-being independent of physiological measures of disease.¹⁵⁴ Palliative care focuses on symptom management, advance directives and end-of-life planning, aiming to improve the quality of life of patients and their families. Palliative care is an integrated and individualized process which should be addressed at all stages of disease and not exclusively at the end of life.¹⁵⁵ It is a dynamic process where goals shift to meet the changing needs of patients.

There are emerging data on palliative treatments and their benefits in IPF,¹⁵⁶ although approaches have often been extrapolated from studies of other chronic lung diseases. Management consists of both non-pharmacological (e.g. counselling and spiritual care support) and pharmacological approaches, and are often used in parallel. In addition to treatment for specific symptoms, effective management of psychological stress¹⁵⁷ and pulmonary rehabilitation^{138,141} is vital, with beneficial effects across multiple domains. The use of oral opioids^{158–161} has been reported to reduce dyspnoea, whilst limited evidence exist for the use of benzodiazepine¹⁶² or supplemental oxygen.^{132,163,164} A thorough search for reversible causes of cough (including gastro-oesophageal reflux, postnasal drip, ACE inhibitor use etc.) is crucial before considering the use of opioids or over the counter cough suppressants, although there is little evidence that these measures are effective in IPF.^{157,165} Low-dose PRED may benefit some patients, although a risk/benefit assessment must be considered for each individual patient.¹⁶⁶ Thalidomide has been reported to significantly reduce cough^{28,167}; however, it is not widely available and is associated with significant side effects.

Although confronting, IPF patients desire information about their prognosis and how IPF manifests in the end stages¹⁶⁸, many physicians fail to address this.^{169–171} This could be due to a number of reasons, including prognostic uncertainty of IPF, fear of diminishing hope, discomfort with palliative care discussions and limited understanding of potential benefits of palliative care.^{170,172–174} The main obstacle is likely to be fear of diminishing hope, although findings from studies of cancer and other terminal illnesses suggest that patients who were referred early to palliative care had a better quality of life, experienced less depressive symptoms and even had a longer survival.¹⁷⁵ Advance care planning should be offered to patients when they are well and are able to discuss their wishes. Palliative care should be viewed as 'supportive care', and should be addressed early as pharmacotherapy in IPF remains largely ineffective for the control of symptoms.

Summary

- **Dyspnoea, cough and fatigue are prominent and debilitating symptoms, independent of disease severity. To date, no therapeutic options in IPF have been shown to improve these symptoms. Early palliative/supportive care may be helpful to address this.**
- **Advance care planning, although daunting to patients, families and their doctors, can be offered**

when patients are relatively well, so that their wishes and those of their families can be heard and respected.

Psychosocial support

Living with IPF is challenging for patients and their families. Patients describe struggling to manage dyspnoea, cough and fatigue; a lack of good quality information about their condition and their treatment options; loss of independence and loss of previous life roles; and inadequate emotional support.^{145,176–179} Because IPF is poorly understood in the community, patients report difficulty in explaining their disease to family and friends.¹⁷⁹ The most common unmet needs reported by patients across the world are for high-quality, honest and reliable disease information that is accessible from the time of diagnosis; emotional support to assist patients and their families to cope with the diagnosis and deal with the ongoing anxiety of living with a progressive disease; and patient-based advocacy groups who could effectively represent the needs of patients with IPF in the broader community.^{145,177–179}

There are a variety of models for patient and family support. A disease management programme for IPF was tested in a randomized controlled trial where 21 patient/carer dyads received either six once-weekly group sessions covering important aspects of IPF management (pathophysiology and treatment; management of stress and depression; cognitive behavioural therapy; end-of-life planning; and symptom management) or usual care.¹⁸⁰ Whilst carers reported a significant reduction in perceived stress at the end of the programme, patients reported worse health-related quality of life and a trend to worse anxiety. However, in qualitative interviews, patients reported benefits including reduced isolation, putting the disease in perspective and providing comfort. An alternative model is IPF Care, which provides support and education for patients receiving pirfenidone in Europe, funded by the supplier.¹⁸¹ Participants receive regular telephone calls and/or home visits from nurses, as well as individually tailored information booklets. Although a major function of the programme is to support treatment adherence, 30% of topics discussed were not related to pirfenidone and included oxygen therapy, test results, home supports, exercise, transplantation and concerns for the future. Retention in the programme was 71% over 18 months and patient-reported satisfaction was high.¹⁸¹

Many tertiary referral centres for IPF in Australia and NZ also provide extensive support to patients and families through their multidisciplinary teams, particularly IPF specialist nurses and clinic coordinators as well as community support organizations. Additionally, local general practitioners continue to provide support and education to patients and their families on a regular basis. In Australia, the Lung Foundation Australia provides patients with IPF and their families with a range of resources for education, psychosocial support and advocacy. These include disease-specific educational materials; a peer support programme that connects patients living with IPF via telephone to share experiences, knowledge and support; regular scientific conferences that include a consumer stream to ensure that patients

and their families can access the most up-to-date information on IPF care; and public advocacy for evidence-based care and research to improve IPF outcomes. Further information can be found on the Lung Foundation Australia website (www.lungfoundation.com.au).¹⁸² Unfortunately, no such resource is currently available for the NZ population specifically.

PRECISION MEDICINE

The heterogeneity of the natural history of IPF has led to a worldwide search for a panel of biomarkers enabling physicians to target treatment to the individual IPF patient. Investigators are searching for biomarkers which can aid in IPF diagnosis and in assessing prognosis. Most of this work is being conducted to identify circulating biomarkers in peripheral blood; however, biomarker discovery using lung biopsies is also underway. Some of the most promising early candidates are the matrix metalloproteinases (MMP, especially MMP-7), surfactant protein-D and endothelin-1.^{183,184}

IPF, including not only its rare familial forms but also its much more common sporadic form, is a disease associated with gene mutations. The genes most commonly mutated are the mucin 5B (MUC5B), surfactant protein and toll-interacting protein (TOLLIP), as well as those associated with maintenance of telomere length. Importantly, not only do mutations in these genes increase the risk of developing IPF, but some of them also provide important prognostic information. For instance, patients with MUC5B mutations appear to have better survival,¹⁸⁵ whilst those with short telomere length have worse survival.¹⁸⁶ In fact, assessing telomere length and identifying germline mutations in genes which assist in telomere maintenance in patients suspected of having a mutation are emerging as a part of the workup for patients presenting with fibrotic ILD (f-ILD) as these mutations lead to a variety of f-ILD but appear to universally confer a worse prognosis.¹⁸⁷

Although prospective studies are awaited, it is likely that determination of a patient's genotype and their specific biomarker profile will become an essential part of clinical practice, for example to not only diagnose IPF, but also to assist the physician in deciding if and when to recommend commencement of anti-fibrotic therapy, and when to refer for transplantation. The strength of these associations mean that future large studies in IPF will likely stratify by genotype and/or biomarker profile, meaning that ultimately specific therapies will be found to be appropriate for a subpopulation of patients with IPF—allowing 'precise' use of powerful medicines.

This idea that treatments should be personalized to maximize efficacy and safety is of course not new, especially in oncology, but does imply a more in-depth understanding of disease pathogenesis. Examples of this kind of approach are already appearing for IPF—for example in a post hoc analysis, mutations in the TOLLIP gene predicted response to NAC in what was otherwise a negative trial when all patients were pooled.¹⁸⁸ Naturally, prospective studies are required to confirm these potentially exciting observations.

Nevertheless, this accumulated experience and the strength and frequency of the genetic associations observed so far point to IPF, alongside cancer, being one of the first respiratory diseases to enter the 'personalized' or 'precision' medicine era.

Summary

- **While biomarkers show early promise in identifying IPF, assessing prognosis and stratifying management, further studies are required before any clinical recommendations can be made.**

SPECIFIC APPLICATION TO AUSTRALIA AND NZ

Regional factors specific to Australia and NZ influence the manner in which the above-described therapies are applied to their respective IPF populations. Within both countries, funding for anti-fibrotic therapy is dependent on the patient displaying features representing an amalgamation of the inclusion criteria of the phase 3 studies of nintedanib and pirfenidone.

In Australia, the PBS (pharmaceutical benefits scheme) has approved funding for both pirfenidone and nintedanib. Specific features of Australia's prescribing criteria include the need for diagnosis to be confirmed by a multidisciplinary team and the presence of a mild to moderate restrictive pattern on lung function testing (Table 4). In NZ, PHARMAC has approved funding of pirfenidone only, but has restricted prescription to patients with moderate disease, providing there is no disease progression (defined as a decline in percent predicted FVC of 10% or more) within any 12-month period while on therapy (Table 4). The differences in the funding criteria between Australia and NZ likely reflect differences in the interpretation of the evidence for these medications. As clinical trials in pirfenidone, the only anti-fibrotic medication approved in NZ, restricted patients to those with moderate disease (FVC: 50–80%), this is reflected in the NZ prescribing guidelines.

These restrictions to supply anti-fibrotic medications for subjects for whom there is clear evidence of efficacy is understandable in the context of the burden of such therapies on health budgets. Equally important though is the reconsideration of such restrictions as further data are published on the use of anti-fibrotic therapy, given the evolving nature of this relatively new therapeutic field. For example, there is gathering evidence to suggest that mandating the cessation of anti-fibrotics based on crossing thresholds of FVC percentage decline may be questionable. Analysis of the pooled ASCEND[®] and CAPACITY[®] data has demonstrated that, after a decline in FVC by $\geq 10\%$ in the initial 6 months of therapy, continued therapy reduced the likelihood of further such decline or death over the subsequent 6 months compared with the placebo group.³¹ As the evidence for these medications continues to grow, physicians as well as patients must advocate for evolution of funding restrictions.

For the non-pharmacological therapies, each country has unique regulations for practice. In Australia, oxygen therapy may be funded by either federal or state

Table 4 National criteria for funded anti-fibrotic therapy

Australia (PBS)	New Zealand (PHARMAC) [†]
Multidisciplinary diagnosis of IPF	Physician diagnosis of IPF, confirmed by CT or biopsy
HRCT consistent with UIP within 12 months	
FVC ≥ 50%	FVC between 50% and 80%
FEV ₁ /FVC ratio > 0.7	
DL _{CO} ≥ 30%	
ILD not due to other known cause	
	Funding discontinued if disease progression (decrease in FVC ≥ 10% in 12 months)

[†]Has only approved pirfenidone.

CT, computed tomography; DL_{CO}, diffusing capacity of lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PBS, pharmaceutical benefits scheme; UIP, usual interstitial pneumonia.

governments and differences exist between jurisdictions with regards to funding criteria, particularly for ambulatory therapy, where a relative absence of evidence exists to confirm its utility. While the limited nature of the availability of donor organs leads to a waiting list for lung transplantation, access is dependent on meeting those criteria outlined in Table 3, and no regional differences exist based on other patient features, such as duration of listing. While pulmonary rehabilitation, advanced care planning and palliative care services are readily available in many regional centres, providing community services in remote and rural locations is challenging.

In NZ, funding for oxygen and other support services, such as pulmonary rehabilitation, is provided by the district health boards as part of a capitated funding system. Lung transplantation is provided by a single centre and criteria for listing are similar to Australia. Rurality impacts access to services for patients with pulmonary fibrosis in both countries, but telemedicine and shared care allow improved access to MDM discussion and a variety of supports.

CONCLUDING STATEMENT

It is an exciting time for IPF management with new therapies shown to decrease disease progression now available. However, enthusiasm to prescribe these medications has to be tempered by the lack of evidence in many subgroups, as well as local restrictions for government funding of these therapies. The management of IPF patients is not constrained to anti-fibrotic therapies, and it is important to address co-morbidities and manage symptoms using pharmacological and non-pharmacological therapies. Despite new treatments, IPF remains a progressive and fatal disease and thus pulmonary rehabilitation, consideration of lung transplantation, palliative care and end-of-life planning are essential to the holistic care of IPF patients.

Disclosure statement

The authors' disclosure statement is provided in Appendix S1 (Supplementary Information).

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Disclosure statement.