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REVIEW

Early Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis: A Narrative Review

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease of unknown aetiology. Patients typically present with symptoms of chronic dyspnoea and cough over a period of months to years. IPF has a poor prognosis, with an average life expectancy of 3–5 years from diagnosis if left untreated. Two anti-fibrotic medications (nintedanib and pirfenidone) have been approved for the treatment of IPF. These drugs slow disease progression by reducing decline in lung function. Early diagnosis is crucial to ensure timely treatment selection and improve outcomes. High-resolution computed tomography (HRCT) plays a major role in the diagnosis of IPF. In this narrative review, we discuss the importance of early diagnosis, awareness among primary care physicians, lung cancer screening programmes and early IPF detection, and barriers to accessing anti-fibrotic medications.

Keywords: Idiopathic pulmonary fibrosis; Early diagnosis; Anti-fibrotic medications

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Key Summary Points

Idiopathic pulmonary fibrosis (IPF) is a rare disease, often diagnosed late due to the overlap of symptoms with other respiratory conditions.

Anti-fibrotic medications slow the decline in lung function in patients with IPF.

There is a growing body of evidence suggesting that anti-fibrotic medications reduce the risk of acute deteriorations in lung function and improve life expectancy in IPF.

Early diagnosis of IPF is crucial to ensure timely treatment selection and improve outcomes.

Early diagnosis can be enhanced by improving awareness among primary care physicians, lung cancer screening programmes and the use of artificial intelligence (AI) systems to analyse computed tomography (CT) images and pulmonary function test results.

In the USA and Europe, prescription of anti-fibrotic medications for patients with confirmed IPF is reported to be between 58% and 70%.

Barriers to the prescription of anti-fibrotic medications include delayed referral to specialist centres, restriction in the prescription based on percentage predicted of forced vital capacity (%FVC) targets, 'watch and wait' approach adopted by patients and clinicians, and the side-effect profile of the medications.

Treatment access could be improved by education of non-respiratory clinicians about the presenting symptoms of IPF, utilising computer-aided informatics, streamlining referral pathways and planned changes to the %FVC requirement for people to start anti-fibrotic medications.

INTRODUCTION

What is Idiopathic Pulmonary Fibrosis?

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial lung disease (ILD) of unknown cause [1]. It is characterised by irreversible loss of lung function due to lung fibrosis and typically presents with symptoms of chronic exertional dyspnoea and dry cough over a period of months to years[1, 2]. IPF remains a rare disease with worldwide incidence recently reported as 0.09–1.30 and prevalence of 0.33–4.51 per 10,000 of the population [3]. The prevalence of IPF appears to be increasing, though it is unclear whether this reflects increased recognition or a true increase in incidence [2]. The prognosis for people living with IPF remains poor, with a median life expectancy of 3–5 years from diagnosis if left untreated [4]. Despite the development of anti-fibrotic medications to slow disease progression, IPF can ultimately be a fatal lung disease. Early diagnosis is crucial to ensure timely treatment selection such as consideration of anti-fibrotic medications, supportive and palliative therapies, and, if appropriate, referral for lung transplantation [5, 6]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EARLY-STAGE DIAGNOSIS IN IPF

Clinical Presentation

IPF is usually diagnosed in the sixth or seventh decade of life and is uncommon below the age of 50 years [7, 8]. Risk factors for IPF include older age, male sex and a history of cigarette smoking [9]. Typically, IPF presents with exertional dyspnoea, dry cough, fatigue and a gradual decline in ability to undertake activities of daily living. Symptoms can be present for many months to years. Bibasal 'velcro-like' mid-to-end inspiratory crackles on chest auscultation and nail clubbing are common physical

examination findings. Resting hypoxaemia or exertional desaturation are also commonly observed in clinical investigations. When radiological features are identified incidentally in patients without any prior suspicion of ILD, they are called interstitial lung abnormalities (ILAs) [10]. Patients with ILAs might be asymptomatic but may eventually progress and be diagnosed as IPF [10].

Pulmonary Function Tests

Pulmonary function tests provide a non-invasive quantitative measure of the severity of IPF, and repeated testing to monitor disease course has become the cornerstone of current practice [11]. In patients with suspected IPF, lung function studies typically identify a reduced forced vital capacity (FVC), reduced total lung capacity (TLC) and a reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) [2]. Patients with early IPF may have normal or only mildly impaired lung function parameters [12]. Moreover, the course of IPF can be highly unpredictable, with significant variation across individuals ranging from patients who have gradual worsening of lung function over years to those who decline rapidly from disease onset [13, 14]. Baseline lung function alone is therefore a poor predictor of mortality in IPF [15] and composite scoring systems such as the Gender–Age–Physiology (GAP) index may offer better prognostic accuracy [16] [see 'High-resolution computed tomography (HRCT)'].

A recent analysis from the Australian IPF registry found that patients with IPF with mild physiological impairment (FVC $\geq$ 80%) had better survival than patients with moderate-to-severe disease (FVC $<$ 80%). However, the overall rate of disease progression was comparable, thus suggesting that better survival in early disease simply reflects an earlier point on the natural history of IPF [12]. Similarly, post-hoc analyses of major clinical drug trials in IPF have found that the rate of FVC decline is similar between patients with more preserved FVC ($\geq$ 80%) and those with less preserved FVC ($<$ 80%) [13, 17].

Research also indicates that patients with early IPF (based on pulmonary function test results) have fewer episodes of acute exacerbation than those with advanced disease [17–19]. Artificial intelligence (AI) software capable of interpreting spirometry has been developed and validated, and has demonstrated superiority in accurate interpretation over pulmonologists, whose interpretations are prone to variability and error [20]. Ray et al. drew upon UK Biobank data to investigate whether AI software can detect ILD based on a spirometry measurement obtained before patients received an ILD diagnosis. Data from subjects who had ILD as a documented cause of death, had performed an acceptable spirometry measurement up to 7 years prior to their death and had not received an ILD diagnosis on the date of their spirometry measurement were analysed. Spirometry data and subject demographic information were used as inputs into an AI software system. In 27% of cases, AI software identified patients with ILD up to 6.8 years before a clinician's diagnosis. Most of these cases had normal lung function (using standard interpretation guidelines), indicating that artificial intelligence software may be able to identify ILD before standard spirometry interpretation [21]. These studies show that AI interpretation of spirometry in the primary care setting has the potential to improve diagnosis of ILD leading to earlier referrals to specialist ILD centres. Although the potential of AI in interpreting PFT is promising, there are still obstacles to overcome. High-quality representative data and the development and continuous update of validated endpoints are needed for the machine learning in AI, and with different suppliers of AI systems there are different formats for data acquisition and sharing [22].

High-Resolution Computed Tomography (HRCT)

IPF is restricted to the lungs and is characterised by the radiographic pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT) imaging of the chest [23].

The ATS/ERS/JRS/ALAT's 2018 Clinical Practice Guidelines for Diagnosis of IPF

Features of the UIP Pattern on HRCT UIP pattern ILD on radiology is typically subpleural in distribution and with an apicobasal gradient [23] Characteristic HRCT features of UIP include honeycombing, traction bronchiectasis and traction bronchiolectasis with the possible presence of ground-glass opacification and fine reticulation [23]. Honeycombing is characterised by clustered cystic airspaces with thick well-defined walls of normally uniform diameter of 3–10 mm with some occasionally larger cysts. Typically, with honeycombing there is also a reticular pattern of traction bronchiectasis and bronchiolectasis present [24]. Traction bronchiolectasis is dilatation of bronchioles that precedes the formation of traction bronchiectasis [25]. Traction bronchiectasis and bronchiolectasis is a key characteristic indicating pulmonary fibrosis, ranging from minor irregularity and non-tapering of the bronchial and/or bronchiolar wall to severe airway distortion [26, 27].

HRCT Patterns of IPF The ATS/ERS/JRS/ALAT's 2018 clinical practice guidelines for a diagnosis of IPF recommend using four diagnostic classifications to describe HRCT features: UIP pattern, probable UIP pattern, indeterminate UIP pattern and alternative diagnosis [23]. The UIP pattern is the hallmark HRCT feature of IPF. Honeycombing, with or without traction bronchiectasis or bronchiolectasis, must be present in the HRCT for a definite UIP pattern diagnosis. Sometimes, mild ground-glass opacification may also be present, usually superimposed on a reticular pattern. To justify a probable UIP pattern diagnosis, a basal predominant subpleural reticular pattern with peripheral traction bronchiectasis or bronchiolectasis must be present. Ground-glass opacification may also be present in patients with probable UIP, but it is not the main abnormality. An indeterminate UIP pattern diagnosis is considered when the HRCT scan captures features of fibrosis that do not meet the criteria for definite UIP or probable UIP pattern and when no signs point to an alternative diagnosis. An alternative diagnosis is made when the HRCT pattern suggests another diagnosis. In some cases, the HRCT pattern may suggest a definite UIP, probable UIP or indeterminate UIP, while additional results indicate an alternative diagnosis. In these cases, an alternative diagnosis should be taken into account [23]. This guideline was updated in 2022, but the four diagnostic classifications of HRCT features remained unchanged [1].

Degree of Fibrosis Based on HRCT

In patients with IPF, the degree of fibrosis on HRCT imaging can be determined by two components: the extent of the fibrosis (% fibrosis) and the radiological features of the fibrosis. While a small percentage of fibrosis on HRCT imaging probably indicates early IPF, there are no standardised cut-off points that define the extent of fibrosis for characterising early IPF. Several studies have found that the extent of fibrosis on HRCT scans in patients with IPF is associated with mortality. Among patients whose scans showed idiopathic interstitial pneumonias (IIPs) with a UIP pattern, an HRCT fibrosis score of $> 30\%$ predicted a worse prognosis [28]. Ley et al. modified the GAP model [which considers gender, age and physiology with FVC and diffusing capacity of the lungs for carbon monoxide (DLCO) by replacing the DLCO with the HRCT scan's extent of fibrosis score. This was divided into three categories ($\leq 10\%$, 11–30%, $> 30\%$], with more fibrosis being associated with an increased risk of mortality [29].

Looking at the features of fibrosis, the presence of honeycombing and traction bronchiectasis may indicate advanced features of IPF, as some patients with an inconsistent or possible UIP pattern on their HRCT eventually develop a definite UIP pattern over months or years [30, 31]. Several studies have identified a poor prognosis for patients with fibrotic lung disease that shows features of honeycombing on HRCT [27, 32, 33]. In an observational study using data from five hospitals in the USA, Adegunsoye et al. evaluated the prognostic value of the presence of honeycombing among various ILD subtypes. Honeycombing was prevalent in various ILD subtypes and was associated with a higher mortality rate than among those without

honeycombing. It is proposed that the honeycombing seen in the HRCT of patients with ILD indicates a progressive fibrotic ILD (PF-ILD). In patients with IPF, no difference in mortality was found on the basis of the presence of honeycombing, probably because IPF is already a PF-ILD phenotype [34]. One study found that patients with IPF and a possible UIP pattern on their HRCT had better survival than those with a definite UIP pattern [35], while others found no differences in survival between patients with possible UIP and those with definite UIP-pattern IPF [36]. Using data drawn from the INPULSIS trials, Raghu et al. evaluated differences in prognosis between the diagnostic subgroups of IPF as well as their responses to the anti-fibrotic medication nintedanib. They found that patients with a possible UIP pattern with traction bronchiectasis on their HRCTs had a similar disease progression and responded similarly to nintedanib as patients whose IPF showed a definite UIP pattern [37].

In diagnosing and evaluating patients with IPF, HRCT plays a crucial rule. The current standard of visually assessing HRCT scans to determine IPF disease extent is hindered by inter-observer variation with poor reproducibility. This has led to research evaluating objective automated computed tomography analysis. Several systems have been developed for the automated analysis of HRCT scans [38]. Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) software can be used for the analysis and quantification of lung abnormalities on HRCT imaging. Jacob et al. have shown that in patients with IPF, automated quantitative computed tomography using CALIPER had superior performance compared with visual scoring [39]. Although automated quantitative CT is promising, there are several obstacles associated with its implementation and interpretation. Variations in CT acquisition technique, and need for validation of utility in clinical setting are still challenges for automated quantitative CT analysis [40]. Several studies have demonstrated that the extent of fibrosis and change over time measured by automated quantification of computed tomography were associated with mortality [41, 42]and FVC decline [43, 44].

Index Systems

Several composite scoring systems have been developed, aiming to accurately prognosticate in patients with IPF (Table 1).These include the Composite Physiologic Index (CPI) [45], du Boise score [46] (Table 2) and the Gender–Age–Physiology (GAP) index and staging system [47] (Table 3).

The GAP index is the most widely used for assessing patients with IPF. This simple tool uses commonly available clinical and physiological variables to predict prognosis in patients with IPF. The GAP index is derived from data on patients' gender, age and respiratory physiology [which includes the percentage predicted of forced vital capacity (FVC %) and percentage predicted of diffusing capacity for carbon monoxide (DLCO %)] as presented in Table 3. The GAP index and staging system classifies patients with IPF into three stages: stage I (0–3 points), stage II (4–5 points) and stage III (6–8 points), with a higher GAP stage signifying higher risk for mortality. The GAP index and staging system is an easy and quick screening approach to predict mortality in patients with IPF [47].

Composite scoring systems capture various aspects of the disease's pathophysiology and offer a broader range of prognostic information. The optimal composite scoring system for staging IPF has not yet been determined, as all the published systems have limitations in either methodology, design, population, sample size or follow-up period[48]. Patients in early stages as determined by composite scoring systems may be considered as having early IPF.

MULTIDISCIPLINARY TEAM DISCUSSION

To confirm a diagnosis of IPF, a multidisciplinary team discussion is recommended between respiratory consultants, radiologists and pathologists based on clinical data, HRCT and lung biopsy if acquired [49]. The 2018 ATS/ERS/JRS/ALAT evidence-based guidelines for IPF diagnosis suggested a multidisciplinary discussion for the diagnosis of IPF (conditional

Table 1 Different composite scoring systems in IPF and their predictor components

Composite scoring systems in IPF	Predictors
Composite physiologic index (CPI)	Extent of disease on CT = 91.0 – (0.65 × percent predicted DLCO) – (0.53 × percent predicted FVC) + (0.34 × percentage predicted FEV1))
Du Boise score	Age
	24-week history of respiratory hospitalization
	FVC % predicted
	24-week change in FVC % predicted
GAP index and staging system	Gender
	Age (years)
	Physiology
	FVC % predicted
	DLCO % predicted

recommendation with very low quality of evidence) [23]. Chaudhuri et al. have shown in their single-centre retrospective review of the multidisciplinary discussion for the diagnosis of ILD that the ILD multidisciplinary discussion meeting often resulted in a change of diagnosis, which affected the subsequent management. In 76% of referred cases with uncertain diagnosis, the multidisciplinary meeting approach was able to establish a diagnosis. Moreover, they have demonstrated that a prior diagnosis of IPF was incorrect in over 50% of cases referred for multidisciplinary team meeting [50]. Jo et al. also showed similar findings, where ILD diagnosis was changed in 53% of patients after ILD multidisciplinary team meeting, and 71% of referred patients with unclassifiable diseases were given a diagnosis [51].

AWARENESS AMONG PRIMARY CARE PHYSICIANS

IPF can be difficult to diagnose in its early stages due to overlap of symptoms with other more common conditions. As patients with IPF usually present with symptoms of cough and shortness of breath, their symptoms are often attributed to ageing, smoking or more prevalent respiratory or cardiovascular conditions [52]. Moreover, patients with early disease may have minimal symptoms or subtle clinical signs, and as such, diagnosis necessitates a high index of clinical suspicion among primary care physicians. Patients with IPF frequently endure significant delays before diagnosis, with a recent study finding an average delay of 2.1 years from the onset of symptoms to diagnosis [52]. Furthermore, ratifying a diagnosis of IPF requires a specialised, multidisciplinary team with expertise in ILD [23, 53], which is typically only available in specialist centres [54].

Primary care physicians are often the first to consult with patients with suspected IPF and are responsible for referral to specialised ILD centres for confirmation of diagnosis and management. Recently, Silva et al. evaluated primary care physicians' awareness of the main ILD subtypes, including IPF. Their questionnaire assessed the respondents' degree of awareness of the basic diagnosis and management of the main ILD conditions, including IPF, in five healthcare centres in Portugal. The participants performed acceptably in the sections related to hypersensitivity pneumonitis, connective tissue disease

Table 2 Du Boise mortality risk scoring system for patients with IPF

First, individual scores are summed for each risk factor		Second, expected 1-year probability of death is identified corresponding to total risk score	
Risk factors	**Score**	**Total risk score**	**Expected 1-year risk of death**
Age (years)			
≥ 70	8	0–4	< 2%
60–69	4	8–14	2–5%
< 60	0	16–21	5–10%
Recent respiratory hospitalization		22–29	10–20%
		30–33	20–30%
Yes	14	34–37	30–40%
No	0	38–40	40–50%
		41–43	50–60%
		44–45	60–70%
Baseline FVC % predicted		47–49	70–80%
≤ 50	18	> 50	>80%
51–65	13		
66–79	8		
≥ 80	0		
24-week change in FVC % predicted			
≤ −10	21		
−5 to −9.9	10		
> −4.9	0		

ILD, sarcoidosis and drug-induced ILD, but, unfortunately, their level of awareness of IPF was deemed to be poor [55].The critical role that primary care physicians play in the early diagnosis of IPF highlights the need for educational intervention to raise awareness of ILD in this setting. This in turn could result in rapid referral of patients to specialist centres and ongoing dialogue between pulmonologists and primary care physicians during patient follow up [55]. A retrospective study conducted in two specialist ILD clinics in two countries (UK and Ireland) investigated patients' outcomes in association to time taken from primary care physician visit to ILD specialist centre referral and start of anti-fibrotic medication. This study showed that patients evaluated by ILD clinic within 12 months had longer time to death and longer duration on anti-fibrotic medication compared with those evaluated later [56].

LUNG CANCER SCREENING AND EARLY IPF DETECTION

In several studies, patients who underwent computed tomography (CT) for lung cancer screening were found to have interstitial lung abnormalities (ILAs) [57–59], and some reported ILD [60]. ILAs are identified when a CT scan

Table 3 The GAP index and staging system

Predictor	Points
Gender	
Female	0
Male	1
Age (years)	
≤ 60	0
61–65	1
> 65	2
Physiology	
FVC % predicted	
> 75	0
50–75	1
< 50	2
DLCO % predicted	
> 55	0
36–55	1
≤ 35	2
Cannot perform	3

finding indicates a potential diagnosis of ILD in patients without clinical suspicion of ILD or in patients with an abdominal CT scan showing only the lower lung lobes. ILA is solely a radiological term that refers to the incidental finding of a CT abnormality [10].

In Hewitt et al.'s recent analysis of ever-smokers aged 55–75 years who received low-dose CT (LDCT) lung cancer screening, ILA was found in 78 of 1853 (4.2%) in the cohort. Fifty-nine participants (3.2%) of the ILA group met the criteria for ILD specialist evaluation, and a diagnosis of ILD was made in 28 patients (1.51%) who underwent LDCT screening, with IPF being present in half those cases. In the same population, lung cancer was found in 2.5% of patients, and the incidence of ILD in this study was comparable to that of lung cancer [58]. Therefore, lung cancer screening provides an opportunity for early ILD detection and treatment, potentially leading to better patient outcomes. The resource efficiency and cost-effectiveness of this strategy in the context of international healthcare settings merits additional analysis [58].

WHEN TO TREAT IPF: THE IMPORTANCE OF EARLY DIAGNOSIS

Anti-fibrotic medication with pirfenidone or nintedanib is recommended by international guidelines for patients with IPF. Randomised clinical trials have shown that the anti-fibrotic medications pirfenidone and nintedanib slow lung function decline, as reflected by FVC [61, 62]. Pirfenidone is a synthetic compound that has anti-fibrotic, anti-inflammatory and antioxidant characteristics. It accomplishes this by inhibiting pro-fibrotic growth factors such as transforming growth factor beta, inhibition of the production of inflammatory cytokines (e.g. tumour necrosis factor-α), and decreasing lipid peroxidation and oxidative stress [63]. Pirfenidone was evaluated in both the CAPACITY [64] and the ASCEND [62] trials and demonstrated reduction in the progression of IPF as indicated by changes in FVC, exercise tolerance (6-min walk test) and progression-free survival [62]. Nintedanib is an intracellular inhibitor that targets several tyrosine kinases such as fibroblast growth factors, vascular endothelial growth factors and platelet-derived growth factor receptors [65]. In the INPULSIS trials, nintedanib slowed the decline in FVC over a 52-week treatment period in patients with IPF [61].

Albera et al. evaluated data pooled from the ASCEND [62] and CAPACITY [64] studies to assess the effect of pirfenidone in patients with IPF with preserved baseline lung volume versus patients with impaired lung volume (FVC ≥ 80% versus FVC < 80% predicted) or by GAP index stage (stage I versus stage II–III). They concluded that the efficacy of pirfenidone was similar regardless of FVC or GAP stage [13]. In a post-hoc analysis using data from the ASCEND [62] and CAPACITY [64] studies, Nathan et al. assessed the efficacy of pirfenidone in patients

with IPF with advanced lung function impairment (FVC < 50% predicted and/or DLCO < 35% predicted) [66]. They found that pirfenidone significantly mitigates the decline in FVC, risk of all-cause mortality and respiratory-related hospitalisation. These results indicate that pirfenidone is beneficial in patients with IPF and advanced lung function impairment, with no increased risk of adverse treatment events [66].

Kolb et al. analysed pooled data from the INPULSIS trials [61] and found that patients with IPF who have preserved lung volume experience a similar rate of FVC decline and a similar benefit from nintedanib as patients with more impaired lung volume [17]. Their post-hoc subgroup analyses compared participants with FVC ≤ 90% predicted with those having FVC > 90% predicted. In patients with FVC > 90% predicted, the annual rates of FVC decline in the nintedanib group versus the placebo group were −91.5 ml/year and −224.6 ml/year, respectively, a difference of 133.1 ml/year. In the group of patients with FVC ≤ 90% predicted, the annual FVC decline in the nintedanib group versus the placebo group were −121.5 ml/year and −223.6 ml/year, respectively, a difference of 102.1 ml/year [17]. Costabel et al. report similar findings, with nintedanib having a similar effect of slowing disease progression in patients with IPF with a baseline FVC ≤ 70% predicted compared with those with a baseline FVC > 70% predicted [67]. Nintedanib has shown acceptable long-term safety and tolerability, allowing patients with IPF to use it for long periods to slow disease progression [68]. The results of these studies encourage the prompt initiation of the anti-fibrotic medications pirfenidone and nintedanib in patients with IPF, regardless of the severity of disease.

IPF is commonly diagnosed late, as its symptoms are often misdiagnosed as those of more common diseases, such as asthma, chronic obstructive pulmonary disease (COPD) or heart disease, resulting in delayed referrals to specialist centres [69]. An early diagnosis of IPF may lead to earlier treatment with anti-fibrotic medications and even though individual clinical trials were not sufficiently powered to demonstrate significant effects on acute exacerbations and mortality, evidence is growing supporting the effects of pirfenidone and nintedanib in decreasing the risk of acute decline in lung function and improving life expectancy by slowing the progression rate of IPF. Anti-fibrotic medications have demonstrated efficacy in slowing the rate of FVC decline and in improving outcomes in patients with IPF. Given that the progress of a patient's condition cannot be anticipated at diagnosis and considering the poor overall prognosis of untreated IPF, anti-fibrotic medications should be considered for all patients with a diagnosis of IPF [70].

WHY ARE TREATMENT LEVELS LOW?

Longitudinal studies based on US registry data have identified varying rates of treatment with anti-fibrotic medications, ranging from 58% to 70% of patients with idiopathic pulmonary fibrosis [71, 72]. Maher et al. reported survey data from European respiratory physicians, which highlighted that only 60% of people with a confirmed diagnosis of idiopathic pulmonary fibrosis received treatment with anti-fibrotic therapy [73]. The low rate of treatment has been attributed to a 'watch and wait' approach adopted by both physicians and patients in the context of mild or moderate disease [73]. The use of anti-fibrotic medications for patients with mild and moderate disease has been debated [74–76] and the guidelines for prescription of these medications varies significantly between countries. Until recently, UK guidelines restricted the prescription of anti-fibrotic medications until the FVC fell to ≤ 80% predicted, although the beneficial effects of anti-fibrotic medications were known to occur at higher FVC values [13, 17]. Guidelines in the UK advise that anti-fibrotic medications are discontinued when a patient's FVC falls by over 10% in a 12-month period [77, 78]. Nathan et al. presented data from pooled pirfenidone trials that demonstrated that even patients with an initial decline in FVC of ≥ 10% may benefit from continued treatment with pirfenidone compared with placebo [79]. These findings

suggest that anti-fibrotic medications should not be discontinued except for intolerable side effects and safety reasons. However, it should be considered that data from registries and surveys often represents the management of a selected group of patients who have been referred to specialist centres and may not reflect the practice outside of these centres. It is important to establish anti-fibrotic medication uptake amongst patients throughout a wide range of healthcare settings to truly understand barriers preventing access to these medications.

The side effect profile of both nintedanib and pirfenidone are cited as the reason for many patients discontinuing treatment. The most commonly reported side effects of pirfenidone in the CAPACITY [64] and ASCEND [62] trials were gastrointestinal and skin rashes which can be managed by dose reduction [80]. RECAP was an open-label extension study to evaluate pirfenidone safety in patients who completed CAPACITY and ASCEND trials. Discontinuation of treatment occurred in 11.3% of patients, with the most common reasons being photosensitive rash and nausea [81]. Nintedanib causes primarily gastrointestinal side effects of diarrhoea, nausea and vomiting, and decreased appetite. The most frequently reported side effect in the INPULSIS trials was diarrhoea, with 63% of patients on nintedanib experiencing this side effect. This led to discontinuation of treatment for less than 5% of patients. However, real-world data suggests that rates of discontinuation of pirfenidone and nintedanib related to side effects are significantly higher, varying between 10% and 20% [82, 83].

For asymptomatic patients, there is a fine balance between reducing potential future symptoms and risk of deterioration, with the well-established side effect profile of anti-fibrotic medications. The ASCEND trial concluded that patients on pirfenidone had improved 6-min walk test compared with placebo, but did not establish any improvement in respiratory symptoms or quality of life [62]. Richeldi et al. reported no improvement in respiratory symptom burden or quality-of-life measures for patients using nintedanib compared with placebo [61]. There is no evidence that anti-fibrotic medications delay the onset of symptoms or improve prognosis in asymptomatic patients as no trials have been conducted to consider these outcomes. Anti-fibrotic medications do not reverse established fibrosis, they merely slow the development of new fibrotic changes, and therefore patients do not feel symptomatic benefit from treatment as the aim is to slow future decline. Therefore, it could be argued that with their established side effect profile, these medications are not warranted for asymptomatic individuals. This raises the question of whether early diagnosis of asymptomatic IPF through lung health screening programmes would actually improve treatment outcomes? As with all medical treatments, it is the prescribing clinician's responsibility to explain the potential benefits and risks of anti-fibrotic medications to facilitate shared decision making with patients.

In the UK, the prescription of anti-fibrotic medications for the treatment of IPF is restricted to specialist ILD centres. Therefore, delayed referral to a specialist centre prevents early initiation of these medications. An American cohort study identified that delayed access to a specialist care centre was associated with a higher risk of death in idiopathic pulmonary fibrosis independent of disease severity [84]. The median delay in referral to specialist centres reported in this study was 2.2 years. A delay of this magnitude would have a significant impact on the number of patients receiving anti-fibrotic medications. Considering that the average life expectancy for a patient with idiopathic pulmonary fibrosis prior to the development of anti-fibrotic medications was 3–5 years [4], it is unsurprising that this delay was also associated with increased mortality. A recent study conducted in Denmark also identified that a diagnostic delay of more than 1 year negatively impacted on progression free survival, quality of life and hospitalisation rates [85]. These studies highlight the importance of early diagnosis to allow proper management of patients with idiopathic pulmonary fibrosis.

When discussing studies that review the impact of early diagnosis on treatment outcomes and prognosis, it is important to examine the effect of lead-time bias [86]. Lead-time bias

occurs if diagnosis through screening programmes increases the perceived survival time, by earlier detection of the disease, without affecting the overall progression of the disease. Until recently, this was a significant issue in IPF as the UK guidelines prohibited prescription of anti-fibrotic medications to people with preserved lung function. Consequently, the detection of ILAs on CT imaging may not have improved the overall survival for those patients who progressed to develop IPF as they did not have earlier access to treatment. The recent change to UK guidance allows patients with preserved lung function to be treated with anti-fibrotic medication [87]. Nevertheless, an early diagnosis does not guarantee an improvement in patient outcomes and may cause unnecessary anxiety and increased burden of investigations for some patients.

HOW MIGHT ACCESS TO TREATMENT BE ADDRESSED?

Current literature has identified that people with IPF are often diagnosed late in the disease trajectory and that there is significant scope to improve treatment outcomes with earlier diagnosis [5, 85, 88]. In the early stages of IPF, delayed diagnosis and misdiagnosis contributes to delay in referral to specialist centres [69, 89]. Education for non-respiratory physicians regarding the early clinical signs and symptoms of IPF could reduce initial misdiagnosis that invariably delays the initiation of treatment. This would lead to earlier access to diagnostic imaging for symptomatic individuals and therefore earlier access to anti-fibrotic medications.

There is a need for more individualised prognostic information to guide treatments decisions for people with IPF. Advances in diagnostic technology in the form of artificial intelligence, lung cancer screening programmes and higher calibre HRCT imaging allows earlier diagnosis of patients with IPF. Although this enables earlier referral to specialist centres, the benefits of prescription of anti-fibrotic medications for asymptomatic patients is unknown and the majority are closely monitored to allow the initiation of medications in the event of disease progression. Instead, more widespread use of multidimensional models to improve staging and prediction of disease progression in IPF would identify patients who require prioritised treatment. There is hope that future research will lead to the development of a model which enables clinicians to discuss personalised risk with patients providing more information to guide treatment decisions.

In February 2023, the NICE guidelines for the prescription of nintedanib were updated to allow treatment for patients with an FVC above 80% predicted, a change that will undoubtedly improve treatment access for many people with IPF [87]. There is widespread agreement that for symptomatic patients, the previous guidelines which prevented prescription of anti-fibrotic medications for people with higher FVC levels, needed to be reviewed in consideration of evidence from recent subgroup analysis data [17]. It is crucial that patients with preserved lung function have access to anti-fibrotic medications at the point of diagnosis to reduce future decline in their lung function. It is recognised that percentage predicted FVC may not correlate with the severity of symptoms or radiological disease pattern seen at diagnosis [90]. However, anti-fibrotic medications are known to reduce the risk of acute exacerbations of idiopathic pulmonary fibrosis which can occur at any point in the disease trajectory [91]. Therefore, the prescription should not be restricted to only those whose FVC falls below 80% predicted. Although many people with IPF will follow a slowly progressive and predictable course, there are people who experience rapidly progressive disease or acute exacerbations, both of which can be fatal, and the risk would be reduced by treatment with anti-fibrotic medications from the time of first diagnosis [67, 91]. Patients should have access to these treatments without requirement for their FVC to decline to a predefined cost–benefit level[92]. The planned change to the guidelines reflects campaigning by clinicians and patient groups who have been in favour of this development for many years.

FUTURE OUTLOOKS

The future treatment of IPF may involve combination therapy including one or more anti-fibrotic medications. The safety and tolerability of therapy with both nintedanib and pirfenidone has been explored, indicating an increase in gastrontestinal side effects when using these medications in combination [93, 94]. Vancheri et al. suggested more stable disease in the group receiving combination therapy than those on nintedanib monotherapy with reduced decline in FVC (−13.3 versus −40.9, respectively) [93]. However, larger trials focused on functional decline would be required to evaluate the efficacy of combination therapy with anti-fibrotic medications. There is significant ongoing research aiming to develop new treatment options for IPF with the aim to find a treatment which can halt or even reverse disease progression. Novel treatments which are under evaluation include the use of stem cell based therapies, pemrevlumab, pentraxin and autotaxin inhibitors [95].

Current research is exploring the use of biomarkers to aid earlier and more specific diagnosis of idiopathic pulmonary fibrosis and to allow prediction of an individual's clinical course and potential to respond to treatment. There is evidence that elevated serum levels of serum protein biomarkers, surfactant protein-A, surfactant protein-D and Krebs von den Lungen-6 (KL-6) are associated with increased mortality [96, 97]. Mutation in the telomerase complex and mucin 5B (MUC5B) have also been studied as possible prognostic biomarkers [98–100]. The use of these biomarkers is not widespread in the clinical management of IPF, and current international guidelines do not mention the role of biomarkers.

In the UK, the care of patients with ILD centres around tertiary hospitals which often cover a large geographical area. The gold standard management of patients with IPF would involve streamlining diagnostic and referral pathways to minimise delay at all stages of the patient journey. Earlier diagnosis could be achieved through lung health screening programmes and education of non-specialist clinicians about the common signs and symptoms of IPF. Prompt referral to specialist ILD centres and multidisciplinary team discussion of patients' radiological, clinical and pathological findings would ensure accurate diagnosis and timely initiation of treatment. Specialist centres should commit to reviewing all appropriate patients within a short time frame, ideally less than 2 months from referral, either in person or at least specialist multidisciplinary team discussion [101]. Finally, patients who are eligible for treatment with anti-fibrotic medications should have these commenced as soon as possible once their diagnosis is confirmed.

CONCLUSION

IPF is a rare disease that can be difficult to diagnosis in its early stages due to the overlap of symptoms with other more common respiratory diseases. Access to anti-fibrotic medications is restricted to patients known to specialist centres and as such any delay in referral to ILD specialist centres results in delayed treatment initiation. Earlier diagnosis can be enhanced through education of non-specialists, access to HRCT and artificial intelligence technology, and lung cancer screening. Specialist multidisciplinary team review of patients and discussion of the individual's risks and benefits of treatment may help with patient adherence to medication.

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