Fibrosing interstitial lung diseases: knowns and unknowns

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ABSTRACT Patients with certain types of fibrosing interstitial lung disease (ILD) are at risk of developing a progressive phenotype characterised by self-sustaining fibrosis, decline in lung function, worsening quality of life, and early mortality. It has been proposed that such progressive fibrosing ILDs, which show commonalities in clinical behaviour and in the pathogenetic mechanisms that drive progressive fibrosis, may be "lumped" together for the purposes of clinical research and, potentially, for treatment. At present, no drugs are approved for the treatment of ILDs other than nintedanib and pirfenidone for the treatment of idiopathic pulmonary fibrosis. For other progressive fibrosing ILDs, the mainstay of drug therapy is immunosuppression. However, it is postulated that, once the response to lung injury in fibrosing ILDs has reached the stage at which fibrosis has become progressive and self-sustaining, targeted antifibrotic therapy would be required to slow disease progression. Nintedanib, an intracellular inhibitor of tyrosine kinases, has shown antifibrotic, anti-inflammatory and vascular remodelling effects in several non-clinical models of fibrosis, irrespective of the trigger for the injury. Ongoing clinical trials will provide insight into the role of antifibrotic treatment with nintedanib or pirfenidone in the management of fibrosing ILDs with a progressive phenotype.

Introduction

Interstitial lung disease (ILD) encompasses a large and heterogeneous group of parenchymal lung disorders, which overlap in their clinical presentations and patterns of lung injury. ILDs include several diseases of unknown cause [1], as well as ILDs known to be related to other diseases or to environmental exposures. One of the most common types of ILD is idiopathic pulmonary fibrosis (IPF). IPF is, by definition, a progressive fibrosing ILD characterised by decline in lung function and early mortality [2]. Patients with certain other types of chronic fibrosing ILD are also at risk of developing a progressive phenotype. These include idiopathic nonspecific interstitial pneumonia (NSIP) [3], unclassifiable idiopathic interstitial pneumonia [4], autoimmune ILDs [5], chronic sarcoidosis [6], chronic hypersensitivity pneumonitis (HP) [7] and exposure-related diseases such as asbestosis and silicosis [8]
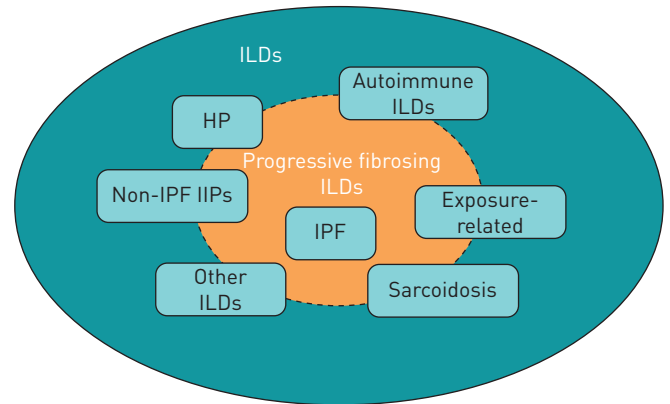
FIGURE 1 Types of interstitial lung disease (ILD) that may be associated with a progressive fibrosing phenotype. HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis; IIPs: idiopathic interstitial pneumonias.

(figure 1). It has been proposed that, for the purposes of clinical research and, potentially, for treatment, IPF be "lumped" with other forms of fibrosing ILD that have similar biological and clinical behaviours, *i.e.* self-sustaining fibrosis, progressive decline in lung function, and early mortality [9, 10]. The terminology "progressive fibrosing ILDs" has been coined to describe ILD in patients who, independent of the classification of the ILD, at some point in time exhibit a progressive fibrosing phenotype.

In this article, we review key knowns and unknowns related to the chronic fibrosing ILDs that may have a progressive phenotype (figure 2). This review is based on a symposium held at the European Respiratory Society International Congress in September 2017.

Defining progression in patients with fibrosing ILDs
End-points in clinical trials
Progression of fibrosing ILDs is reflected in an increase in fibrosis evident on a computed tomography scan, a decline in forced vital capacity (FVC) and gas exchange (*i.e.* diffusing capacity of the lung for carbon monoxide (D_{LCO})), worsening of symptoms and exercise capacity, and deterioration in health-related quality of life. There is no consensus as to how disease progression should be defined in patients with ILDs. Most clinical trials and observational studies in patients with ILDs have defined disease progression in terms of decline in FVC, measured as the change from baseline in mL or as a percentage of the predicted value, or as a categorical change (typically ⩾10% predicted), or as a composite of categorical change and mortality. In patients with IPF, decline in FVC is a well-established predictor of mortality [11, 12]. In a retrospective analysis of data from 1132 patients with IPF who received placebo in the TOMORROW, INPULSIS, CAPACITY and ASCEND trials, patients who had an absolute FVC decline of 10–15% predicted had a more than two-fold greater risk of mortality compared with those with an absolute FVC decline of <5% predicted (hazard ratio (HR) 2.20, 95% CI 1.10–4.37) [12]. Acute deteriorations in respiratory function accompanied by evidence of new abnormalities on imaging (known as acute exacerbations) are believed to be a reflection of disease progression. In patients with IPF, acute exacerbations are associated with very high mortality [13, 14]. In the retrospective analysis of data from
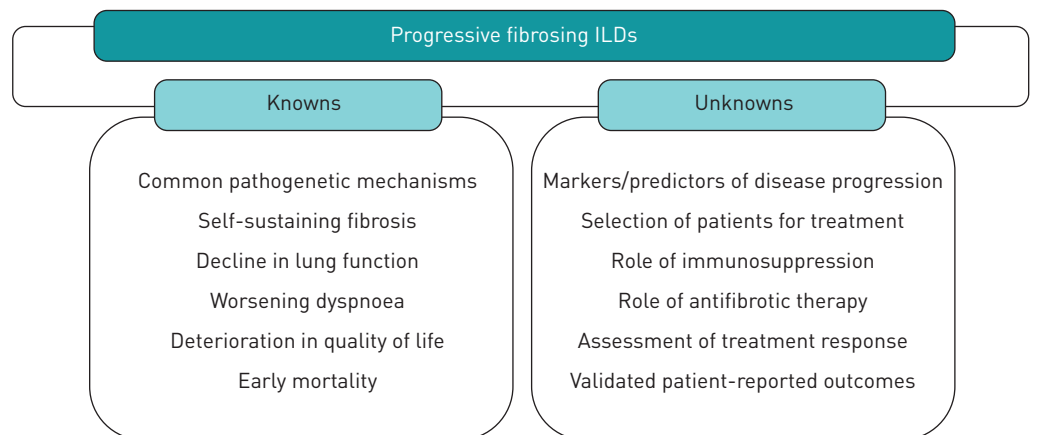

FIGURE 2 Knowns and unknowns in progressive fibrosing interstitial lung diseases (ILDs).

the TOMORROW, INPULSIS, CAPACITY and ASCEND trials, having an acute exacerbation was associated with a HR for mortality of 10.3 [12]. Respiratory-related hospitalisations, which capture most acute exacerbations, appear to be associated with an even higher risk of mortality [12].

In addition to lung function parameters, several other end-points have been used to assess disease progression in clinical trials in IPF (table 1). All these end-points have value in assessing the effects of patient characteristics and interventions on disease progression in patients with ILDs, but they do not always reflect the outcomes that are most relevant to patients. Patients are more concerned about the impact that their disease has on their daily lives and fear hospitalisations and the initiation of oxygen therapy. The use of long-term oxygen therapy to alleviate breathlessness and hypoxaemia in patients with ILDs is likely to indicate that lung function impairment has progressed to a severe stage and is associated with a large increase in the risk of mortality [15, 16].

Assessing progression in clinical practice

In clinical practice, progression of ILD is typically monitored through pulmonary function tests, evaluation of symptoms, and, less frequently, by chest imaging. In-clinic measurements of FVC are essential to monitor how a patient's disease is progressing, but are limited by the test variability and, potentially, by confounding effects of comorbidities such as emphysema. Furthermore, previous decline in FVC is not a good predictor of future decline in FVC. In an analysis of FVC measurements from two databases, of 50 patients with IPF who had a decline in FVC of $\geqslant$10% predicted during year 1, 84% had stable FVC over year 2; of 135 patients who had stable FVC during year 1, 19% had a decline in FVC of $\geqslant$10% predicted during year 2 [17]. Similarly, a pooled analysis of data from the ASCEND and CAPACITY trials found only a weak negative correlation between changes in FVC in two consecutive 6-month intervals [18]. Weekly or even daily measurement of FVC using home spirometry may provide a more accurate picture of disease behaviour and enable therapeutic decisions to be made more swiftly [19, 20].

TABLE 1 End-points used in clinical trials to assess disease progression in idiopathic pulmonary fibrosis

Lung function	Rate of decline in FVC (mL·year^{-1})
	Absolute or relative changes in FVC (mL or % predicted)
	Absolute or relative changes in D_{LCO} % predicted
	Categorical declines in FVC or D_{LCO} (mL or % predicted)
Exercise capacity	Absolute change in 6-min walk test distance
	Categorical decline in 6-min walk test distance
	Change in oxygen saturation nadir during 6-min walk test
Patient-reported outcomes	Open question(s) on symptoms
	St George's Respiratory Questionnaire (SGRQ)
	University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ)
	Cough and Sputum Assessment Questionnaire (CASA-Q)
	EuroQol 5-Dimensional Quality of Life Questionnaire (EQ-5D)
	Short-Form Health Survey (SF-36)
Acute worsenings	Acute exacerbations
	Respiratory hospitalisations
	All-cause hospitalisations
Mortality	All-cause mortality
	Death due to respiratory cause
	Progression-free survival
Radiological markers	Quantitative fibrosis scores based on HRCT
Serum biomarkers	Krebs von den Lungen-6 protein (KL-6)
	Surfactant proteins D and A
	Neoepitopes (biomarkers of extracellular matrix turnover)

FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography.

Although several studies have identified predictors of disease progression in patients with ILDs, the course of disease for an individual patient remains impossible to predict. This creates a huge challenge in defining treatment response in patients with progressive disease, as disease progression does not necessarily equal treatment failure. There is great interest in applying the concept of precision medicine to ILDs. Identification of patient subgroups based on genetic or molecular profiles, or on environmental or behavioural factors, may enable better prediction of the course of disease for individual patients and facilitate the selection of therapies that are most likely to be effective in those patients [10, 21–23].

In the following sections, we will focus on autoimmune ILDs and chronic HP as examples of chronic ILDs that may develop a progressive phenotype.

Autoimmune ILDs

Autoimmune diseases are commonly associated with pulmonary complications including ILD [5]. Patients across the spectrum of connective tissue diseases (CTDs) are at risk of developing ILD, including those with systemic sclerosis (SSc) [24]; rheumatoid arthritis (RA) [25]; inflammatory myopathies such as polymyositis, dermatomyositis and anti-synthetase syndrome [26, 27]; and Sjögren's syndrome [28]. A further group of patients develops interstitial pneumonia with features suggestive of an autoimmune disease that do not meet criteria for a defined disease. The term "interstitial pneumonia with autoimmune features" (IPAF) has been proposed to describe this constellation [29]. Discussion continues as to how patients with IPAF should be classified and managed in clinical practice [30, 31].

Systemic sclerosis

ILD associated with autoimmune disease is particularly common in patients with SSc. ILD tends to occur early in the course of SSc. In an analysis of 695 patients with SSc in the EUSTAR database, approximately one third of patients developed D_{LCO} <50% predicted within 3 months of the onset of Raynaud's phenomenon [32]. ILD is one of the leading causes of death related to SSc [33, 34]. A greater extent of fibrosis on a high-resolution computed tomography (HRCT) scan is highly predictive of mortality: in a seminal study, the risk of mortality was over three times greater (HR 3.46) in patients with extensive disease, defined as >30% extent of fibrosis on HRCT or 10–30% extent of fibrosis on HRCT plus FVC <70% predicted, than in patients with more limited disease [35].

Rheumatoid arthritis

The lifetime risk of developing clinically significant ILD in patients with RA is estimated to be 10% and ILD accounts for approximately 7% of RA-related deaths [36]. In a recent study, the *MUC5B* promoter variant rs35705950, an established genetic risk factor for IPF, was identified as a risk factor for RA-ILD, particularly RA-ILD with a usual interstitial pneumonia (UIP) pattern on HRCT [37]. RA-ILD has a variable clinical course but may result in severe impairment in lung function [38]. In a retrospective study of 167 patients with RA-ILD treated at a single centre, the proportion of patients with FVC <50% predicted rose from 14% at diagnosis to 22% at 5 years, while the proportion of patients with D_{LCO} <40% predicted rose from 29% at diagnosis to 40% at 5 years. Patients with a UIP pattern on HRCT, who comprised 53% of the patients in this study, were more likely to progress to D_{LCO} <40% predicted than those with NSIP [39]. In a retrospective review of hospital records from 84 patients with RA-ILD and UIP, after a median of 33 months, one third of patients had experienced a decline in FVC of >10% predicted and/or a decline in D_{LCO} of >15% predicted, and 17% had experienced an acute exacerbation [40]. The presence of a UIP pattern also confers a worse prognosis than other patterns on HRCT in patients with IPAF [41] and unclassifiable ILD [42]. In a study of data from 144 patients with IPAF in a US registry, patients with a UIP pattern had similar survival to patients with IPF, while those with IPAF and patterns other than UIP had a similar survival to patients with CTD-ILDs [41]. A greater extent of fibrosis on HRCT and worse lung function (FVC or D_{LCO}) have also been shown to be predictors of mortality in patients with RA-ILD [43, 44].

Treatment

No drugs are licensed for the treatment of ILDs related to autoimmune diseases. Treatment guidelines issued by the European League Against Rheumatism (EULAR) recommend tailored therapy with cyclophosphamide (CYC) for SSc-ILD, in particular for patients with progressive ILD [45, 46]. This recommendation was made based on the results of two randomised controlled trials [47, 48]. In the Fibrosing Alveolitis in Scleroderma Trial (FAST), 45 patients with SSc and pulmonary fibrosis received oral prednisolone on alternate days plus monthly intravenous infusions of CYC for 6 months followed by oral azathioprine for 6 months, or placebo for 12 months [47]. There was an improvement of 2.4% in FVC % predicted with active treatment *versus* a decline of 3.0% with placebo (p=0.08), but 32% and 43% of patients in these groups, respectively, withdrew prior to month 12 [47]. In the Scleroderma Lung Study

(SLS) I, 158 patients with SSc-ILD were randomised to oral CYC or placebo, of whom 145 had lung function measurements after 1 year. At 1 year, the mean decline from baseline in FVC % predicted was 1.0% in the CYC group *versus* 2.6% in the placebo group (p<0.05) [48]. In SLS II, CYC was compared to the immunosuppressant mycophenolate mofetil (MMF) [49]. A total of 142 patients with SSc-ILD were randomised to receive oral MMF for 2 years or oral CYC for 1 year followed by placebo for 1 year. At 2 years, there were improvements in FVC % predicted in both treatment groups (2.2% with MMF and 2.9% with CYC; p=0.56). MMF was associated with less toxicity than CYC, with a lower incidence of adverse events and fewer premature treatment withdrawals [49].

Other than for SSc-ILD, there are no data from randomised controlled trials to inform treatment decisions in patients with autoimmune ILDs and no treatment guidelines issued by a professional association. Treatment of autoimmune ILDs usually involves corticosteroids or other immunosuppressants such as azathioprine, CYC or MMF, based on clinical experience rather than scientific evidence. Corticosteroids are usually given as first-line therapy but should not be used at a dose above 15 mg·day^{-1} in patients with SSc and are not a viable option for long-term treatment. Biological therapies such as rituximab [50, 51] have shown positive effects on lung function in some studies in patients with autoimmune ILDs, but are not approved for the treatment of ILD. Non-drug approaches such as pulmonary rehabilitation, supplemental oxygen and supportive care are important elements of the overall care of patients with autoimmune ILDs, as is the management of extrapulmonary manifestations of disease and comorbidities. Patient monitoring should include longitudinal assessments of FVC, D_{LCO}, symptoms, exercise capacity and HRCT scans, in addition to a careful assessment of medication tolerance. In most cases, stability of these factors may be considered a successful outcome.

The role of antifibrotic drugs shown to slow disease progression in patients with IPF [52, 53] in patients with other forms of fibrosing ILD remains to be determined, but several trials are ongoing, including trials of nintedanib in patients with SSc-ILD (NCT02597933) and in patients with progressive fibrosing ILDs other than IPF (NCT02999178) and trials of pirfenidone in patients with RA-ILD (NCT02808871), progressive unclassifiable ILD (NCT03099187) [54], and as add-on to MMF (*versus* MMF alone) in patients with SSc-ILD (NCT03221257). In future, if trials of antifibrotic therapies are positive, the treatment of fibrosing autoimmune ILDs might involve both immunosuppression and antifibrotic therapy.

Chronic hypersensitivity pneumonitis

HP is a complex syndrome caused by sensitisation to an inhaled antigen that leads to an aberrant immune response in the small airways and lung parenchyma. Susceptibility is believed to be affected by genetics, antigen concentration and frequency of exposure, and immune tolerance [55]. Even in the context of multidisciplinary teams (MDTs), making a diagnosis of HP is challenging due to the difficulty in identifying causative antigens, variability in the patterns observed on HRCT and histopathology, overlap in presentation between HP and other ILDs, and the lack of a standardised diagnostic algorithm. In an analysis of inter-MDT agreement for the diagnosis of ILDs, the weighted kappa value for diagnosis of HP (indicating the level of agreement) was 0.29 (interquartile range (IQR) 0.24–0.40), compared with 0.73 (IQR 0.64–0.77) for IPF [56]. In a prospective case–cohort study at a single centre, of 46 patients diagnosed with IPF, 20 were diagnosed with chronic HP after additional testing [57].

Some patients with acute HP go on to develop chronic HP, and some of these patients develop a progressive fibrosing phenotype [58, 59]. Several studies have demonstrated that fibrosis on HRCT or biopsy is associated with worse survival in patients with HP [7, 60–62]. In a retrospective study of 142 patients with chronic HP, patients with fibrosis on HRCT and surgical lung biopsy had a median survival of 4.9 years, compared with 16.9 years in those without fibrosis. An inability to identify the inciting antigen, older age, lower FVC % predicted and a history of smoking were also predictive of mortality [7]. As in IPF, the single nucleotide polymorphism *MUC5B rs35705950* and short telomere length have been associated with reduced survival in patients with chronic HP [63].

There is no established treatment algorithm for HP and a poor evidence base to inform therapeutic decision-making. Management of HP typically involves removal of the antigen (if it can be identified) and the use of corticosteroids or other immunosuppressants, despite very limited evidence to support their efficacy [58, 59, 64]. As such, much remains unknown regarding the treatment of patients with chronic HP, including the risks and benefits of immunosuppression and antifibrotic therapies.

Nintedanib as a potential treatment for chronic fibrosing ILDs with a progressive phenotype

Nintedanib is a tyrosine kinase inhibitor that targets receptors including the platelet-derived growth factor receptor α and β, fibroblast growth factor receptor 1–3, and vascular endothelial growth factor receptor 1–3, as well as the non-receptor Src family kinase Lck (lymphocyte-specific tyrosine-protein kinase) and

TABLE 2 Animal models in which nintedanib has demonstrated antifibrotic effects	
Trigger	**Model**
Chemical	Bleomycin-induced lung fibrosis [73, 75, 76]
Environmental	Silica-induced lung fibrosis [73]
Allergic	Ovalbumin-induced lung fibrosis and remodelling [77]
Vascular	Fra-2 transgenic mice (model of systemic sclerosis) [69]
Immunological	SKG transgenic mice+zymosan (model of RA-ILD) [78]

RA-ILD: rheumatoid arthritis-associated interstitial lung disease.

the colony-stimulating factor 1 receptor [65, 66]. Experiments conducted *in vitro* in human cells with relevance to ILDs have shown that nintedanib inhibits a number of processes involved in the initiation and progression of fibrosis, including pro-fibrotic mediator release [67]; M2 macrophage differentiation [68, 69]; the migration and differentiation of fibrocytes [70]; the proliferation, migration and differentiation of fibroblasts [71–74]; and the release of collagen [68, 73, 74]. Data from animal models with features of fibrosing ILDs suggest that nintedanib has antifibrotic and anti-inflammatory effects, irrespective of the trigger that caused the lung injury (table 2) [69, 73, 75–78]. Taken together, these data suggest that nintedanib inhibits processes that are fundamental to the progression of fibrosis.

Clinical trials have demonstrated that nintedanib reduces decline in lung function and the risk of acute exacerbations in patients with IPF with a manageable side-effect profile [52, 79, 80]. Nintedanib has been approved as a treatment for IPF in many countries and received a conditional recommendation for use in the latest international clinical practice guideline for IPF [81]. Similarities in biological and clinical behaviours (*i.e.* self-sustaining fibrosis, progressive decline in lung function, early mortality), together with the non-clinical data showing that nintedanib has antifibrotic effects irrespective of the trigger, provide a rationale for the investigation of nintedanib as a treatment for chronic fibrosing ILDs other than IPF. It is postulated that, once the response to lung injury in fibrosing ILDs has reached the stage at which fibrosis has become progressive and self-sustaining, targeted antifibrotic therapy would be required to slow disease progression.

The efficacy and safety of nintedanib *versus* placebo in patients with progressive fibrosing ILDs other than IPF are being investigated in the randomised double-blind INBUILD trial [9]. This trial recruited patients with features of diffuse fibrosing lung disease of >10% extent on an HRCT scan who met criteria for disease progression in the 24 months before screening, based on decline in FVC, worsening of symptoms, or an increased extent of fibrotic changes on chest imaging. Patients who had received (unapproved) medications to treat ILD were eligible to participate if defined washout periods were observed prior to randomisation [9]. The primary end-point is the annual rate of decline in FVC in mL·year^{-1} assessed over 52 weeks. The trial is powered to show a treatment effect in two co-primary analysis populations: all patients and patients with a UIP-like fibrotic pattern on HRCT. Change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score at week 52, time to first acute exacerbation of ILD or death over 52 weeks, and time to death over 52 weeks are being assessed as secondary end-points. In a separate trial, known as the SENSCIS trial, patients with SSc, onset of disease (first non-Raynaud symptom) ⩽7 years before screening, and ⩾10% fibrosis of the lungs on an HRCT scan have been randomised to receive nintedanib or placebo double-blind for at least 52 weeks [82]. Patients receiving prednisone (⩽10 mg·day^{-1}) and/or stable background therapy with mycophenolate or methotrexate are eligible to participate. As in the INBUILD trial, the primary end-point is the annual rate of decline in FVC in mL·year^{-1} assessed over 52 weeks. Key secondary end-points in the SENSCIS trial are absolute changes from baseline in modified Rodnan skin score (a measure of skin fibrosis) and in St George's Respiratory Questionnaire total score at week 52.

Conclusions

IPF is the "prototype" chronic fibrosing ILD with a progressive phenotype as it is, by definition, an ILD associated with progressive pulmonary fibrosis and has no known cause. A proportion of patients with certain other types of chronic fibrosing ILD also develop a progressive phenotype characterised by decline in lung function, worsening quality of life and, ultimately, early mortality. It has been suggested that these diseases may be considered as a group for the purposes of clinical research and, potentially, for treatment. There is no consensus as to how disease progression should be defined in patients with ILDs, but in clinical practice it is typically assessed through assessment of lung function, symptoms, imaging features and clinical events such as acute exacerbations and respiratory hospitalisations. Other than nintedanib and

pirfenidone for the treatment of IPF, no drugs are approved for the treatment of ILDs and there is a poor evidence base to inform therapeutic decision-making. Non-clinical evidence suggests that nintedanib inhibits fundamental processes in the pathogenesis of fibrosis, irrespective of the trigger. Ongoing clinical trials will provide insight into the role of antifibrotic therapies in the treatment of fibrosing ILDs with a progressive phenotype.

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