# Progressive fibrosing interstitial lung disease: clinical uncertainties, consensus recommendations, and research priorities

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**Within the spectrum of fibrosing interstitial lung diseases (ILDs) is a subset of patients who have inexorable progression of pulmonary fibrosis despite treatment, which is known as the progressive fibrotic phenotype. Although the concept of progressive fibrosing ILD has been applied largely to patients with idiopathic pulmonary fibrosis (IPF), there is now an increasing focus on irreversible progressive fibrosis in a proportion of patients with a range of underlying ILD diagnoses. Evidence has emerged to support a possible role for antifibrotic therapy in these patients. In this Position Paper, we discuss the importance of retaining diagnostic scrutiny within the multidisciplinary team and suggest a multidomain definition for progressive fibrosis. We consider the potential role of antifibrotic drugs as second-line therapy in the treatment algorithm for patients with progressive non-IPF ILD. We highlight risk factors that might predispose individuals to developing progressive fibrosis. Finally, we discuss key uncertainties and future directions for research and clinical practice.**

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## Introduction

The fibrosing interstitial lung diseases (ILDs) are a heterogeneous group of conditions with differing causes and treatment options,[1] as well as a range of disease behaviours.[2] Idiopathic pulmonary fibrosis (IPF) is the archetypal progressive fibrosing ILD, with relentless lung function decline in almost every affected individual.[3–5] Although the other fibrosing ILDs, such as chronic hypersensitivity pneumonitis, those associated with connective tissue diseases—including systemic sclerosis-associated ILD, myositis-associated ILD, and rheumatoid arthritis-associated ILD—and idiopathic non-specific interstitial pneumonia (NSIP), have the potential for improvement and stabilisation with appropriate management, a subset of patients with these conditions will continue to have progressive fibrosis despite immunosuppressive therapy and the elimination of disease-promoting stimuli (Wijsenbeek M and Cottin V, unpublished).[6]

The antifibrotic drugs pirfenidone[7] and nintedanib[8] have been shown to attenuate the annual rate of lung function decline (forced vital capacity [FVC]) in patients with IPF by approximately 50%. In the SENSCIS trial,[9] 2019, nintedanib was shown to be efficacious in slowing the rate of functional decline of systemic sclerosis-associated ILD. Until 2019, a role for antifibrotic therapy in the treatment of other fibrotic lung diseases had only been hypothesised,[10,11] but several studies of potential treatments for patients with progressive fibrosing ILD are underway or have been completed (table 1). The INBUILD study,[12] published in 2019, has provided evidence that nintedanib is an effective treatment for patients with progressive fibrosing ILD despite maintenance therapy, across a range of underlying diagnoses. In an important subgroup analysis of the five major diagnostic labels included in INBUILD[15]—hypersensitivity pneumonitis, autoimmune ILDs, idiopathic NSIP, unclassifiable idiopathic interstitial pneumonia, and other ILDs—the effect of nintedanib in attenuating disease progression remained consistent across diagnoses and regardless of the underlying pattern of fibrosis on CT. Pirfenidone has also shown efficacy in the treatment of patients with

### Key messages

- Progressive fibrosing interstitial lung disease is a phenotype in which patients continue to progress despite conventional treatment directed at the underlying diagnosis; the definition of progressive fibrosis should integrate combinations of deteriorating lung function, CT appearances, and patient symptoms
- It is important to make an accurate diagnosis to ensure that patients are treated optimally before progressive fibrosis can be ascertained
- The multidisciplinary team should have a central role in establishing an underlying diagnosis and then assessing longitudinal disease behaviour on conventional therapy
- Antifibrotic therapy for non-idiopathic pulmonary fibrosis interstitial lung disease could be considered as a second-line therapy after demonstration of progressive fibrosis despite conventional treatment
- In the absence of clinical trial data, the decision to initiate combination treatment with antifibrotic therapy and immunosuppression should be made on a case-by-case basis by a multidisciplinary team, taking into account a number of patient and disease factors
- A range of approaches including epidemiological studies, randomised controlled trials, and deep learning algorithms will be needed to address key uncertainties in the identification and management of the progressive fibrotic phenotype

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progressive unclassifiable ILD, although the primary endpoint was not met for this drug because of measurement variability of home spirometry.[13] Pirfenidone has been studied in a range of progressive non-IPF ILDs in the RELIEF study,[14] which was terminated early because of futility due to low recruitment, with the final publication eagerly awaited.

Although several review articles and opinion pieces have been published on the subject of progressive fibrosing ILDs, the majority pre-date the publication of these pivotal studies and subsequent subanalyses. Although data from these studies underscore the importance of the progressive fibrosing ILD phenotype, providing evidence that antifibrotic therapy is effective for this group of patients, important areas of uncertainty remain with regard to definitions, diagnosis, and management. To agree areas for which evidence now exists and questions for which evidence is insufficient or absent at present, a working group of ILD physicians was convened at the third International Summit for Interstitial Lung Diseases. An expert consensus on key questions relating to the definitions, diagnosis, and

| | Treatment | Phase and study design | Status | Primary outcome | Estimated enrolment | Inclusion criteria |
|---|---|---|---|---|---|---|
| Nintedanib in PF-ILDs (INBUILD; NCT02999178)[12] | 150 mg nintedanib twice daily versus placebo | Phase 3, randomised, double-blind, placebo-controlled trial | Completed | Annual rate of change in FVC | 663 patients aged ≥18 years with fibrosing lung disease on HRCT | PF-ILD defined by the presence of at least one of the following (within 24 months before screening): relative decline in FVC of ≥10% of the predictive value; relative decline in FVC of 5% to <10% of the predicted value and worsening of respiratory symptoms or increased extent of fibrosis on HRCT; worsening of respiratory symptoms and increased extent of fibrosis on HRCT; extent of fibrosis on HRCT >10%, FVC >45% predicted, or DLCO ≥30% and <80% predicted |
| Pirfenidone in unclassifiable PF-ILD (NCT03099187)[13] | 801 mg pirfenidone three times daily versus placebo | Phase 2, randomised, double-blind, placebo-controlled trial | Completed | Rate of decline in FVC (measured daily by hand-held spirometer) from baseline to week 24 | 253 patients aged ≥18–85 years with unclassifiable PF-ILD | Progressive disease defined as a decline in FVC of >5% or significant symptomatic worsening; extent of fibrosis >10% on HRCT; FVC ≥45% predicted; DLCO ≥30% predicted |
| Pirfenidone in progressive fibrotic sarcoidosis (PirFS; NCT03260556) | 801 mg pirfenidone three times daily versus placebo | Phase 4, randomised, double-blind, placebo-controlled trial | Unknown | Time to clinical worsening | 60 patients aged >18 and <90 years with progressive fibrotic pulmonary sarcoidosis | Pulmonary function testing with a composite physiological index score >40; >20% fibrosis on chest HRCT; stable dose of prednisone or immunosuppressive drugs, or both |
| Pirfenidone in pulmonary fibrosis with anti-MPO antibodies (PIRFENIVAS; NCT03385668) | 801 mg pirfenidone three times daily | Phase 2, open-label pilot study | Recruiting | Change in percentage of predicted FVC from baseline to week 52 | 15 patients aged >18 years with pulmonary fibrosis | Anti-MPO antibody at inclusion or during follow-up, or diagnosis of anti-MPO vasculitis, or both; pulmonary fibrosis refractory to conventional therapy for anti-MPO vasculitis; definite or possible UIP or NSIP on chest HRCT; FVC ≥50% and <90% predicted; DLCO ≥30% and <90% predicted |
| Pirfenidone in progressive, non-IPF lung fibrosis (RELIEF; EudraCT 2014-000861-32)[14] | 801 mg pirfenidone three times daily versus placebo | Phase 2, randomised, double-blind, placebo-controlled trial | Completed; stopped for futility (low recruitment) | Change in percentage of predicted FVC from baseline to week 48 | 127 patients aged ≥18 and ≤80 years with a confident diagnosis of progressive, non-IPF ILD | Progressive disease documented by at least three pulmonary function tests within 6–24 months before enrolment, demonstrating an annualised percentage of predicted FVC decline of ≥5% (absolute); FVC ≥40% and <90% predicted; DLCO ≥10% and <90% predicted |
| BMS-986278 in IPF (NCT04308681) | BMS-986278, a lysophosphatidic acid 1 (LPA1) receptor antagonist, versus placebo | Phase 2, randomised, double-blind, placebo-controlled trial | Not yet recruiting | Rate of change in percentage of predicted FVC in participants with IPF from baseline to week 26 | 360 patients with PF-ILD aged ≥21 years or IPF aged ≥40 years | A diagnosis of ILD or IPF within 7 years |
| Epidemiology, clinical characteristics, prognosis, and health-care costs of PF-ILD and SSc-ILD (PROGRESS; NCT03858842) | Non-interventional* | Retrospective, observational study | Not yet recruiting | Incidence, prevalence, patient characteristics, health-care resource use, and associated costs | 100 patients aged ≥18 years at diagnosis, hospitalised in France for PF-ILD or SSc-ILD | Patients recruited between Jan 1, 2010, and Dec 31, 2017 |

(Table 1 continues on next page)

| | Treatment | Phase and study design | Status | Primary outcome | Estimated enrolment | Inclusion criteria |
|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | |
| Long-term nintedanib in PF-ILD (INBUILD-ON; NCT03820726) | 150 mg nintedanib twice daily | Open-label, non-randomised, extension study | Active, not recruiting | Incidence of overall adverse events over the course of the trial (up to 36 months) | 435 patients who completed the INBUILD trial | Patients who did not prematurely discontinue trial medication |
| Nintedanib in progressive pneumoconiosis (NiPPS; NCT04161014) | 150 mg nintedanib twice daily | Phase 2, open-label study | Not yet recruiting | Annual decline in FVC | 100 patients with a diagnosis of pneumoconiosis (asbestosis, silicosis, coal worker's pneumoconiosis, or diffuse dust fibrosis) | Patients with >10% fibrosis on chest HRCT; FVC ≥45% predicted; DLCO >30% predicted |
| Allogeneic MSCs in rapidly progressing ILD (NCT02594839) | Two infusions of $2 \times 10^8$ allogeneic bone marrow MSCs at intervals of 7 days, every 3 months for 1 year, versus placebo in phase 2 | Phase 1–2, randomised, open-label trial | Completed | Number of serious adverse events at 12 months | 20 patients with a diagnosis of IIP or ILD secondary to CTD | Histological or radiological diagnosis of ILD; FVC ≥40% predicted; DLCO ≥20% predicted; loss of FVC and DLCO >10% during the previous 12 months |

CTD=connective tissue disease. DLCO=diffusing capacity of the lung for carbon monoxide. FVC=forced vital capacity. HRCT=high-resolution CT. IIP=idiopathic interstitial pneumonia. ILD=interstitial lung disease. IPF=idiopathic pulmonary fibrosis. MPO=myeloperoxidase. MSCs=mesenchymal stem cells. NSIP=non-specific interstitial pneumonia. PF-ILD=progressive fibrosing interstitial lung disease. SSc=systemic sclerosis. UIP=usual interstitial pneumonia. *This is a non-interventional study that will not explore any treatments; however, it is included here because it is expected to inform clinical practice.

***Table 1:*** **Completed and ongoing clinical studies of treatments for progressive fibrosing interstitial lung disease**

management of progressive fibrosing ILDs was developed at the meeting and in subsequent discussions during the writing of this Position Paper, which included a review of available evidence. The aim of this paper is to provide an overview of evidence relating to these central issues, to provide recommendations for evidence-based management, and to highlight priorities for research.

## Development of recommendations

From Dec 9 to Dec 12, 2019, an expert group of ILD physicians convened in Erice, Italy, for the third International Summit for Interstitial Lung Diseases. The topic of progressive fibrosing ILD was discussed in detail with the intention of identifying areas of consensus as well as areas in which there are knowledge gaps and insufficient evidence to draw clear conclusions. The session started with a pros and cons debate focusing on whether a specific diagnosis is required any longer in the context of progressive fibrosing ILD, prepared in advance of the meeting and presented by PMG and UC, with a subsequent question-and-answer session. There then followed a larger, wide-ranging group discussion between all named authors, in which aspects of the progressive fibrotic phenotype were further discussed and published data were scrutinised. Priority areas were identified for discussion with a view to reaching consensus at the meeting. These included the definition of the progressive fibrotic phenotype, its epidemiology, risk factors for poor prognosis, diagnostic dilemmas, management options, and future research priorities. The views agreed at the meeting were further developed, including an update of the literature, as the manuscript was written and revised. This Position Paper represents a distillation of the views of the Erice ILD working group.

## How and when should progressive fibrosis be defined?

Until the publication of the INBUILD study,[12] no clear consensus existed as to the definition of progressive fibrosing ILD. This study was transformative in defining the clinical and research landscape, and details of the study therefore warrant further description. The INBUILD study recruited patients with any progressive fibrosing ILD aside from IPF. Over 52 weeks, the FVC of patients treated with nintedanib declined by an average of 81 mL compared with 188 mL for those in the placebo group. Nintedanib was efficacious in reducing the rate of lung function decline in all patients, regardless of the underlying pattern of fibrosis. The study was designed to maximise the chances of recruiting patients with evidence of progressive fibrosis over the preceding 24 months, using criteria from three separate domains: physiology, radiology, and symptomatology. Specifically, to be eligible for the study, patients needed to have had progression despite standard treatment, defined as a relative decline in predicted FVC of at least 10%; or a relative decline in predicted FVC of 5–10% with worsening respiratory symptoms or increased fibrosis on high-resolution CT (HRCT) scan; or worsening respiratory symptoms and increased fibrosis on HRCT. The fact that, using these criteria, the FVC of patients in the placebo group declined by an average of 188 mL over 52 weeks suggests that these parameters did indeed capture those individuals in whom there was true progression of fibrotic ILD. As anticipated, the annual FVC decline for the placebo group was greater in patients with a usual interstitial pneumonia (UIP)

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See **Online** for appendix

pattern than in those with other fibrotic patterns (211 mL *vs* 154 mL).

These enrolment criteria were crucial in ensuring appropriate selection of patients in the setting of a clinical trial, but in practice, clinicians use additional features to consider the diagnosis of progressive fibrosis. In the CAPACITY study[16] of pirfenidone, a reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) of at least 15% was considered as one component of the composite endpoint definition of progression-free survival. A decline in DLCO is often considered a sign of progressive ILD, particularly when accompanied by a decrease in FVC or increased radiological evidence of fibrosis on HRCT over time. An isolated sustained decrease in DLCO can occur in the context of pulmonary vasculopathy without any change in the extent of pulmonary fibrosis, and so should be used with caution when the only other affected domain is worsening symptoms. Furthermore, DLCO is more susceptible to both interlaboratory and intralaboratory measurement variability than is FVC,[17] and so was not used in the setting of this multinational clinical trial. However, in the correct clinical context, with regularly internally calibrated lung function laboratories, DLCO can provide supportive evidence for progressive fibrosis, particularly when accompanied by FVC decline.[18] The 6-min walk distance (6MWD) is an accessible and reproducible test:[19] a decline in the 6MWD can provide supportive evidence for progressive fibrosis[20] and serial measurement can be helpful in this regard. It should, however, be noted that in patients with progressive fibrosing ILD, in which systemic symptoms can coexist, a decline in the 6MWD might be suggestive of musculoskeletal involvement, anaemia, or left ventricular dysfunction, so rising oxygen requirements on exertion are a corroborative finding. The potential role of supervening pulmonary vascular disease should also be considered. Acute exacerbations are a devastating complication of IPF in which patients have accelerated disease progression and are at high risk of mortality.[21] Although there are no accepted definitions of acute exacerbations for other ILDs, there is an acceptance that acute exacerbations of non-IPF ILD are also life-threatening events with a similar clinical presentation.[22] Because lung function irreversibly declines after an acute exacerbation, this event can be considered an indicator of progressive fibrosis. With IPF progression, patients have a decline in quality of life that associates closely with clinically relevant endpoints, including change in lung function, hospitalisation, and mortality.[23,24] Although confirmatory data is required, it is reasonable to assume that the same association between decline in quality of life and progressive fibrosis exists in non-IPF ILD.

The definition of the progressive fibrotic phenotype is predicated upon the fact that patients have demonstrated progression despite maximal conventional treatment, which means that antifibrotic therapy is, by definition, a second-line therapy (figure). No detailed information is available from published studies of the treatments patients were taking in the months preceding enrolment. It is, however, important to state clearly that a patient can be labelled as having progressive fibrosis only if the disease continues to deteriorate despite appropriate management. Furthermore, because of the nature of medicine, the concept of appropriate management is dynamic and will evolve pending the emergence of new therapies.

The earliest time at which progression can be ascertained requires further study. In patients with chronic hypersensitivity pneumonitis and NSIP, if the disease cannot be stabilised early in the disease course (within 6–12 months), patients have ongoing lung function decline and increased mortality.[25,26] It would therefore be appropriate to suggest that once alternative explanations such as respiratory tract infection have been excluded and treated, patients meeting the criteria presented in panel 1 can be considered to have had progressive fibrosis.

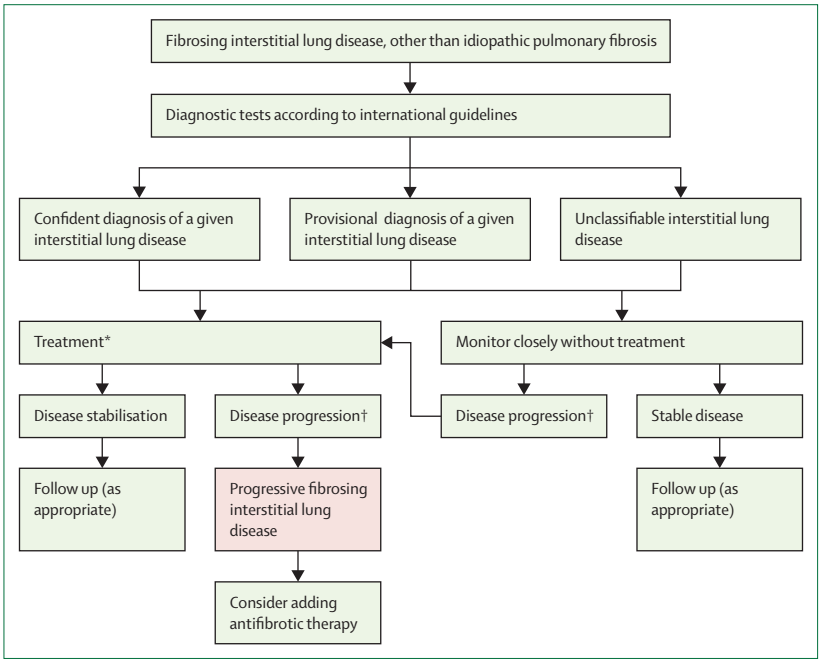


***Figure:*** **Approach to diagnosis and management of progressive fibrosing interstitial lung disease, other than idiopathic pulmonary fibrosis**

*Standard of care based on the specific interstitial lung disease. †The definition of disease progression is described in panel 1. Figure adapted from Cottin et al,[18] by permission of the European Respiratory Society.

## What is the prevalence of progressive fibrosis despite treatment?

The prevalence of progressive fibrosis is challenging to establish and can be estimated only from retrospective analyses at present. For example, in a cohort of 35 patients with NSIP, 26 (74%) had idiopathic disease and five (14%) patients had disease progression despite

immunosuppression.[27] In another study, 35 (31%) of 112 treated patients with fibrotic hypersensitivity pneumonitis had a 10% or more decline in predicted FVC after 6–12 months.[26] Those who had lung function decline on treatment had a median survival of 53 months, significantly less than 139 months for those whose disease stabilised within the first 6–12 months.[26] It has also been shown that 26 (60%) of 43 patients with idiopathic NSIP, 13 (50%) of 26 patients with undifferentiated connective tissue disease, and 10 (43%) of 23 patients with a defined connective tissue disease progressed despite treatment over a mean follow-up time between 4·6 years (SD 3·9) and 5·6 (3·8) years.[25] In a study of 162 patients with systemic sclerosis-associated ILD, 71 (44%) patients had a greater than 10% decline in FVC over 12 months and this was predictive of mortality (hazard ratio 1·84).[28] In a large survey of international ILD physicians, it was estimated that 18–32% of patients diagnosed with non-IPF ILDs develop a progressive fibrotic phenotype and the time from symptom onset to death in these patients was 61–80 months.[6]

## Is a specific ILD diagnosis needed and is there a role for lung biopsy?

Although a UIP pattern of fibrosis is appropriately considered to be associated with the worst outcomes, some patients with NSIP who progress over 6–12 months have similar rates of lung function decline to those with UIP;[29,30] however, NSIP is far more likely to respond to immunomodulatory therapy, with the potential for stabilisation and even reversal. Histological assessment can be limited by sampling error and interobserver variability when discriminating between fibrotic NSIP and UIP.[31] Moreover, UIP might coexist with NSIP and can be neglected when considering HRCT in isolation without the integration of lung biopsy, particularly for indeterminate cases. Novel molecular techniques might improve diagnostic accuracy,[32] so the future contribution of lung biopsy (both surgical biopsy and transbronchial cryobiopsy) remains relevant. The INBUILD trial provides data on UIP-like features of fibrotic ILDs on the basis of HRCT findings, but no histological data to clarify whether UIP on biopsy was present and to what extent this can predict disease progression despite immunosuppression or response to antifibrotic treatment.

Antifibrotic therapy can, at best, slow down the rate of lung function decline, but for patients with fibrotic NSIP[25] or chronic hypersensitivity pneumonitis,[26] early institution of immunomodulatory therapy can be associated with improvements in lung function and an excellent long-term prognosis. In the context of chronic hypersensitivity pneumonitis, antigen avoidance plays a crucial role in disease stabilisation[26,33] or in slowing disease progression and improving survival;[34] for connective tissue disease-associated ILD, immunosuppression with mycophenolate mofetil, azathioprine, or cyclophosphamide can stabilise the lung and musculoskeletal disease in the majority of patients.[35,36] It is obligatory not to miss this opportunity to reverse ILD by declaring a progressive fibrotic phenotype before an appropriate period of immunosuppression has been attempted, and in chronic hypersensitivity pneumonitis, before the effect of antigen avoidance has been assessed.

Consequently, making accurate diagnoses of ILD at baseline continues to be of central importance. In the correct clinical setting, a lung biopsy can be helpful in determining the appropriate initial course of treatment, particularly where there is clinical and radiological uncertainty.[3] The possibility that antifibrotic therapy will be approved for use in a range of ILDs should not detract from the fact that, in many cases of non-IPF ILD, there will be no requirement for antifibrotic therapy, sparing patients all of the attendant side-effects and stretched health-care systems the added resource burden. The current guidelines for the diagnosis of ILD remain valid[3] and multidisciplinary teams should continue to strive to assimilate all available clinical information, serology, HRCT appearances, and pathology (to include bronchoalveolar lavage and, where appropriate, surgical lung biopsy or transbronchial lung cryobiopsy) in an attempt to make consensus diagnoses.[37]

## Which patients are at risk of developing progressive fibrosis?

Several factors predispose certain patients to a higher risk of progressive fibrosis (panel 2). It has been shown that, regardless of specific ILD diagnosis, patients with a UIP pattern of pulmonary fibrosis decline at the greatest rate and have the poorest survival. For example, patients with rheumatoid arthritis-associated ILD and a UIP pattern might have a similar survival to patients with IPF.[38,39] Furthermore, patients with chronic hypersensitivity pneumonitis and a UIP pattern on lung biopsy[40] or an HRCT scan with extensive traction bronchiectasis or honeycombing,[41,42] have survival rates that approach those of IPF patients. In chronic hypersensitivity pneumonitis,

***Panel 1:* Suggested definitions of progressive fibrosis in clinical practice**

- Relative decline of 10% or more in forced vital capacity (FVC) over 24 months despite treatment
- Relative decline in FVC of 5% or more with decline in diffusing capacity of the lung for carbon monoxide of 15% or more over 24 months despite treatment
- Relative decline in FVC of 5% or more with increased fibrosis on high-resolution CT (HRCT)* over 24 months despite treatment
- Relative decline in FVC of 5% or more with progressive symptoms over 24 months despite treatment
- Progressive symptoms with increased fibrosis on HRCT* over 24 months despite treatment

*As assessed by an expert thoracic radiologist.

***Panel 2*: Established risk factors for progressive fibrosis despite treatment**

**Generalisable risk factors**

- Usual interstitial pneumonia pattern of pulmonary fibrosis[38–42]
- Extensive traction bronchiectasis on high-resolution CT (HRCT)[41,42]
- Rapid disease progression[38,40–42]
- No disease regression or stabilisation with initial therapy[25,26]
- Presence of a short telomere syndrome[43–49]
- Older age[42,50–52]

**Risk factors specific to certain conditions**

- In systemic sclerosis: older age at diagnosis, shorter disease course, Black American ethnicity, gastro-oesophageal reflux[50–54]
- In rheumatoid arthritis: smoking status[55]
- In rheumatoid arthritis and systemic sclerosis: extensive interstitial lung disease on HRCT[56–58,51]
- In chronic hypersensitivity pneumonitis: no identified antigen, increasing age[26,34]

older age is an independent prognostic factor for poor survival because survival worsens with each additional year of age.[42] Pleuroparenchymal fibroelastosis, a rare ILD characterised by marked pleural and parenchymal involvement with upper lobe predominance, can be idiopathic or coexist with fibrotic lung diseases such as IPF, systemic sclerosis, or chronic hypersensitivity pneumonitis in 18–30% of cases.[56–58] Pleuroparenchymal fibroelastosis is associated with progressive lung function decline and poor survival, so patients with this disease might be considered at higher risk of progressive fibrosis.

Patients with extensive fibrotic lung disease are also at the greatest risk of disease progression, which supports the concept that fibrosis begets fibrosis. In patients with systemic sclerosis-associated ILD, those with extensive disease—defined by an ILD extent on HRCT of more than 20% or, if indeterminate on HRCT, an FVC of less than 70% of the predicted value—have more than a three-times increased risk of death than those with less extensive disease.[59] In a population-based systemic sclerosis cohort, this finding has been replicated, with more than 10% extent of fibrosis on HRCT being associated with mortality.[60] The same concept has been confirmed in patients with rheumatoid arthritis-associated ILD, with extensive disease being associated with poorer survival.[61] Patients with systemic sclerosis who are at the highest risk of disease progression are those who are older at diagnosis, those with a shorter disease course, and those of Black American ethnicity.[50–52] In patients with ILD, it is hypothesised that gastro-oesophageal reflux disease (GORD) is associated with progressive fibrosis through repeated microaspiration events.[62] The strongest evidence for this association is in patients with systemic sclerosis, in which GORD is considered a pathogenic driver for pulmonary fibrosis,[53,54] and in patients with IPF, in which the presence of hiatus hernia—a known risk factor for GORD—is associated with more rapid lung function decline and increased mortality.[63–65] Because GORD and hiatus hernia are associated with worse outcomes in at least two ILDs of separate cause, it is possible that GORD and hiatus hernia confer a higher risk of developing the progressive fibrotic phenotype in other ILDs; however, this proposed association requires a dedicated prospective study.

Telomere dysfunction is now understood to be a key pathological determinant of the rate of progression of fibrosis and survival for patients with IPF[43–45] and with non-IPF ILDs including NSIP, chronic hypersensitivity pneumonitis,[46,47] and connective tissue disease-associated ILD.[48,49] Patients with chronic hypersensitivity pneumonitis and telomere dysfunction are more likely to have more extensive fibrosis, honeycombing, and traction bronchiectasis on HRCT, and have worse survival regardless of cause, radiological appearance, and pathological subtype of fibrosis.[46,47] Furthermore, patients with telomere dysfunction and non-IPF ILDs, including connective tissue disease, pleuroparenchymal fibroelastosis, NSIP, and unclassifiable disease, uniformly have a mean FVC decline of approximately 300 mL per year with an IPF-like median survival of 3 years.[48] Patients with familial pulmonary fibrosis might present at a younger age (a phenomenon known as genetic anticipation), so genetic testing should be considered in younger patients with progressive fibrosing ILD. Although testing for peripheral blood leucocyte telomere length and telomerase gene mutations is not yet widely available for routine clinical use, we support the provision of resources to facilitate the use of these tests in selected patients. The detection of telomere dysfunction should prompt more regular clinical contact, with close surveillance and early consideration of antifibrotic therapy if progressive fibrosis is shown. The case for more widespread testing of telomere dysfunction is substantiated further by its effect on immunosuppressive regimes after lung transplantation: patients with telomere shortening are at higher risk of bone marrow suppression and severe side-effects with immunosuppressive regimes used to prevent organ rejection than those without telomere shortening.[5]

Patients with fibrotic hypersensitivity pneumonitis and an identified inciting antigen, which is then avoided, are more likely to have an improved clinical course—with clinical and physiological stabilisation—than are those for whom an antigen is not identified, who have more rapid FVC decline and worse survival.[26,34] The absence of an identified antigen is therefore a risk factor for poor prognosis in chronic hypersensitivity pneumonitis, with a higher risk of progressive fibrosis. This example once again highlights the central importance of establishing a cause and specific diagnosis when

| | Suggested study types |
|---|---|
| What is the prevalence of progressive fibrosing interstitial lung disease? | Epidemiological studies and large cohort studies of patients with specific interstitial lung diseases |
| What is the optimal means of establishing progressive fibrosis and what is the earliest stage at which it can be identified? | Integration of data on serum biomarkers, imaging, physiology, and pathology within deep learning algorithms; retrospective analyses of longitudinal cohort studies |
| Is there a robust set of host and disease parameters that can predict disease progression? | Prospective studies of carefully phenotyped patients with specific subtypes of interstitial lung disease |
| Is there a subset of patients or diseases in which immunosuppression is harmful? | Randomised controlled trials of carefully phenotyped patients |
| Is it possible to predict which patients will develop the progressive fibrotic phenotype at diagnosis? | Retrospective analyses of longitudinal cohort studies; use of artificial intelligence, including deep learning algorithms |
| What is the most accurate means of assessing pulmonary inflammation that is suggestive of reversible disease? | Randomised controlled trials of immunosuppressive therapy in carefully phenotyped patients with consideration of artificial intelligence approaches |
| In which patients is a combination of immunomodulatory and antifibrotic therapy likely to be efficacious? | Randomised controlled trials in carefully phenotyped patients |
| What is the role of biomarkers in predicting progressive fibrosis? | Longitudinal cohort studies in carefully phenotyped patients with specific subtypes of interstitial lung disease |

*Table 2:* **Suggested study types to address key uncertainties in understanding and managing progressive fibrosing interstitial lung disease**

assessing patients with fibrosing ILD. Absence of response to treatment was an indicator of poor prognosis in a mixed cohort of patients with NSIP, undifferentiated connective tissue disease, defined connective tissue disease, and chronic hypersensitivity pneumonitis.[25] It is therefore appropriate to reassess patients' response to treatment at 3 months, because those in whom lung function has not stabilised at this stage are at increased risk of death.

## What is the optimal management for patients with progressive fibrosing ILD?

The key to ensuring the best outcomes for patients with progressive fibrosis is early, accurate diagnosis, antigen avoidance in relevant patients, initiation of the appropriate level of immunosuppressive therapy, and early clinical follow-up with lung function testing by 3 months. The choice of agent, route of administration, dose, and whether to use single or combination immunosuppressive treatment should be made on a case-by-case basis with the patient's wishes at the centre of the decision making process. If at this stage of the disease course, or indeed at any stage, there is evidence of progressive fibrosis, it is possible that the best treatment will consist of a combination of antifibrotic and immunosuppressant therapy. Combination therapy of mycophenolate mofetil with either nintedanib (in the SENSCIS trial[9] of patients with systemic sclerosis-associated ILD) or pirfenidone (in the uILD trial[13] of patients with progressive unclassifiable ILD) is tolerable and safe. However, as immunosuppression is associated with harm and increased risk of death for patients with IPF,[66] multidisciplinary teams will need to take into account the likelihood that IPF remains within the differential diagnosis, and consider the risks and benefits of combination therapy on a case-by-case basis. It is also important to recognise that, in some cases, if a patient is clinically deteriorating on oral immunosuppression, an opportunity might exist to stabilise the disease with escalation to intravenous therapy with, for example, methylprednisolone,[67] cyclophosphamide,[68] or rituximab.[69] Weighing up the risks and benefits of such an approach must be considered on an individual basis, taking into account the likelihood of response. The decision as to whether best management for a patient with progressive fibrosis on treatment is to intensify immunosuppression, to introduce second-line therapy with antifibrotic therapy, or perhaps to combine these two approaches might be challenging. Serial multidisciplinary team discussion provides an opportunity to reconsider the original diagnosis based on initial level of diagnostic confidence[37] and treated disease behaviour,[1] and then to consider empirical combination therapy with antifibrotic therapy and the appropriate level of immunosuppression should the diagnosis remain secure.

An important question is how to determine the appropriate level of immunosuppression, and several variables must be taken into account by the treating team. The presence of a bronchoalveolar lavage lymphocytosis increases the likelihood of a diagnosis of chronic hypersensitivity pneumonitis[33,70,71] and is associated with improved survival in patients with fibrotic idiopathic interstitial pneumonias,[72] and although there is a view that the presence of bronchoalveolar lavage lymphocytosis also dictates the likely response to immunosuppression, data to support this are awaited. The imaging pattern will also dictate the therapeutic strategy; for example, the presence of organising pneumonia on CT can be associated with a good prognosis[73] and affected patients might respond to escalation of immunosuppression. Autoantibody profiles also need to be taken into account; for example, patients with systemic sclerosis should not be treated with high-dose corticosteroids because they are at risk of developing scleroderma renal crisis. Other factors must be

### Search strategy and selection criteria

We searched PubMed for articles published from Jan 1, 1990, to July 10, 2020, using combinations of the individual search terms "IPF", "idiopathic pulmonary fibrosis", "interstitial lung disease", "ILD", "hypersensitivity pneumonitis", "HP", "CHP", "rheumatoid arthritis", "RA-ILD", "systemic sclerosis", "SSc", "scleroderma", "SSc-ILD", "non-specific interstitial pneumonia", "NSIP", "usual interstitial pneumonia", "UIP", "antifibrotic therapy", "nintedanib", "pirfenidone", "PANTHER", "INBUILD", "unclassifiable", "connective tissue disease associated ILD", "CTD-ILD", "progressive fibrotic phenotype", "autoimmune", "RELIEF", "lung function", "biopsy", "surgical lung biopsy", "cryobiopsy", "quality of life", "6 minute walk distance", "6MWD", "forced vital capacity", "FVC", "DLCO", "survival", "mortality", "bronchoalveolar lavage", "BAL, "pleuroparenchymal fibroelastosis", "PPFE", "gastroesophageal reflux", "GERD", "hiatus hernia", "high resolution CT", "HRCT", "telomere", "telomeropathy", and "genetics". Only articles written in English were included. The final reference list was generated on the basis of relevance to the topics covered in this Position Paper, with the aim of encompassing all relevant factors for consideration when addressing the priorities and uncertainties associated with progressive fibrosing interstitial lung disease. We searched the ClinicalTrials.gov and Deutsches Register Klinischer Studien trial registries for randomised controlled trials and observational studies using the search terms "IPF", "progressive fibrosing ILD", and "ILD" from Jan 1, 1990, to July 10, 2020.

considered when deciding on the intensity of immunosuppression, particularly in the presence of progressive fibrosis. These considerations include age, patient wishes, comorbidities, pathological findings if available, susceptibility to infection, side-effects of therapy, and measures of peripheral blood leucocyte telomere length, if available.

In patients with IPF, the evidence is clear that immunosuppressive therapy is associated with poor survival compared with placebo[66] and telomere dysfunction might contribute to these worse outcomes.[44] In other ILDs, there is currently no evidence that poorer prognosis seen in patients with a short telomere syndrome is a consequence of treatment with heavy immunosuppression, but there is a suspicion that this might be the case, especially in those with a UIP pattern. This is an area in which more research is urgently needed.

## Summary of recommendations and future directions

There is now compelling evidence that antifibrotic therapy is efficacious in the treatment of patients with non-IPF progressive fibrosing ILDs who do not respond to initial management, substantially slowing down the rate of disease progression.[12,13] There is also evidence that the progressive fibrotic phenotype is uniformly consistent in behaviour across different diagnoses and regardless of HRCT imaging pattern.[15] Although current antifibrotic therapy works across a range of progressive fibrosing ILDs, it should not be assumed that this will also be the case for future treatments, and these should be tested on their individual merits based on biological plausibility.

To achieve the best outcomes for patients, clinical teams should continue to provide timely, accurate diagnoses by using data from multiple domains to inform treatment. A review of response to treatment is required before ascertaining whether there is disease stability or evidence of progressive fibrosis, and whether the maximal and appropriate level of immunosuppression has been reached; in this setting, it is likely that a combination of immunosuppressive and antifibrotic therapy will be most effective, but prospective studies are required to explore this further. There are several factors that put patients in a high-risk group for progressive fibrosis; these individuals should be monitored more closely. In future, there might emerge evidence for risk prediction algorithms, whereby a subset of patients will be treated with a combination of immunosuppression and antifibrotic therapy at diagnosis, but for the time being, antifibrotic therapy in patients with non-IPF ILD should be considered as second-line therapy.

To address key uncertainties listed in table 2, future research should focus on the identification of individuals at risk of progressive fibrosis from the point of diagnosis. Approaches might involve HRCT deep learning algorithms and artificial intelligence to identify factors predictive of progressive fibrosis from baseline scans.[74] The quest for biomarkers to predict those at risk of progressive fibrosis is set to gather pace, as is the integration of telomere length and genetics in clinical practice. The same holds true for biomarkers that will predict, for the individual patient, the likely response to a given therapy. While these exciting advances are awaited, patients should be meticulously assessed and reassessed by multidisciplinary teams at regular intervals, using existing criteria, so that at the earliest possible opportunity, those who meet the definition of the progressive fibrotic phenotype are identified. With this approach, it is envisaged that teams will be able to modulate the disease trajectory of affected patients, with the goal of improving long-term outcomes.

**Contributors**

All authors contributed equally to the literature search and the writing and approval of the final manuscript.

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