

The Course and Management of Interstitial Lung Diseases

HIGHLIGHTS

- › Real-World Data on the Course of Idiopathic Pulmonary Fibrosis
- › Detection and Management of Autoimmune Disease–Associated Interstitial Lung Diseases
- › Identification, Course, and Management of Progressive Pulmonary Fibrosis

The Course and Management of Interstitial Lung Diseases

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The Course and Management of Interstitial Lung Diseases

OVERVIEW

This supplement to *The American Journal of Managed Care*[®] provides an overview of the course and management of interstitial lung diseases (ILDs). Data from real-world studies of patients with idiopathic pulmonary fibrosis (IPF) will be discussed along with a review of the identification, course, and management of autoimmune disease-associated ILDs and progressive pulmonary fibrosis (PPF).

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Real-World Data on the Course of Idiopathic Pulmonary Fibrosis

Steven D. Nathan, MD; and Joyce S. Lee, MD

Introduction

Idiopathic pulmonary fibrosis (IPF) is a type of interstitial lung disease (ILD) that is progressive over time.¹ However, the rate at which IPF progresses is variable and its trajectory can be slowed by the use of antifibrotic drugs.^{2,3} Real-world studies have informed our knowledge of the course of IPF. In this article, we discuss the data from those studies, with a focus on recent evidence.

Delays in Diagnosis of IPF

A diagnosis of IPF is often not made for some time after the onset of symptoms. A survey of US physicians conducted from 2018 to 2019 suggested that the typical delay from symptom onset to diagnosis of IPF was 1.7 years.⁴ Among 347 patients enrolled in a US registry between 2014 and 2019, approximately 50% were diagnosed more than a year after symptom onset.⁵ A diagnosis of IPF is often delayed due to an incorrect diagnosis having been made. In a retrospective study of Medicare claims data from 44,891 US patients between 2014 and 2019, a diagnosis of IPF was preceded by other respiratory diagnoses in almost all cases, and the mean time from an initial respiratory diagnosis to a diagnosis of IPF was 2.7 years.⁶

Delays in diagnosis may result in lung function being significantly impaired by the time IPF is diagnosed. Among 253 incident cases of IPF in the Canadian Registry for Pulmonary Fibrosis (CARE-PF), the mean forced vital capacity (FVC) was 73% predicted and the mean diffusing capacity for carbon monoxide (DL_{CO}) was 50% predicted.⁷ Similarly, among 498 patients who received a new diagnosis of IPF at the enrolling center for the US IPF-PRO Registry, the median FVC at enrollment was 71% predicted and the median DL_{CO} was 42% predicted.⁵ There is some evidence that a delayed diagnosis of IPF is associated with worse outcomes. A study of 264 patients diagnosed with IPF at 2 specialist ILD centers in Denmark from April 2016 to June 2021 found that patients who were not diagnosed with IPF for more than a year after their first IPF-related symptom had a higher rate of hospital admissions (0.7 vs 0.6 admissions per person-year) and worse progression-free survival (HR, 1.70; 95% CI, 1.18-2.46; $P = .004$) than patients diagnosed less than a year after their first IPF-related symptom, over a follow-up period of up to

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is characterized by a progressive decline in lung function, worsening quality of life, and high mortality. However, the rate and pattern of progression of IPF are variable. Real-world studies, which include a broader population of patients than clinical trials and collect data over longer periods, have provided important information on the clinical course of IPF and further insights into the efficacy and safety of antifibrotic therapies. They also highlight the worsening of patients' quality of life as lung function is lost, the high frequency of hospitalizations, and the impact of acute exacerbations on mortality in patients with IPF. Data from patient registries and analyses of claims data suggest that antifibrotic therapy is more likely to be used in patients who have worse lung function and that its use is associated with an improvement in life expectancy. The safety profile of antifibrotic therapies in real-world populations is consistent with that observed in clinical trials. Further real-world studies are needed to improve understanding of the course and impact of IPF in specific groups of patients and how the care provided to these patients might be improved.

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For author information and disclosures, see end of text.

TAKEAWAY POINTS

Idiopathic pulmonary fibrosis (IPF) is a progressive disease that is associated with high morbidity and mortality. Real-world studies have demonstrated that:

- ▶ A diagnosis of IPF is usually not made for more than a year after the onset of symptoms.
- ▶ Progression of IPF is associated with deterioration in lung function and health-related quality of life.
- ▶ Hospitalizations are frequent in patients with IPF and are associated with high mortality.
- ▶ Antifibrotic therapies may extend life in patients with IPF.

5 years.⁸ However, in an analysis of data from 498 patients in the US IPF-PRO Registry, there was no significant difference in time to death or lung transplant between patients who were diagnosed more than versus less than 1 year after symptom onset.⁵

Progression of IPF

IPF is associated with a progressive decline in FVC, but FVC does not decline at the same rate in all patients and patients may experience periods of stability or even slight increases in FVC.^{9,10} A machine learning–based analysis of data from 415 patients with IPF in a multicenter UK study (with IPF diagnosed \leq 6 months prior) or at the University of Chicago (with IPF diagnosed \geq 3 months prior), identified 4 clusters of patients with different trajectories of FVC over 3 years. In 34% of the cohort, there was a linear decline in FVC, in 24% there was an initial improvement followed by a decline, in 27% there was an initial decline then stabilization, while stability was evident in 15% of the cohort.¹⁰ Joint modeling of data from over 900 patients in the IPF-PRO Registry that were collected over a median follow-up period of almost 3 years suggested that mean declines in the FVC percentage predicted and DL_{co} percentage predicted were 2.8% per year and 2.9% per year, respectively.¹¹ A retrospective study of data from 249 patients on antifibrotic therapy (nintedanib or pirfenidone) referred to 3 ILD centers in Italy between 2011 and 2017 found an FVC decline over the first year of approximately 100 mL, with no significant difference between patients with a definite usual interstitial pneumonia (UIP) pattern on high-resolution CT (HRCT) or biopsy and those with a possible UIP pattern on HRCT.¹²

As IPF progresses, patients experience deterioration in health-related quality of life (HRQOL) due to worsening of symptoms and deterioration in physical function. At enrollment into the IPF-PRO Registry, a lower FVC percentage predicted was associated with worse HRQOL based on the St George's Respiratory Questionnaire (SGRQ) score.¹³ Among 424 patients with IPF in the German INSIGHTS-IPF

registry, HRQOL worsened over 3 years based on several patient-reported outcomes, including the SGRQ total score (mean change, 1.47; 95% CI, 1.17-1.76; $P < .001$).¹⁴ Data from 92 patients in the Finnish IPF Registry showed significant increases in the severity of impairment in several domains of physical and emotional health during the last 24 months of life (Figure 1).¹⁵

A minority of patients with IPF experience acute deteriorations in lung function, accompanied by worsening of radiologic abnormalities, which are known as acute exacerbations.¹⁶ In a retrospective analysis of data from 195 Japanese patients, the cumulative incidence of acute exacerbations in the 1, 2, and 3 years following initiation of antifibrotic therapy was 9%, 22%, and 25%, respectively.¹⁷ Similarly, in an analysis of claims data from 9961 newly diagnosed Japanese patients with IPF, the annual incidence of acute exacerbations was approximately 10%.¹⁸ In a prospective analysis of data from 676 Italian patients with newly diagnosed IPF, of whom 40% received antifibrotic therapy, 37% experienced at least 1 acute exacerbation over 5 years.¹⁹ Acute exacerbations are associated with high short-term mortality.^{20,21} In an analysis of data from 462 Japanese patients evaluated at a Japanese referral center, the median survival after evaluation at the center was 2.9 years in patients who had an acute exacerbation versus 5.8 years for those who did not ($P < .001$) (Figure 2); 90-day mortality following an acute exacerbation was 47%.²⁰

Utility of Antifibrotic Therapy

Two antifibrotic therapies were approved in the US for the treatment of IPF in 2014: nintedanib and pirfenidone. In an analysis of claims data from 10,996 US patients with IPF collected between October 2014 and July 2019, approximately 26% had started antifibrotic therapy.²² More recent data from a patient registry in Canada suggest that 54% of patients with IPF are receiving antifibrotic therapy.²³ Data from a patient registry in the US suggest that 70% of patients with IPF are receiving antifibrotic therapy and that its use is more frequent in patients who are younger (OR, 0.87; 95% CI, 0.79-0.97, per 5-year higher), have worse FVC percentage predicted (OR, 0.91; 95% CI, 0.84-1.00, per 10% higher), or use supplemental oxygen with activity (OR, 1.55; 95% CI, 1.11-2.16).²⁴ However, most of the patients in these registries were receiving their care at specialized centers, and the use of antifibrotic therapy in the community is likely to be lower. In a US cohort of 14,792 veterans with IPF, patients were less likely to receive antifibrotic therapy if they lived in a rural area (OR, 0.88; 95% CI, 0.80-0.97; $P = .012$) or received their care outside of the Veterans Affairs Healthcare System (OR, 0.15; 95% CI, 0.10-0.22; $P < .001$).²⁵

Real-world studies provide data on the use of antifibrotic therapies in broader patient populations than those enrolled in clinical trials. These include patients who are elderly, have severe lung function impairment, have several comorbidities, and are taking medications for comorbid conditions. Data from 2 single-center

Korean studies suggested that antifibrotic therapy reduced FVC decline both in patients with advanced lung function impairment (FVC < 50% predicted and/or DL_{CO} < 35% predicted) and in those with more preserved lung function, with similar adverse event profiles.²⁶ Among 1009 patients enrolled in the German INSIGHTS-IPF registry, the decline in FVC percentage predicted over the 24 months after initiation of antifibrotic therapy was similar in patients aged ≥75 versus those aged <75 years (difference, -0.05; 95% CI, -0.20 to 0.09; *P* = .478).²⁷ Data from multiple real-world studies suggest that the safety and tolerability profiles of antifibrotic therapies in clinical practice are similar to those observed in clinical trials.²⁸⁻³¹

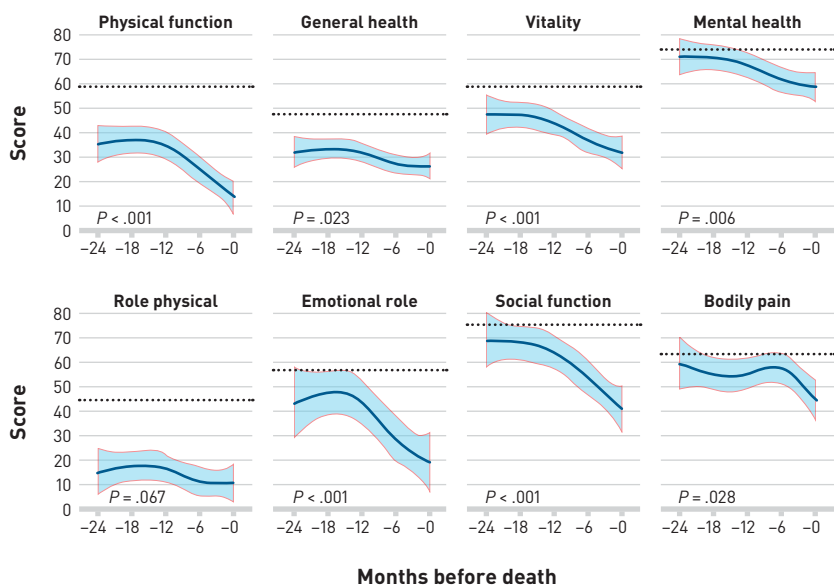
Real-world studies also shed light on the rate of discontinuation of antifibrotic therapy when prescribed in clinical practice. Among 703 patients with IPF enrolled in the US Pulmonary Fibrosis Foundation Patient Registry, 11% had discontinued antifibrotic therapy within the 12 months prior to enrollment.²⁴ In the Finnish IPF registry, 22% of patients were no longer taking antifibrotic therapy 1 year after drug initiation.³² In an Italian study of 263 patients, 8% of subjects discontinued antifibrotic therapy due to adverse events over an average follow-up of almost 2 and a half years.³⁰ Real-world studies have revealed factors associated with a higher risk of discontinuation of antifibrotic therapy. In a study of 104 patients in the UK, a number of factors were associated with discontinuation of antifibrotic therapy over 12 months including age 75 years or older (OR, 3.17; 95% CI, 1.16-8.68; *P* = .025), female sex (OR, 4.57; 95% CI, 1.40-14.88; *P* = .012), and BMI ≤25 kg/m² (OR, 3.74; 95% CI, 1.22-11.53; *P* = .021).³³ Pharmacovigilance data from 219 patients who received pirfenidone in Korea suggested that the rate of discontinuation was higher among those with FVC <50% predicted and/or DL_{CO} <35% predicted at baseline than in those with less severe impairment in lung function (74% vs 50%; *P* = .006).³⁴ In a study of 104 Japanese patients, poor overall health (performance status) at initiation of nintedanib was a risk factor for treatment discontinuation over 12 months (OR, 0.014; 95% CI, 0.002-0.167; *P* = .007).³⁵

Hospitalizations in Patients With IPF

In patients with IPF, hospitalizations are frequent and have a strong association with mortality. Among 1002 patients enrolled in the US IPF-PRO Registry, 57% had at least 1 hospitalization (of any cause) over a median follow-up of 23.7 months.³⁶ Risk factors associated with hospitalization during follow-up

included lower DL_{CO} percentage predicted, oxygen use at rest, and hospitalization in the year prior to enrollment. There was an 8-fold increase in the risk of mortality during hospitalization or within 90 days of discharge compared with the risk of mortality outside this period (*P* < .001).³⁶ An analysis of administrative data from 93,680 US patients with IPF hospitalized between 2013 and 2019 found that the in-hospital mortality rate was 11%.³⁷ Similarly, an analysis of claims data from 9667 US patients hospitalized between 2015 and 2018 found that 11% of patients died during the first hospitalization, while 29% of patients were readmitted to the hospital within 90 days of that first visit.³⁸ In-hospital mortality rates in patients with IPF are particularly high in patients who receive mechanical ventilation.^{36,38,39} In the same dataset, mechanical ventilation was associated with a more than 6-fold increase in the risk of in-hospital mortality or lung transplant (OR, 6.41; 95% CI, 5.24-7.84).³⁸ There is some evidence that the use of antifibrotic therapy might reduce the rate of hospitalization in patients with IPF. In a study of 948 patients in which treated and untreated patients were matched using propensity scores, the proportion of patients with respiratory-related hospitalization over 27 months was 22.2% in the treated group and 36.9% in the untreated group (*P* < .001).⁴⁰ An analysis of claims data from 9282 US patients also suggested that antifibrotic therapy was associated with a lower risk of both all-cause (HR, 0.71;

FIGURE 1. Change in HRQOL Based on RAND 36-Item Health Survey Domains in the 2 Years Before Death Among Patients in the Finnish IPF Registry^{15,a,b}

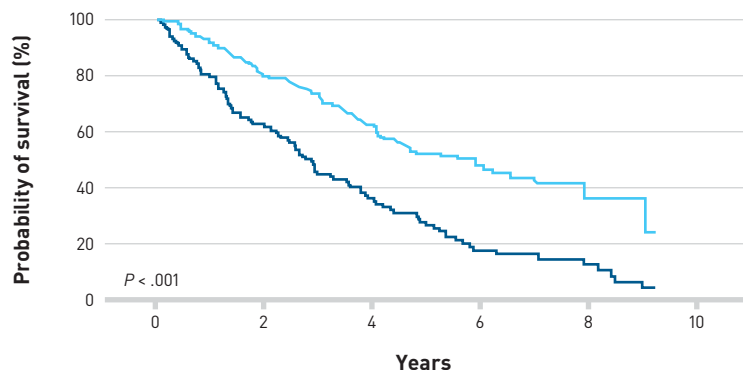


HRQOL, health-related quality of life.

^aCurves were derived from 5-knot restricted cubic splines regression models and adjusted for age and sex.

^bThe shaded area represents the 95% CI. Dashed lines denote the value in the Finnish general population weighted to match the age and sex distribution of the study population.

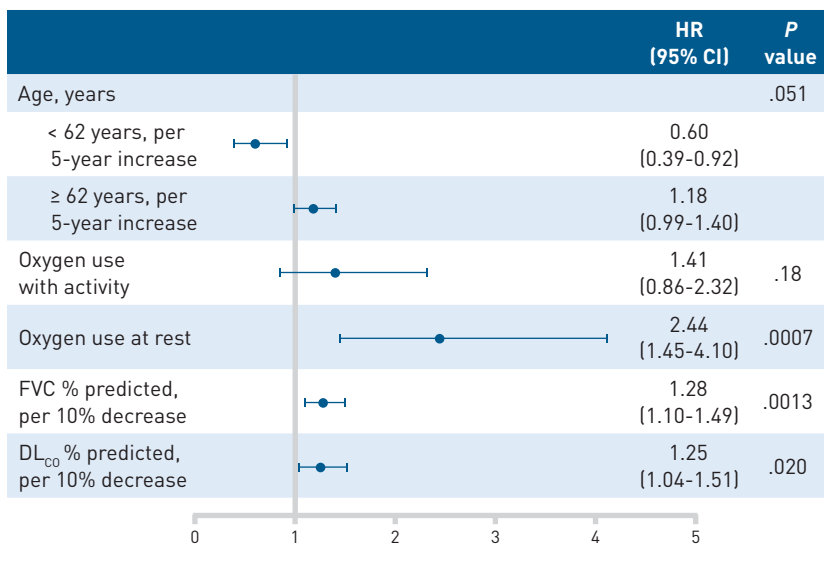
FIGURE 2. Survival in Patients With IPF Who Were Treated at a Japanese Center and Who Had and Did Not Have an Acute Exacerbation²⁰



Number at risk		0	2	4	6	8	10
— No acute exacerbation		338	230	110	37	7	
— Acute exacerbation		124	77	36	15	6	

IPF, idiopathic pulmonary fibrosis.

FIGURE 3. Associations Between Age and Markers of Disease Severity at Enrollment and Risk of Death or Lung Transplant in a Multivariable Analysis of Data From the IPF-PRO Registry⁴⁴



DL_{co}, diffusing capacity for carbon monoxide; FVC, forced vital capacity.

95% CI, 0.67-0.76) and respiratory-related (HR, 0.70; 95% CI, 0.64-0.76) hospitalization.⁴¹

Survival in Patients With IPF

Recent real-world studies provide the best estimates of life expectancy following a diagnosis of IPF. In a Korean patient registry, the 3-year survival rate among 1345 patients diagnosed with IPF between 2012 and 2018 was 70%.⁴² In a Danish study, median survival among 260 patients diagnosed with IPF between 2011 and 2016 was 4.0 years, compared with 3.2 years among 121 patients diagnosed between 2003 and 2009.⁴³ While observations vary across studies, male sex, a greater extent of fibrosis on CT, worse lung function, worse symptoms/HRQOL, and weight loss have been associated with increased short-term mortality.⁴⁴⁻⁵⁰

Among 662 patients in the US IPF-PRO Registry, oxygen use at rest (HR, 2.44; 95% CI, 1.45-4.10; $P = .0007$), lower FVC percentage predicted (HR, 1.28; 95% CI, 1.10-1.49; $P = .0013$, per 10% lower), and lower DL_{co} percentage predicted (HR, 1.25; 95% CI, 1.04-1.51; $P = .020$, per 10% lower) were significantly associated with an increased risk of death or lung transplant over a follow-up period of 30 months (Figure 3).⁴⁴ Furthermore, patients with IPF commonly have comorbid conditions such as pulmonary hypertension and cardiovascular disease that place them at risk for increased mortality.⁵¹ Among 272 patients treated at a tertiary referral center in Germany, median survival was 66 months in patients without comorbidities, 48 months in patients with up to 3 comorbidities and 35 months for patients with 4 to 7 comorbidities.⁵² In a study of 3580 patients with IPF enrolled in the EMPIRE registry, pulmonary hypertension, stroke, respiratory infection, emphysema, lung cancer, and obesity were associated with an increased risk of mortality over a median follow-up of 13.8 months.⁵³

Analyses of data from registries, other observational studies, and insurance claims have shown a reduced risk of mortality in patients with IPF who receive antifibrotic therapy.^{19,40-42,53-56} These studies should be interpreted with caution, as they are based on comparison of nonrandomized groups and, in most cases,

are affected by immortal time bias and biases arising from the initiation or discontinuation of antifibrotic therapy during follow-up.⁵⁷ To avoid such biases, an analysis of data from 499 patients in the US IPF-PRO Registry used a new-user design, comparing newly-treated patients with never-treated patients, and a causal inference methodology, which accounted for treatment initiations and discontinuations during follow-up. This analysis found a 47% reduction in the risk of death in the patients who received treatment (HR, 0.53; 95% CI, 0.28-1.03; $P = .060$).⁵⁶ Similarly, in a study of 948 patients, in which propensity scores were used to match the treated and untreated patients, use of antifibrotic therapy was associated with a 41% reduction in the risk of mortality over 27 months (HR, 0.59; 95% CI, 0.48-0.72; $P < .001$) (Figure 4).⁴⁰ An analysis of claims data from 48,638 patients with IPF, based on a time-varying Cox proportional hazards model, suggested that use of antifibrotic therapy reduced mortality by 31% compared with never receiving treatment (HR, 0.69; 95% CI, 0.66-0.72; $P < 0.001$).⁵⁸ A study of claims data from 9282 patients aged at least 67 years suggested that antifibrotic therapy provided a similar reduction in the risk of mortality in this age group (HR, 0.62; 95% CI, 0.57-0.68).⁴¹

The growing real-world evidence suggesting that the use of antifibrotic therapy is associated with reduced mortality underscores the value of patient registries and other big data sources in clarifying the role of therapies post approval. This is especially important in IPF, where the approval of antifibrotic drugs was based on the surrogate end point of change in FVC,^{59,60} and change in FVC continues to be the end point used in most clinical trials. Real-world studies, as well as further analyses of data from clinical trials,⁶¹ are providing additional evidence to support the use of change in FVC as the end point to assess the efficacy of drugs to treat IPF.

Lung Transplant in Patients With IPF

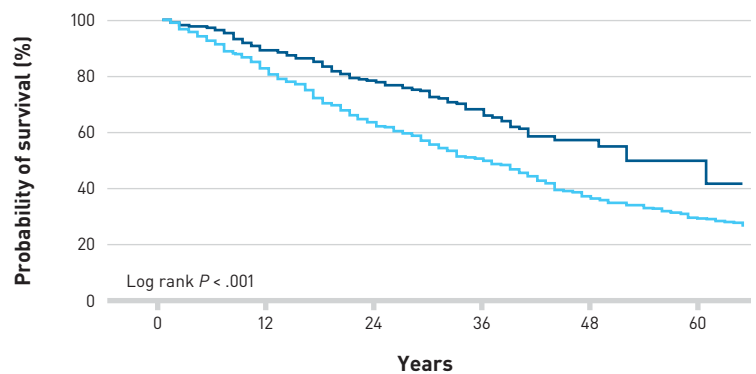
The International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend that any patient with histopathologic or radiographic evidence of UIP is appropriate for lung transplant referral, and that evaluation for lung transplant should include a thorough assessment of the severity of lung disease, frailty, the presence and severity of comorbidities, and psychosocial circumstances.⁶² In 2023, 986 patients with IPF received a lung transplant in the US.⁶³ However, patients with IPF still comprise about 20% of patients on the wait list.⁶³ A multivariable analysis of data from 475 patients with IPF in the US Pulmonary Fibrosis

Foundation (PFF) Registry found that younger age, lower FVC percentage predicted, and use of supplemental oxygen at rest were predictors of being placed on a list for lung transplant.⁶⁴ Socioeconomic and geographic factors may also play a role.^{65,66} An analysis of data from the US IPF-PRO Registry showed that, irrespective of eligibility factors, patients who lived in a zip code with higher median household income or who were enrolled at a center with a lung transplant program had a higher likelihood of receiving a lung transplant.⁶⁶

The number of lung transplants performed in patients with IPF is increasing. In the US, the number of lung transplants performed in patients with IPF increased from 231 in 2003 to 984 in 2023.⁶³ This likely reflects the increasing upper age limit for lung transplants at most transplant centers. In addition, the greater availability of extracorporeal membrane oxygenation as a bridge to transplant has enabled more end-stage patients to survive to transplant. The number of transplantable organs is also increasing, with novel technologies to preserve and resuscitate lungs, such as ex-vivo lung perfusion. Furthermore, there have been modifications to the lung allocation score, updated in March 2023 with the implementation of the continuous allocation score,⁶⁷ which aim to reduce deaths on the waiting list, increase transplants for the sickest patients, and reduce geographic variability in access to transplants.

There has been concern that the use of antifibrotic therapy close to lung transplant may increase the risk of bleeding or delay wound healing. However, observational studies suggest that the

FIGURE 4. Survival in Patients With IPF Who Were Treated and Not Treated With Antifibrotic Therapy, Matched by Propensity Scoring⁴⁰



Number at risk:						
	0	12	24	36	48	60
— Antifibrotic treatment	474	393	240	122	28	8
— No antifibrotic treatment	474	392	294	224	160	122

IPF, idiopathic pulmonary fibrosis.

use of antifibrotic therapy before transplant surgery does not have a negative impact on the incidence of complications during and following the surgery.⁶⁸⁻⁷¹ For example, a study of data from 297 US patients taking nintedanib (n = 107) or pirfenidone (n = 190) found that the use of antifibrotic therapy until ≤ 5 drug half-lives before lung transplant surgery did not affect the incidence of surgical wound dehiscence or survival to discharge.⁷¹

Conclusions

Real-world studies provide important information on the course, impact, and treatment of IPF in the varied population of patients managed in clinical practice. These studies illustrate the heavy burden that IPF places on patients and health care resources, the variability in the course of the disease, and the utility of antifibrotic therapies in improving outcomes. Clinical trials are, by their nature, “discriminatory” in that they exclude patients who do not meet strict inclusion and exclusion criteria. Real-world studies serve as the backfill to evaluate how these drugs perform in a more general population. These studies are important not only to provide further support for the utility of these drugs, but also to identify unmet needs, systemic inequities, and areas for future research. Future real-world studies in patients with IPF are strongly encouraged since they may help improve the provision of care for all patients with this devastating disease. ■

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Detection and Management of Autoimmune Disease–Associated Interstitial Lung Diseases

Anthony J. Esposito, MD; and Ali Ajam, MBBS

Introduction

Interstitial lung disease (ILD) is a common complication of systemic autoimmune rheumatic diseases¹⁻⁵ and a cause of significant morbidity and mortality in affected patients.^{1,6-8} Progression of ILD and the development of lung fibrosis is associated with particularly poor outcomes.^{1,6,9-11} It is important that ILD is detected promptly and that patients with this diagnosis are monitored closely and managed appropriately; however, ILD may be asymptomatic or present with nonspecific symptoms that are attributed to other manifestations of autoimmune disease or to comorbidities.^{2,6} This commonly results in delays in its identification,¹²⁻¹⁴ and lung function may be substantially impaired by the time that ILD is diagnosed.^{15,16}

This article discusses the detection, monitoring, and management of autoimmune disease–associated ILDs with a particular focus on guidelines recently issued by professional associations.

Screening for ILD in Patients With Autoimmune Diseases

The poor outcomes associated with ILD have generated debate about the potential benefits of screening in patients with autoimmune diseases. The high prevalence of autoimmune diseases—particularly rheumatoid arthritis (RA)—limits the feasibility of screening all patients with autoimmune disease for ILD. Screening therefore must be guided by assessment of risk factors. The risk of ILD varies depending upon the autoimmune disease involved; the highest risk has been observed in patients with systemic sclerosis (SSc) and mixed connective tissue disease (MCTD).¹⁷ Several demographic, clinical, serologic, and genetic risk factors for the development of ILD have been identified^{4,18-20}; however, the absolute risk associated with specific characteristics has not been established, and ILD may develop even when there are no obvious risk factors.

ILD may be present in the absence of respiratory symptoms,^{2,6,21} so waiting for patients to develop symptoms may result in delayed detection of ILD. Results from pulmonary function tests (PFTs) such as forced vital capacity (FVC) assist in identifying patients with impaired lung function; however, these tests are much less sensitive for detecting ILD than is high-resolution CT (HRCT).²²⁻²⁴

ABSTRACT

Interstitial lung disease (ILD) causes significant morbidity and mortality in patients with systemic autoimmune rheumatic diseases. Patients at high risk of ILD should be screened using high-resolution CT (HRCT), but there is no consensus as to which risk factors—or combination of risk factors—should prompt referral for HRCT. The course of autoimmune disease–associated ILD is highly variable, and it may not mirror the activity of the underlying autoimmune disease. Patients require close monitoring with periodic pulmonary function testing and symptom assessment and with repeat HRCT considered based on clinical assessment. The relevance of clinical and radiologic signs of progression—and their implications for management—ideally should be discussed by a multidisciplinary team. Management of autoimmune disease–associated ILD may involve immunosuppressant and/or antifibrotic therapy in addition to supportive care. It is important that treatment decisions be individualized to the needs and wishes of the patient. Regular follow-up is important to monitor disease progression and manage the adverse effects related to treatment.

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For author information and disclosures, see end of text.

In a study of 212 patients with early diffuse cutaneous SSc, 37% of patients who had ILD on HRCT had an FVC of 80% or more of the predicted value²³; however, detection of ILD solely by HRCT and in the absence of symptoms or evidence of recent progression raises the question of whether treatment is warranted. Close monitoring may be an appropriate course of action in some patients, but risk factors for progression and the patient’s preferences should be considered. Of note, ILD may develop so early in the course of autoimmune disease that it is the first manifestation to be detected.^{25,26}

Practice guidelines recently issued by the American College of Rheumatology (ACR) conditionally recommended screening for ILD with both HRCT and PFTs (FVC, lung volume, diffusing capacity for carbon monoxide [DL_{CO}]) in people with newly diagnosed autoimmune disease who are at increased risk of ILD (Figure 1).²⁷ These guidelines provide a list of risk factors for ILD, but they do not specify which risk factors detected alone or in combination should prompt screening.²⁸ Consensus statements issued by experts in Spain and Austria recommended screening for ILD using HRCT and PFTs in patients with RA who have risk factors or respiratory symptoms; again, however, they did not define risk factors that should lead to screening.^{29,30} Consensus statements issued by experts in Europe³¹ and the US³² have recommended that all patients with SSc be screened for ILD at diagnosis using HRCT, that PFTs also be performed, and that repeat HRCT be guided by risk factors, lung function, and symptoms.

ILD is associated with distinct sounds on chest auscultation, which often are described as *Velcro*-like crackles.³³ Experts have recommended that auscultation of the chest be performed at diagnosis in patients with SSc³² and RA.^{29,31} A case could also be made for chest auscultation on diagnosis of other autoimmune diseases, particularly in patients with risk factors for ILD; nevertheless, chest auscultation was not included in the recommendations recently issued by the ACR.²⁷

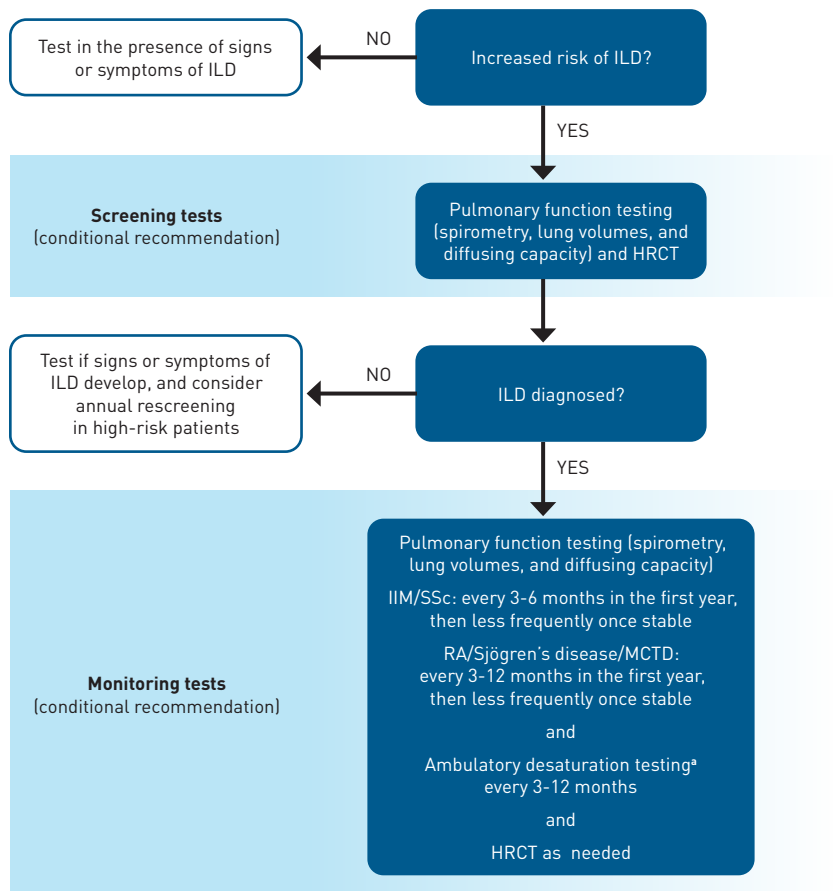
Concerns over the cost and radiation exposure associated with HRCT have generated

TAKEAWAY POINTS

Interstitial lung disease (ILD) is a major cause of morbidity and mortality in patients with systemic autoimmune rheumatic diseases.

- ▶ Patients with autoimmune disease who are at high risk of ILD should be screened using high-resolution computed tomography.
- ▶ Autoimmune disease-associated ILD requires close monitoring including regular pulmonary function testing.
- ▶ Management of autoimmune disease-associated ILD requires a multidisciplinary, individualized approach; it may include immunosuppressant and/or antifibrotic therapy.

FIGURE 1. American College of Rheumatology Recommendations for Screening and Monitoring of ILD in Patients With Systemic Autoimmune Rheumatic Disease.²⁷



HRCT, high-resolution computed tomography; IIM, idiopathic inflammatory myositis; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; SSc, systemic sclerosis.

*Can be done during routine office visit or as part of 6-minute walk testing.

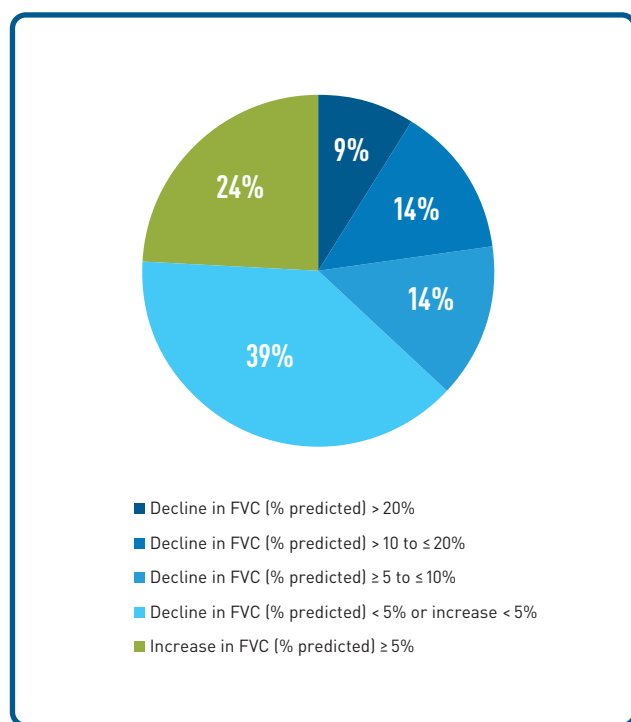
Adapted from Johnson SR, Bernstein EJ, Bolster MB, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the screening and monitoring of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Rheumatol.* 2024;76(8):1201-1213. doi:10.1002/art.42860

interest in lung ultrasound as a risk stratification tool for identifying patients who should undergo HRCT. Recent study results have demonstrated that lung ultrasound has high specificity and sensitivity for the detection of ILD compared with HRCT in patients with SSc³⁴⁻³⁷ and RA.^{38,39} In a study of 180 patients with autoimmune diseases, the sensitivity and specificity of ultrasound performed by an experienced examiner to detect ILD relative to HRCT were 99% and 96%, respectively.⁴⁰ However, the use of lung ultrasound to detect ILD requires training, and guidelines for its use to detect ILD in patients with autoimmune diseases have not yet been issued by any professional association.

Monitoring Patients With Autoimmune Disease–Associated ILDs

The course of autoimmune disease–associated ILDs varies greatly between patients. Some decline slowly, whereas others exhibit rapid progression.^{16,41,42} Over several years of follow-up, a patient may experience periods of deterioration, stability, or even improvement in lung function (Figure 2).^{16,42,43} Progression of ILD may not mirror the activity of the underlying autoimmune disease⁴²; thus,

FIGURE 2. Changes in FVC Over a Median Follow-Up of 5 Years in Patients With SSc-ILD in the EUSTAR Database¹⁶



FVC, forced vital capacity; ILD, interstitial lung disease; SSc, systemic sclerosis.

stable or improving joint or skin disease does not necessarily indicate that a patient's ILD is stable.

A decline in FVC or DL_{CO} or an increase in the extent of ILD on HRCT indicates progression and is associated with an increased risk of mortality.^{6,9,10,44,45} In a retrospective analysis of data from 137 patients with RA-ILD followed for a median of 5 years, a decline in FVC (% predicted) of at least 10% was associated with a 2.5-fold increased risk of mortality ($P < .0001$).⁹ In a retrospective analysis of data from 162 patients with SSc-ILD followed for 15 years, a decline in FVC (mL) of 10% or more over 12 months was associated with a 1.8-fold greater risk of subsequent mortality ($P = .01$).¹⁰ In Scleroderma Lung Study I, patients who had an increase in the extent of ILD on HRCT (assessed using the quantitative ILD [QILD] score) of at least 2% at 12 months had a greater risk of mortality over the following 12 years than did those with smaller increases in QILD score ($P = .01$) (Figure 3).⁴⁵

Patients with autoimmune disease–associated ILDs require close monitoring so that progression can be identified promptly.^{27,31,32,46} The guidelines issued by the ACR conditionally recommended monitoring with PFTs every 3 to 6 months in patients with myositis-ILD or SSc-ILD and every 3 to 12 months in patients with ILD associated with RA, Sjögren disease, or MCTD for the first year and then less frequently if the disease is stable.²⁷ Experts have recommended monitoring patients with SSc-ILD using multiple measures, including PFTs, HRCT, and symptom assessment.^{31,32} PFTs are also useful to detect pulmonary hypertension, which is associated with high mortality if not treated.⁴⁷ Exercise tests such as the 6-minute walk and ambulatory desaturation testing (including uptitration of supplemental oxygen as necessary) can provide valuable additional information but should not be the sole tool used for monitoring autoimmune disease–associated ILDs.^{27,31,32} HRCT scans should be repeated as clinically indicated.^{27,31,32} Worsening in lung function or radiologic abnormalities may not be straightforward to interpret, and there may not be a close relationship between decline in FVC and worsening of features observed on HRCT.^{48,49} Ideally, the relevance of clinical and radiologic signs of progression and their implications for management should be discussed by a multidisciplinary team.^{50,51}

In May 2022, international thoracic societies published criteria for the definition of progressive pulmonary fibrosis (PPF) in patients with fibrosing ILDs other than idiopathic pulmonary fibrosis (IPF).⁴⁶ Different criteria have been used to select patients with progressive fibrosing ILDs for enrollment into clinical trials,⁵²⁻⁵⁴ yet criteria for the identification of PPF are generally based on categorical declines in lung function (FVC and/or DL_{CO} [percentage predicted]), increase in radiological abnormalities, and worsening of respiratory symptoms. Patients identified based upon these criteria exhibit progressive decline in lung function and high mortality.⁵⁵⁻⁵⁷ Importantly, progression of lung fibrosis is a self-perpetuating and irreversible process.⁵⁸ Evidence of progression should prompt a

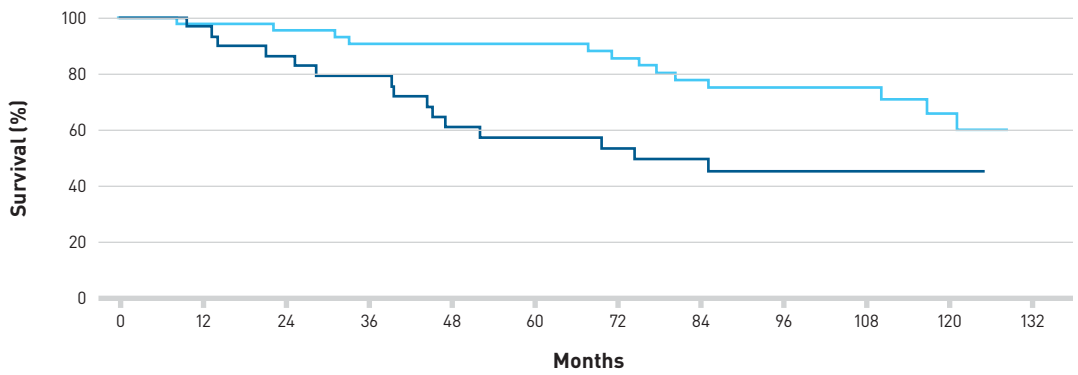
discussion with the patient about the worsening of their disease and consideration of initiation or escalation of treatment.

Management of Autoimmune Disease-Associated ILDs

Managing autoimmune disease-associated ILDs requires a multi-disciplinary approach that considers the type of autoimmune

disease, the severity of the ILD and evidence of its progression, risk factors for further progression, comorbidities, and the patient's preferences (Figure 4).^{59,60} Close collaboration between pulmonologists and rheumatologists is essential, whereas input from a radiologist may help identify patients at greater risk of progression.⁵⁰ Specialist nurses/nurse practitioners and physical therapists can make an important contribution to the provision of patient

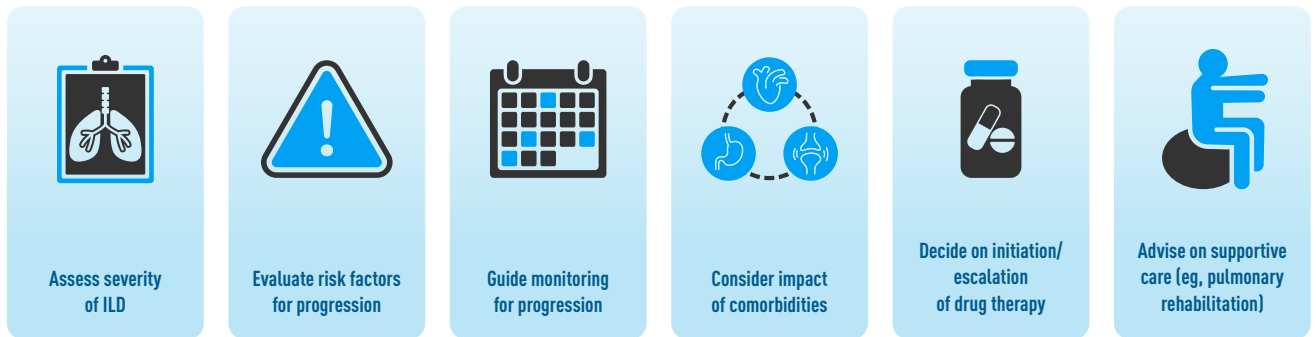
FIGURE 3. Survival in Patients With SSc-ILD in Scleroderma Lung Study I⁴⁵



Number at risk												
— Increase in extent of ILD on HRCT (QILD score) <2% over the previous 12 months	48	46	42	38	37	35	33	30	24	20	12	0
— Increase in extent of ILD on HRCT (QILD score) ≥2% over the previous 12 months	34	31	24	22	17	16	13	12	10	6	1	0

HRCT, high-resolution computed tomography; ILD, interstitial lung disease; QILD, quantitative interstitial lung disease; SSc, systemic sclerosis.
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FIGURE 4. Role of Multidisciplinary Discussion in the Management of Autoimmune Disease-Associated ILDs



ILD, interstitial lung disease.

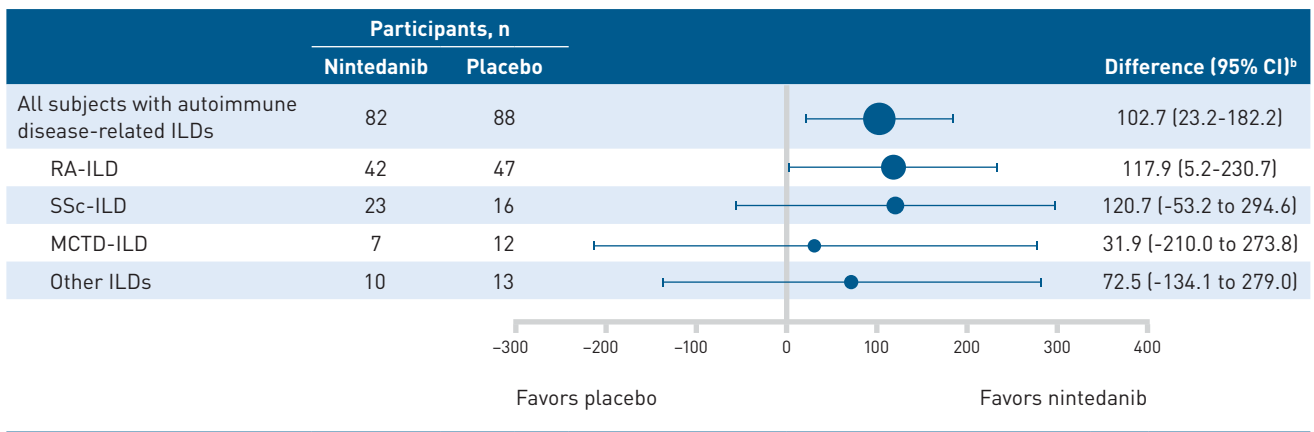
information and supportive care.⁶¹ In deciding on a therapeutic regimen, the benefits of slowing ILD progression and potentially preventing acute exacerbations should be weighed against the risk of adverse effects (AEs).

There is no established treatment algorithm for autoimmune disease-associated ILDs, but initial standard of care employs immunosuppression. Glucocorticoids are commonly used, but their efficacy has not been demonstrated. In the guidelines issued by the ACR, conditional recommendations were made for the use of mycophenolate, azathioprine, rituximab, and cyclophosphamide as first-line treatment for autoimmune ILDs.⁶² The immunosuppressant mycophenolate is commonly used in the treatment of SSc-ILD based on the results of Scleroderma Lung Study II, which showed that it had similar efficacy to cyclophosphamide in preserving lung function but with a better safety profile.⁶³ The tyrosine kinase inhibitor nintedanib and the interleukin-6 receptor antagonist tocilizumab have been approved by the FDA for slowing decline in lung function in patients with SSc-ILD. In the randomized, placebo-controlled SENSCLIS trial, nintedanib therapy reduced the rate of decline in FVC (mL/year) over 52 weeks by 44% (-52.4 vs -93.3 mL/year; difference, 41.0 mL/year; 95% CI, 2.9-79.0; $P = .04$).⁶⁴ The absolute effect of nintedanib versus placebo was numerically lower in patients taking mycophenolate at baseline than in those not taking mycophenolate (difference, 26.3 vs 55.4 mL/year), but the relative reduction was similar between these subgroups (40% and 46%, respectively).⁶⁵ In the subgroup of patients with SSc-ILD in the focuSSced trial, FVC was preserved over 48 weeks in the tocilizumab

group (least squares mean change in FVC % predicted, -0.1 with tocilizumab vs -6.3% with placebo; $P < .0001$).⁶⁶ In the RECITAL trial conducted in patients with various autoimmune disease-associated ILDs, similar increases in FVC over 24 weeks were observed with rituximab and cyclophosphamide (97 and 99 mL, respectively; $P = .49$).⁶⁷ In the EvER-ILD trial in patients with ILD and a nonspecific interstitial pneumonia pattern who were on background therapy with mycophenolate, FVC (% predicted) increased over 6 months in the rituximab group and decreased in the placebo group (1.6 vs -2.0; difference, 3.6; 95% CI, 0.41-6.80; $P = .0273$).⁶⁸ Guidelines for the treatment of SSc-ILD recently issued by the American Thoracic Society (ATS) included a strong recommendation for the use of mycophenolate and conditional recommendations for the use of cyclophosphamide, nintedanib, tocilizumab, rituximab, and the combination of nintedanib and mycophenolate.⁶⁹ In addition, autologous hematopoietic stem cell transplantation is a treatment option for a select group of patients with severe and treatment-refractory SSc. This procedure has shown benefits on long-term survival.^{70,71} However, it is associated with a risk of short-term mortality, and it should only be performed at experienced centers.⁷²

In the US, the only drug approved for the treatment of autoimmune disease-associated ILDs other than SSc-ILD is nintedanib, which is approved for the treatment of progressive fibrosing ILDs (PPF) irrespective of etiology. Nintedanib received a conditional recommendation for the treatment of PPF in patients who have failed standard management in a clinical practice guideline issued by thoracic societies including the ATS.⁴⁶ In the INBUILD trial in patients

FIGURE 5. Rate of Decline in FVC in Subjects With Progressive Fibrosing Autoimmune Disease-Associated ILDs in the INBUILD Trial^{75,a}



FVC, forced vital capacity; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; SSc, systemic sclerosis.

^aReflects rate of decline over 52 weeks in subjects with progressive fibrosing autoimmune disease-associated ILDs treated with nintedanib vs placebo.

^b $P = .91$ for treatment-by-subgroup-by-time interaction.

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with PPF, nintedanib slowed the rate of decline in FVC (mL/year) over 52 weeks by 57% versus placebo (−80.8 vs −187.8 mL/year; difference, 107.0 mL/year; 95% CI, 65.4-148.5; $P < .001$),⁵² with a consistent effect noted across patients with different disease severities⁷³ and diagnoses (Figure 5).^{74,75} In the subgroup of patients with RA-ILD, nintedanib slowed the rate of decline in FVC by 59% vs placebo (difference, 116.7 mL/year; 95% CI, 7.4-226.1; nominal $P = .037$). AEs led to treatment discontinuation in 24% of the nintedanib group versus 17% of the placebo group; the most frequent AE leading to treatment discontinuation was an increase in alanine aminotransferase, which led to discontinuation in 7.1% of the nintedanib group and none of the placebo group.⁷⁶ Data collected using the Living with Pulmonary Fibrosis questionnaire suggested that over 52 weeks, treatment with nintedanib reduced dyspnea, cough, fatigue, and the impact of ILD on patients' lives, although these benefits were less pronounced in patients with autoimmune disease-related ILDs than in those with other ILDs.⁷⁷ Data collected in real-world settings are providing more information on the utility of antifibrotic therapies in patients with autoimmune disease-associated ILDs in clinical practice.⁷⁸

In addition to drug therapy, patients with autoimmune disease-associated ILDs may benefit from supportive care such as symptom management, pulmonary rehabilitation,⁷⁹ and advice on strategies to minimize the impact of the disease on their lives.⁸⁰ Patient support groups can be highly valuable in helping patients to manage the physical and emotional challenges of living with ILD.⁸¹ Regular follow-up is needed to manage AEs of treatment and assist patients in remaining on therapy. Patients with hypoxemia may benefit from supplemental oxygen,⁸² but they need support to manage the impact that oxygen therapy has on their daily lives.⁸³ Lung transplantation should be considered for patients who meet eligibility criteria.⁸⁴ Recent evidence suggests that outcomes after lung transplantation in patients with autoimmune disease-associated ILDs are similar to those in patients with IPF.^{85,86} Palliative and end-of-life care should be discussed with the patient as appropriate, and it should be individualized to their needs.⁸⁷

Conclusions

ILD is a common complication of autoimmune disease that can cause significant morbidity and mortality. Detection of ILD is often delayed, as it may be asymptomatic or nonspecific in presentation during its early stages. Prompt detection is important to assess the severity of ILD and risk factors for its progression. Monitoring should include regular PFTs, symptom assessment, and HRCT as clinically indicated. Management of autoimmune disease-associated ILDs requires a multidisciplinary approach that depends upon the type of autoimmune disease, the severity and progression of the ILD, and the patient's preferences. Antifibrotic and immunosuppressant therapies slow the progression of autoimmune disease-associated

ILDs; however, there is no established treatment algorithm to guide the clinician. Symptom relief, pulmonary rehabilitation, and patient information and support are important elements of a holistic approach to patient care. ■

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Identification, Course, and Management of Progressive Pulmonary Fibrosis

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Introduction

Interstitial lung diseases (ILDs) comprise a large group of disorders characterized by inflammation and/or fibrosis of the lung parenchyma. Some ILDs have a known cause, for example, ILDs related to autoimmune diseases¹ or occupational exposures,² while others are idiopathic, the most common of which is idiopathic pulmonary fibrosis (IPF).³ Environmental factors, such as exposures to dusts, molds, or chemicals,⁴ and genetic variants⁵ contribute to the development of ILD. A proportion of patients with ILDs develops pulmonary fibrosis that becomes progressive. The term “progressive pulmonary fibrosis” (PPF) or “progressive fibrosing ILD” (PF-ILD) is generally used to describe progressive lung fibrosis in an individual with an ILD other than IPF (which is, by definition, a progressive disease).³ This article describes the identification, course, and management of PPF.

Criteria for Defining PPF

Several sets of criteria have been proposed for the identification of PPF, mainly based on expert consensus and extrapolation from what is known about disease behavior and prognosis in IPF.^{3,6-10} The most widely used criteria are those developed to identify patients with PPF for enrollment in the INBUILD trial of nintedanib⁶ and those later proposed in a clinical practice guideline published by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) in May 2022 (Table).^{3,6} Most definitions of PPF include some combination of a decline in forced vital capacity (FVC) and/or diffusing capacity for carbon monoxide (DL_{CO}), a worsening of respiratory symptoms, and an increase in the extent of fibrosis on high-resolution CT (HRCT). However, there is variability in terms of the magnitude of change in these parameters that should define progression and the time period over which progression should be assessed. The ATS/ERS/JRS/ALAT guideline stated that the criteria for identification of PPF may be fulfilled at any time within a 1-year period,³ while other criteria use a 2-year window.^{6,7,9,10} It is important to note that progression may occur at any time within the specified time period and needs not be assessed

ABSTRACT

The term “progressive pulmonary fibrosis” or “PPF” is generally used to describe progressive lung fibrosis in an individual with an interstitial lung disease (ILD) other than idiopathic pulmonary fibrosis (IPF). Several sets of criteria have been proposed for the identification of PPF, most of which are based on a combination of a decline in forced vital capacity, worsening of respiratory symptoms, and increase in the extent of fibrosis on radiology. Although some risk factors for faster progression of fibrosing ILD have been identified, it remains challenging to predict which individuals will develop PPF. Close monitoring, including regular pulmonary function tests, is required to detect the earliest signs of worsening disease. PPF is associated with high rates of hospitalization and death. Management of PPF requires a multidisciplinary and multimodal approach, including pharmacological therapy and supportive care. Discussions about palliative care should begin at an early stage, individualized to the needs of the patient.

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For author information and disclosures, see end of text.

over its whole duration. Further, some experts have argued that no time frame should be applied when assessing progression in clinical practice, as progression is predictive of a poor prognosis regardless of the time period over which it occurs.¹¹

In addition to the debate over the criteria that should be used to define PPF, discussion continues over whether PPF should be identified only in patients in whom standard management for the respective ILD has failed. A requirement for patients to have progressed despite standard management was included in the inclusion criteria for the INBUILD trial of nintedanib in patients with PPF,⁶ the RELIEF trial of pirfenidone in patients with PPF,⁹ and a trial of pirfenidone in patients with progressive fibrotic hypersensitivity pneumonitis.¹² However, in many fibrotic ILDs, “standard management” is not well defined, and varies based on patient characteristics, drug availability and coverage, and other factors. The ATS/ERS/JRS/ALAT guideline did not mandate that patients receive standard management for ILD prior to PPF being identified; however, its conditional recommendation for the use of nintedanib in patients with PPF was limited to patients who have failed standard management.³ A consensus statement published by an expert group in 2023 suggested that a distinction should be made between a first presentation of PPF and PPF that has occurred despite management of the ILD, as this may have discrete treatment implications.¹³

Risk Factors for Development of PPF

PPF affects patients with a wide range of ILDs.¹⁴⁻¹⁷ Different studies have provided broad estimates for the risk of PPF in patients with ILDs, depending on the population, criteria, and methodology.¹⁸⁻²¹ Among 1749 patients with non-IPF fibrotic ILDs receiving care at

TAKEAWAY POINTS

Progressive pulmonary fibrosis (PPF) in patients with interstitial lung diseases (ILDs) places a heavy burden on patients and health care resources.

- ▶ PPF is associated with progressive decline in lung function, worsening of symptoms, and high rates of hospitalization and death.
- ▶ Patients with fibrosing ILDs require close monitoring, including regular pulmonary function tests, so that PPF can be detected and managed promptly.
- ▶ Management of PPF requires a multidisciplinary and individualized approach, including pharmacological therapy, supportive care, and advance care planning.

9 ILD referral centers, 14% met the INBUILD trial criteria for PPF.²² In a study of registry data from 753 patients with non-IPF fibrotic ILDs, 30% of patients met the international guideline criteria for PPF, 37% met the INBUILD trial criteria, 32% met the criteria from the trial of pirfenidone in patients with unclassifiable ILD, and 23% met the RELIEF trial criteria.²¹ In an analysis of claims data, 30,771 patients were identified as having a fibrosing ILD other than IPF and, of these, 47% were predicted to have progressive disease.¹⁸ Children with fibrosing ILDs such as those related to genetic diseases, autoimmune diseases, or exposures may also develop progressive lung fibrosis,²³ but the proportions of pediatric patients who fulfill specific criteria for PPF are unknown.

TABLE. Criteria for PPF Used in the INBUILD Trial of Nintedanib⁶ and Proposed in the ATS/ERS/JRS/ALAT Clinical Practice Guideline³

INBUILD trial of nintedanib ⁶	ATS/ERS/JRS/ALAT clinical practice guideline ³
<p>≥ 1 of the following at any time within 2 years, despite management deemed appropriate in clinical practice:</p> <ol style="list-style-type: none"> 1. Relative decline in FVC % predicted ≥ 10% 2. Relative decline in FVC % predicted ≥ 5 to < 10% and increased extent of fibrosis on HRCT 3. Relative decline in FVC % predicted ≥ 5 to < 10% and worsened respiratory symptoms 4. Worsened respiratory symptoms and increased extent of fibrosis on HRCT 	<p>≥ 2 of the following at any time within 1 year:</p> <ol style="list-style-type: none"> 1. Worsening respiratory symptoms 2. Physiological evidence of disease progression, defined as either: <ol style="list-style-type: none"> a. Absolute decline in FVC % predicted > 5% b. Absolute decline in DL_{CO} % predicted > 10% 3. Radiological evidence of disease progression, defined as ≥ 1 of the following: <ol style="list-style-type: none"> a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss

ALAT, Asociación Latinoamericana de Tórax; ATS, American Thoracic Society; DL_{CO}, diffusing capacity of the lung for carbon monoxide; ERS, European Respiratory Society; FVC, forced vital capacity; HRCT, high-resolution CT; JRS, Japanese Respiratory Society; PPF, progressive pulmonary fibrosis.

Different types of ILD appear to be associated with differing risks of PPF. In a retrospective analysis of 1227 consecutive patients with non-IPF fibrotic ILDs, the proportion of patients with PPF (defined as a relative decline in FVC % predicted $\geq 10\%$, or a relative decline in FVC % predicted ≥ 5 to $< 10\%$ plus any 1 of the following: hospitalization, increased extent of fibrosis on HRCT, increased oxygen use, or respiratory death, within 2 years) ranged from 10.3% in patients with ILD due to sarcoidosis to 41.9% in patients with unclassifiable idiopathic interstitial pneumonia.²¹

Several risk factors for progression of fibrotic ILDs have been identified. Demographic risk factors for progression include older age^{24,25} and male sex.^{26,27} Cigarette smoking is also a risk factor.^{26,28} A lower FVC^{15,29} or diffusing capacity of the lung for carbon monoxide (DL_{CO})^{30,31} is also associated with a greater risk of short-term progression. Among 2746 patients in the CARE-PF registry, FVC $< 70\%$ predicted and $DL_{CO} < 75\%$ predicted at baseline were independent risk factors for the development of PPF (defined as a relative decline in FVC % predicted $\geq 10\%$, death, lung transplant, or any 2 of a relative decline in FVC % predicted between ≥ 5 and $< 10\%$, worsening respiratory symptoms, or worsening fibrosis on HRCT) over 2 years.²⁵ On radiology, a greater extent of lung fibrosis^{15,24,32,33} and a usual interstitial pneumonia (UIP) pattern^{24,26,34,35} are associated with faster progression. Genetic risk factors for faster progression of fibrotic ILDs have also been identified, such as mutations associated with short telomeres.³⁶

Although some risk factors have been identified, it remains challenging to predict which individuals with fibrosing ILD will progress, when, and at what rate. Recognition of PPF requires close monitoring of disease behavior to detect the earliest clinical, physiologic, and/or radiologic signs of worsening disease. No biomarker has been shown to have sufficient accuracy to predict progression before it occurs. Patients with fibrosing ILDs should be monitored with regular symptom assessment and pulmonary function tests (PFTs) and repeat HRCT as clinically indicated, so that if progression has occurred, it is detected promptly.^{13,37-39} Experts in the management of patients with ILD suggest that PFTs should be performed at least every 3 to 4 months.^{13,38} HRCT should be performed less frequently, but may be valuable for assessing progression in patients in whom lung function has declined or symptoms have worsened.^{13,37,39} Repeated HRCT may be appropriate in some patients (eg, every 12 to 24 months to evaluate for complications), as an adjunct to PFTs, to assess whether patients meet PPF criteria, as well as to screen for lung cancer,⁴⁰ which may be more common in patients with ILD.⁴¹ Other evaluations, such as a 6-minute walk test, may also provide valuable information about the progression of a patient's ILD.⁴²

Course of PPF

The pathobiology of fibrosis involves fibroproliferation and excess production of extracellular matrix, leading to destruction of the

lung architecture.^{43,44} The mechanisms that drive fibrosis are self-perpetuating^{43,44} and, in the absence of treatment, PPF will inevitably progress. Even in patients receiving proven therapies for PPF, lung function may continue to decline.⁴⁵⁻⁵⁰ There is some evidence that decline in FVC may be more rapid in patients with PPF who have a UIP-like fibrotic pattern on HRCT.⁵¹⁻⁵³ Heterogeneity in the trajectory of FVC decline has been observed among patients with PPF and differing ILD diagnoses. In a retrospective analysis, the decline in FVC in patients with PPF due to autoimmune diseases was significantly smaller than in patients with PPF and either hypersensitivity pneumonitis or idiopathic interstitial pneumonia.⁵³ Differing risks of mortality have also been observed among patients with PPF and different ILD diagnoses (**Figure 1**).^{18,52}

Patients identified as having PPF using different criteria show differences in short-term mortality.^{22,25,54} In a retrospective analysis of 1341 patients, the risk of death or lung transplant over ≥ 1 year was greater in patients who had PPF defined as a decline in FVC % predicted of $> 10\%$ than in patients who met other criteria indicating disease progression (**Figure 2**).⁵⁴ However, it is important to bear in mind that regardless of how PPF is identified, it is associated with high rates of hospitalization and death.^{18,19,22,25,54-56} In a descriptive analysis, over a mean follow-up of 69 months, 46% of 135 patients with PPF had a respiratory hospitalization compared with 22% of 261 patients with fibrosing ILD but without PPF at the same center.⁵⁵ In the same study, 5-year survival was 64.5% in the patients with PPF compared with 89.5% in the patients without PPF.⁵⁵ Patients with non-IPF fibrosing ILDs may experience acute lung function deterioration (acute exacerbation), which is associated with high mortality.⁵⁷⁻⁶⁰

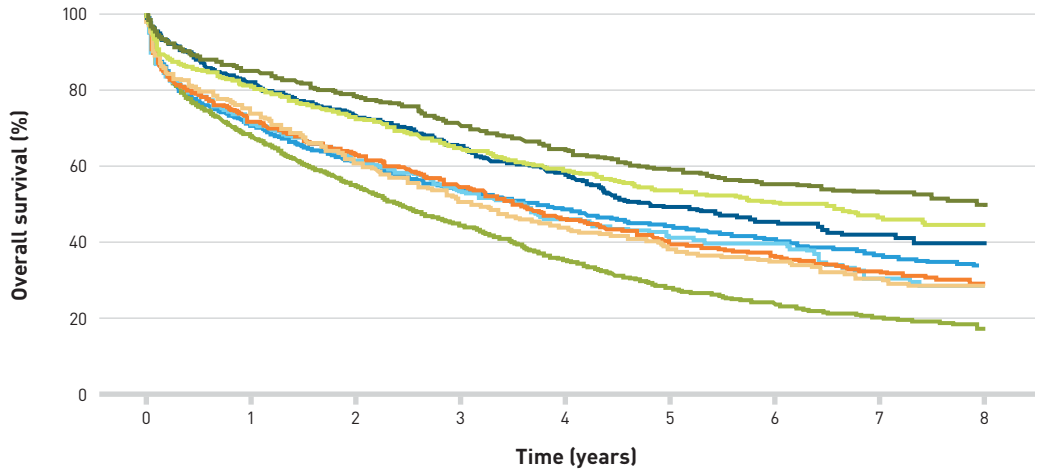
Monitoring of PPF

PPF progresses at a variable rate, which is not necessarily linear in an individual patient.^{53,61} Further, lung function decline may not correlate with a patient's perception of their health status or symptoms.^{62,63} It is important that patients with PPF are regularly monitored so that progression can be evaluated and management, including the provision of supportive/palliative care, adjusted if necessary. Monitoring should comprise PFTs, assessment of symptoms, and where clinically indicated, repeat imaging. As well as monitoring disease progression, any adverse effects (AEs) of therapies should be identified and managed; the potential of immunosuppressant and antifibrotic therapies to cause AEs should not be underestimated.

Management of PPF

The management of PPF requires that patients receive an accurate diagnosis of the underlying ILD, ideally in the context of a multidisciplinary discussion.⁶⁴ This has implications for prognosis and guides the optimal approach to management. Many ILDs have an identifiable cause or associated condition, which may require distinct

FIGURE 1. Survival After Identification of PPF in a Retrospective Cohort Study¹⁸

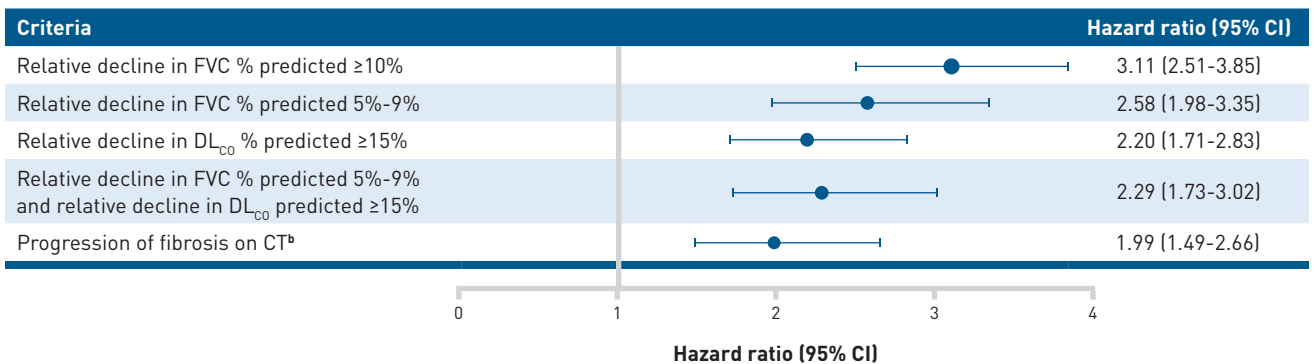


Number of patients at risk:									
■ Hypersensitivity pneumonitis	728	520	383	283	197	125	77	43	13
■ Idiopathic interstitial pneumonia	3113	1848	1338	998	726	510	349	193	68
■ MCTD-ILD	655	383	284	199	130	86	62	34	19
■ RA-ILD	2521	1504	1101	792	541	362	238	140	59
■ SSc-ILD	907	557	401	263	185	128	78	49	16
■ Sarcoidosis-ILD	1500	1120	888	685	534	392	280	154	68
■ Other exposure-related ILD	3486	1939	1311	904	592	362	236	129	44
■ Other autoimmune ILD	1503	1068	821	611	448	309	209	108	53

ILD, interstitial lung disease; MCTD-ILD, mixed connective tissue disease-associated interstitial lung disease; PPF, progressive pulmonary fibrosis; RA-ILD, rheumatoid arthritis-associated lung disease; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

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FIGURE 2. Risk of Death or Lung Transplant Over ≥1 Year After Identification of PPF Based on Different Criteria^{54,a}



DL_{co}, diffusing capacity of the lung for carbon monoxide; FVC forced vital capacity; ILD, interstitial lung disease; PPF, progressive pulmonary fibrosis.

^aData were pooled from patients in a US cohort (n = 828; 3 centers) and a UK cohort (n = 513; single center). Hazard ratios were only calculated for criteria that showed a significant association with the outcome in each cohort separately.

^bAny “worsening” or “progression” of fibrosis or ILD noted on the radiology report.

treatment approaches. The work-up includes obtaining a detailed medical, family, occupational, environmental, and social history and conducting a physical examination. Tests include PFTs, HRCT scans, and serologic testing to identify potential exposures and exclude autoimmune diseases. For patients who have undergone bronchoscopy or surgical biopsies, histopathological features should be integrated with clinical findings in multidisciplinary discussion, including, at minimum, input from pulmonology, radiology, and pathology.⁶⁵⁻⁶⁸ In patients with hypersensitivity pneumonitis, identification and avoidance of the inciting antigen is associated with improved survival²⁸ and may help to prevent progression.⁶⁹

Management of PPF requires a multidisciplinary and multimodal approach (**Figure 3**).^{37,38,69} Patients should be given adequate information about their disease and emotional support.⁷⁰⁻⁷² Supportive care focuses on symptom management and preserving quality of life and may include pulmonary rehabilitation, which can improve exercise capacity, quality of life and dyspnea.⁷³ Oxygen use is recommended for patients with ILD and severe chronic resting hypoxemia or severe exertional hypoxemia.⁷⁴ Worsening

of health status, such as decline in physical functioning or initiation of oxygen, should prompt a consideration of palliative care to help manage symptoms and quality of life, individualized to the patient's physical, emotional, and spiritual needs.⁷¹ Advance care planning, and discussion of the patient's goals and preferences for end-of-life care, should be initiated as early as possible.^{75,76} Referral for lung transplantation should be considered in individuals with PPF who meet relevant criteria.⁷⁷

Pharmacological Therapy for PPF

Pharmacologic therapy for PPF differs based on the ILD diagnosis. The standard treatment for ILD associated with autoimmune disease is immunosuppression, with antifibrotic therapy in certain cases. Randomized controlled trials have shown that cyclophosphamide,⁷⁸ mycophenolate,⁷⁹ nintedanib,⁸⁰ tocilizumab,⁸¹ and rituximab⁸² slow the progression of ILD associated with systemic sclerosis (SSc-ILD). Nintedanib and tocilizumab have been approved by the FDA for the treatment of SSc-ILD. A clinical practice guideline for the treatment of SSc-ILD published by the ATS in October 2023 included a strong recommendation for the use of mycophenolate and conditional recommendations for the use of cyclophosphamide, tocilizumab, nintedanib, nintedanib plus mycophenolate, and rituximab.⁸³ A guideline for the treatment of ILD in patients with autoimmune disease issued by the American College of Rheumatology (ACR) and American College of Chest Physicians (CHEST)⁸⁴ provided similar recommendations for the treatment of SSc-ILD and conditional recommendations for first-line treatment of autoimmune ILDs other than SSc-ILD for mycophenolate, azathioprine, rituximab, and cyclophosphamide.

Immunosuppressants are commonly used in patients with hypersensitivity pneumonitis,^{85,86} and have shown benefits in some patients, but it is not clear whether they slow the progression of fibrotic forms of the disease, which often behave similarly to IPF.⁸⁷⁻⁹⁰ The use of corticosteroids alone or combined with immunomodulatory therapy is not recommended in patients with IPF^{91,92} and combination therapy with prednisone, azathioprine, and N-acetylcysteine is harmful in these patients.⁹³ Immunosuppressant therapies, including rituximab and tocilizumab, are associated with an increased risk of infection.^{82,90,94} In addition, mycophenolate and azathioprine are associated with gastrointestinal AEs^{79,86,88} and cyclophosphamide with leukopenia and neutropenia.⁷⁸

In patients with PPF, clinicians should consider use of a treatment shown to slow its progression. In the US, the FDA has approved nintedanib for the treatment of progressive fibrosing ILDs of any etiology. ATS/ERS/JRS/ALAT guidelines provide a conditional recommendation for nintedanib as a treatment option for patients with PPF for whom standard management (not defined) has failed.³ In the INBUILD trial in 663 patients with PPF despite management in clinical practice, nintedanib slowed the rate of decline in FVC over 52 weeks

FIGURE 3. Multimodal Approach to the Management of PPF^{37,38,69}



PPF, progressive pulmonary fibrosis.

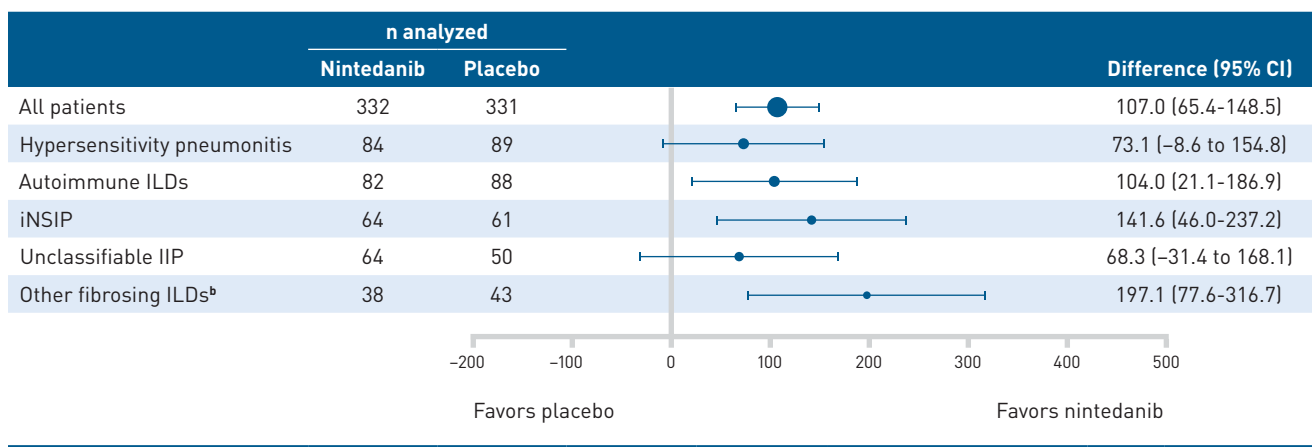
by 57% compared with placebo (−81 mL/year in the nintedanib group compared with −188 mL/year in the placebo group; $P < .001$),⁶ with a consistent effect among patients with different diagnoses (Figure 4)⁹⁵ and disease severities⁹⁶ and evidence of a significant benefit on respiratory symptoms based on patients' responses to the Living with Pulmonary Fibrosis (L-PF) questionnaire.⁹⁷ The AEs associated with nintedanib are mainly gastrointestinal, particularly diarrhea, which was reported in 66.9% of patients in the nintedanib group and 23.9% of patients in the placebo group over 52 weeks of the INBUILD trial.⁶ Pirfenidone, an approved treatment for IPF, has also been investigated in randomized placebo-controlled trials in patients with other progressive fibrosing ILDs. In a trial in patients with progressive unclassifiable fibrosing ILD, the decline in FVC (mL) over 24 weeks was lower in the pirfenidone group ($n = 118$) (−17.8 mL) than in the placebo group ($n = 119$) (−113.0 mL) ($P = .002$).⁸ In the TRAIL1 trial in 123 patients with rheumatoid arthritis-associated ILD, pirfenidone slowed the decline in FVC over 52 weeks versus placebo (−66 vs −146 mL/year; $P = .0082$).⁹⁸ In the RELIEF trial, among 67 patients with progressive fibrosing ILDs related to autoimmune diseases, nonspecific interstitial pneumonia, hypersensitivity pneumonitis, or asbestosis, the decline in FVC over 48 weeks was numerically lower in patients treated with pirfenidone than placebo (−36.6 mL vs −114.4 mL), but the difference was not statistically significant ($P = .21$).⁹ Pirfenidone is not licensed in any country for the treatment of ILDs other than IPF. The ATS/ERS/JRS/ALAT guidelines issued a recommendation for more research

into the efficacy of pirfenidone in PPF.³ AEs of pirfenidone include gastrointestinal discomfort and photosensitivity. In a meta-analysis of data from patients with PPF, pirfenidone use was associated with an increased risk of gastrointestinal discomfort (relative risk, 1.83; 95% CI, 1.29-2.60) and photosensitivity (relative risk, 4.88; 95% CI, 1.09-21.83) versus placebo.⁹⁹

Comorbidities such as gastroesophageal reflux disease, obstructive sleep apnea, pulmonary hypertension, and heart failure are common in patients with PPF,^{55,56,100} and should be screened for and managed, as they can contribute to symptoms and morbidity. Pulmonary hypertension is associated with reduced exercise tolerance and poor prognosis in patients with ILDs.¹⁰¹⁻¹⁰³ In the INCREASE study in patients with pulmonary hypertension (documented by right heart catheterization) due to ILD, inhaled treprostinil was associated with an improvement in 6-minute walk test distance compared with placebo at week 16 (primary end point [mean difference vs placebo], 31.12 m; 95% CI, 16.85-45.39; $P < .001$).¹⁰⁴ Based on these results, the FDA approved inhaled treprostinil to improve exercise capacity in patients with pulmonary hypertension associated with ILD.

The randomized, placebo-controlled InPedILD trial investigated the effects of nintedanib, administered using weight-based dosing, in 39 children and adolescents with fibrosing ILD.⁴⁷ The proportion of patients with AEs over 24 weeks (primary end point relating to safety) was 84.6% in both the nintedanib and placebo groups. Diarrhea, the most frequent AE, was reported in 38.5% of patients

FIGURE 4. Rate of Decline in FVC (mL/year) Over 52 Weeks With Nintedanib Versus Placebo in Groups by ILD Diagnosis in INBUILD in Patients With PPF^{95,a}



FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; iNSIP, idiopathic nonspecific interstitial pneumonia.

^aTreatment-by-subgroup-by-time interaction $P = .41$.

^bIncluded sarcoidosis-related ILD, exposure-related ILDs and selected other terms in "Other fibrosing ILDs."

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in the nintedanib group and 15.4% of patients in the placebo group.⁴⁷ The trial was not powered to show a difference in FVC, but changes in FVC % predicted over 24 weeks were numerically in favor of nintedanib.⁴⁷

Conclusions

While various definitions are used for PPF, most include a combination of decline in lung function, worsening of symptoms, and increase in radiological abnormalities. In most trials, PPF was identified only in patients who had failed “standard management” for their particular ILD, but in most ILDs, standard management is not well defined. Patients with worse lung function, a greater extent of fibrosis on HRCT, or a UIP pattern on HRCT are at higher risk of progression of their ILD. However, predicting the onset of PPF remains challenging. PPF confers a poor prognosis and needs to be detected promptly. It is important that patients with fibrosing ILDs are closely monitored, including with regular lung function tests. Management of PPF requires a multimodal approach, including pharmacological therapy, supportive care, and the identification and treatment of comorbidities. Advance care planning and palliative care should be discussed with the patient from an early stage. ■

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