Advances in the management of idiopathic pulmonary fibrosis and progressive pulmonary fibrosis

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Abstract

Similarly to idiopathic pulmonary fibrosis (IPF), other interstitial lung diseases can develop progressive pulmonary fibrosis (PPF) characterized by declining lung function, a poor response to immunomodulatory therapies, and early mortality. The pathophysiology of disordered lung repair involves common downstream pathways that lead to pulmonary fibrosis in both IPF and PPF. The antifibrotic drugs, such as nintedanib, are indicated for the treatment of IPF and PPF, and new therapies are being evaluated in clinical trials. Clinical, radiographic, and molecular biomarkers are needed to identify patients with PPF and subgroups of patients likely to respond to specific therapies. This article reviews the evidence supporting the use of specific therapies in patients with IPF and PPF, discusses agents being considered in clinical trials, and considers potential biomarkers based on disease pathogenesis that might be used to provide a personalized approach to care.

Introduction

The term interstitial lung disease (ILD) encompasses a group of diffuse parenchymal lung diseases with varied clinical, radiographic, and pathologic manifestations reflecting their diverse underlying pathobiology. A subset of ILDs have a progressive fibrosing phenotype. Idiopathic pulmonary fibrosis (IPF) almost invariably has this phenotype. However, other ILDs may also develop this and are thereby termed progressive pulmonary fibrosis (PPF), previously known as progressive fibrosing interstitial lung disease (PF-ILD).1-4 In this review, we will use PPF to refer specifically to non-IPF ILDs that have a progressive fibrosing phenotype. IPF and PPF share common downstream mechanistic pathways resulting in self-sustaining fibrosis that may be independent of the initial injury or trigger. However, PPF often begins with an inflammatory phase triggered by either an endogenous autoantigen or an exogenous antigen, such as an environmental trigger.5-7 Therefore, making a distinction between the two is important, particularly when designing clinical trials and research studies for PPF.

Connective tissue disease associated ILD (CTD-ILD), including rheumatoid arthritis associated ILD (RA-ILD), systemic sclerosis associated ILD (SSc-ILD), and myositis associated ILD, as well as chronic hypersensitivity pneumonitis (cHP), sarcoidosis, idiopathic nonspecific interstitial pneumonia (INSIP), and unclassifiable ILD, are the ILDs most likely to develop a progressive fibrosing phenotype. However, the proportion of patients with these ILDs who develop this phenotype can vary significantly—from an estimated 13% of patients with fibrotic INSIP to an estimated 87% of patients with cHP.8 9 Beyond prognostication, identifying patients with PPF is clinically important because evidence from randomized placebo controlled clinical trials shows that nintedanib can slow decline in lung function in both patients with IPF and those with PPF.10-12 This review summarizes the epidemiology and pathophysiology of IPF and PPF, their currently approved treatments, and promising therapies in the pipeline. It highlights the need for therapeutic trials based on specific biomarkers to develop a more personalized approach to therapy for patients with IPF and PPF in the future.

Sources and selection criteria

We searched PubMed and Ovid MEDLINE databases from 2000 to April 2021 using the following search terms: progressive fibrosing interstitial lung disease, idiopathic pulmonary fibrosis, pulmonary fibrosis, connective tissue disease associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic sclerosis associated interstitial lung disease, systemic sclerosis interstitial lung disease, sarcoidosis, myositis interstitial lung disease, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, unclassifiable interstitial lung disease, biomarkers interstitial lung disease, biomarkers idiopathic pulmonary fibrosis. We reviewed published management guidelines from websites of professional societies and governmental...
bodies, including the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), Latin American Thoracic Association (ALAT), UK National Institute for Health and Care Excellence (NICE), Thoracic Society of Australia and New Zealand (TSANZ), and Lung Foundation of Australia (LFA). We also searched clinicaltrials.gov for all active phase 3 clinical trials for the treatment of idiopathic pulmonary fibrosis, as well as all active and completed phase 2 and 3 clinical trials of nintedanib and pirfenidone for the treatment of PF-ILDs/PPF. We included only full length, peer reviewed studies published in English. We prioritized phase 3 randomized controlled trials (RCTs), phase 2 RCTs, systematic reviews with meta-analyses, and observational cohort studies, in that order. Case reports were excluded. We also focused on high quality basic science manuscripts that contribute to the understanding of the pathobiology of pulmonary fibrosis and lung injury repair and the key mechanisms of action underlying the therapies reviewed. We reviewed basic science manuscripts with preclinical studies in mouse models of pulmonary fibrosis that provide insights into the pathobiology of lung fibrosis. We determined the quality of basic science papers by their selection for publication in high impact journals, their reproducibility across laboratories, their citations by other investigators, and qualitative assessment by the authors. The abstracts of more than 250 papers were reviewed by at least one of the authors, and more than 169 papers were reviewed in detail.

After the original search date in April 2021, the ATS/ERS/JRS/ALAT clinical practice guideline on IPF (an update) and PPF in adults was published in May 2022. Therefore, this review was updated to use the term “PPF” rather than “PF-ILD,” as determined by this guideline. We updated the algorithm (fig 1) to include the conditional recommendation that transbronchial lung cryobiopsy may be used as an alternative to surgical lung biopsy for making a histopathologic diagnosis in patients with ILD of undetermined type. We also updated the sections on “Conceptualizing and defining PPF,” “Currently approved therapy for PPF: Antacid therapy,” and “Guidelines” to reflect the updated clinical practice guideline.

### Conceptualizing and defining PPF

The concept of grouping several non-IPF fibrosing ILDs together grew in part out of the recognition that an unmet need existed for treatment options for these lung diseases. Apart from SSc-ILD, robust RCT data to support the use of immunosuppression in fibrosing ILDs have been lacking. Additionally, many patients with fibrosing ILDs progressed despite conventional treatment. However, a challenge to the design of a robust randomized clinical trial to evaluate new therapies was the fact that the prevalence of each individual fibrosing ILD is relatively low. Thus, the term PF-ILD first came into use in 2017 with the design and development of the INBUILD trial (clinicaltrials.org; NCT02999178). INBUILD was a randomized, double blind, placebo controlled trial to study the efficacy and safety of nintedanib in patients with ILD diagnoses that were noted to behave similarly to IPF in that they were characterized by progressive pulmonary fibrosis, declining lung function, resistance to immunomodulatory therapies, and early mortality.

Before the publication of the ATS/ERS/JRS/ALAT clinical practice guideline on PPF in 2022, PF-ILD had been largely defined by selection criteria for clinical trials. Three randomized clinical trials—INBUILD, RELIEF (German Clinical Trials Register; DRKS00009822), and a phase 2 clinical trial evaluating the use of pirfenidone in patients with progressive fibrosing unclassifiable ILD (NCT03099187)—have proposed criteria for progressive fibrosis. The Erice ILD Working Group also proposed criteria for defining PPF. These criteria shared several common elements. Firstly, the diagnosis must be an ILD other than IPF. This distinction is particularly important when considering the use of these criteria for the purpose of selecting populations for clinical trials. The ATS/ERS/JRS/ALAT clinical practice guideline underscores that PPF is not a diagnosis, but rather a manifestation of certain ILDs, and is agnostic to the underlying condition. Secondly, evidence of fibrotic changes on high resolution computed tomography (HRCT) imaging must be present. These fibrotic features include coarse reticulation with traction bronchiectasis and honeycombing. INBUILD and the study of pirfenidone in unclassifiable ILD both required that participants have fibrotic changes on HRCT affecting at least 10% of lung volume at the time of enrollment. Thirdly, evidence of progression of lung disease despite conventional treatment must exist. Each of these groups and trials had defined progression differently; however, with the 2022 ATS/ERS/JRS/ALAT clinical practice guideline, a consensus definition of PPF was determined and is shown in box 1.

Progression of fibrosis may be more relevant than just its presence. A study that followed patients from the Scleroderma Lung Studies I and II for a median of eight years found that decline in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) over two years was a better predictor of mortality than baseline FVC and DLCO. However, progression can be determined only by serial testing, which may delay lung preserving therapy. Figure 1 shows a suggested algorithm for the evaluation and management of patients with suspected fibrosing ILD.

### Epidemiology

**Idiopathic pulmonary fibrosis**

IPF is the first or second most commonly encountered ILD in pulmonary practice and is estimated to account for 17-37% of all ILD diagnoses. The incidence of IPF in the US and Europe is estimated to be 3-17 per 100,000 person years. The lowest incidence rate of IPF globally is in Asia, with rates ranging from 1.2 to 4.6 per 100,000 per year. In a study using Medicare data limited to people in the US aged 65 years and older, the incidence of IPF was
Fig 1 | Suggested algorithm for the evaluation and management of suspect fibrosing interstitial lung disease (ILD). *†American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines suggest bronchoalveolar lavage (BAL) cellular analysis and surgical lung biopsy or transbronchial lung cryobiopsy in the evaluation of patients in whom IPF is clinically suspected or who have an ILD of uncertain etiology and have a high resolution computed tomography (HRCT) pattern of probable usual interstitial pneumonia (UIP), indeterminate for UIP, or an alternative diagnosis. BAL cellular fluid analysis, surgical lung biopsy, and transbronchial lung biopsy are not recommended in patients in whom idiopathic pulmonary fibrosis (IPF) is clinically suspected and who have an HRCT pattern of UIP. CTD-ILD=connective tissue disease associated interstitial lung disease; DLCO=diffusing capacity of the lung for carbon monoxide; FVC=forced vital capacity; GERD=gastresophageal reflux; INSIP=idiopathic nonspecific interstitial pneumonia; IPAF=interstitial pneumonia with autoimmune features; LTOT=long term oxygen therapy; PFT=pulmonary function test; PPF=progressive pulmonary fibrosis.
Box 1: Identifying progressive pulmonary fibrosis

- Interstitial lung disease diagnosis other than idiopathic pulmonary fibrosis
- Radiologic evidence of pulmonary fibrosis
- Evidence of progression, defined as meeting at least two of three criteria within the previous year with no alternative explanation:
  1. Worsening respiratory symptoms
  2. Absolute decline in FVC >5% predicted or absolute decline in DLCOc ≥10% predicted within one year of follow-up
  3. Radiologic evidence of progression, including:
     a. Increased extent or severity of traction bronchiectasis or bronchiolectasis
     b. New ground glass opacity with traction bronchiectasis
     c. New fine reticulation
     d. Increased extent or coarseness of reticulations
     e. New or increased honeycombing
     f. Increased lobar volume loss

FVC=forced vital capacity; DLCOc=diffusing capacity of the lung for carbon monoxide corrected for hemoglobin; RT=reticulation

as high as 93.7 per 100 000 person years and the prevalence was 494.5 cases per 100 000, reflecting age as the major risk factor for IPF.22

Most common ILDs manifesting PPF

RA-ILD
Rheumatoid arthritis is the most common autoimmune disease worldwide and is estimated to have a prevalence of 400-1000 cases per 100 000.21 Clinically significant ILD occurs in 8-20% of patients with rheumatoid arthritis and is more common in men and those with greater overall disease severity.21-23 The proportion of patients with RA-ILD who have progressive decline in lung function is estimated at 40%, on the basis of a study that found that 40% of patients with RA-ILD had a DLCO <40% predicted by five years after diagnosis of ILD.24 The detection of a usual interstitial pneumonia (UIP) pattern on HRCT scan is associated with increased risk of both progressive lung disease and death, compared with a nonspecific interstitial pneumonia (NSIP) or organizing pneumonia pattern.24-25

SSc-ILD
The prevalence of systemic sclerosis is estimated to be 7.2-33.9 cases per 100 000 in Europe and 13.5-44.3 cases per 100 000 in North America.26 The proportion of people with systemic sclerosis who have SSc-ILD is as high as 90% on the basis of HRCT scanning.27 Of patients with SSc-ILD, 18-25% have progressive worsening of lung function or HRCT findings.10-28-30 Clinical features that predict progressive ILD include Black/African-American race, older age at disease onset, diffuse cutaneous skin disease, detection of antitopoisomerase antibodies, and lower baseline FVC and DLCO.31,32 Histologic patterns of NSIP or UIP are not significantly associated with overall mortality in SSc-ILD.33

Myositis related ILD
Idiopathic inflammatory myopathies are a group of rare systemic autoimmune disorders characterized by inflammation of skeletal muscle and sometimes skin, with a reported incidence of 0.2-0.9 cases per 100 000 person years.34 The subtypes most commonly associated with ILD are dermatomyositis, polymyositis, and antisynthetase syndrome.35 The reported prevalence of ILD in myositis ranges widely from 19.9% to 86%.35 In a single center retrospective study, 31% of patients diagnosed as having myositis had ILD.36 Of the patients with ILD, 33% had complete resolution of their lung disease with treatment and 16% had deterioration of their ILD after a median 34 months of follow-up.36 An organizing pneumonia pattern on HRCT often responds to immunosuppressive therapy leading to clinical resolution of disease, whereas a UIP pattern is associated more often with progressive disease and clinical deterioration.36-39

Chronic hypersensitivity pneumonitis
In a study using US administrative claims based data, the prevalence of hypersensitivity pneumonitis was estimated to be only 1.67-2.71 cases per 100 000, of which approximately 25% met criteria for fibrotic or chronic hypersensitivity pneumonitis.40 However, in studies from cohorts of patients with ILD of new onset, a clinical diagnosis of hypersensitivity pneumonitis is made in 18-47% of patients.41-43 Most patients with hypersensitivity pneumonitis who have fibrotic disease at baseline will have progressive disease.8,44-45 Salisbury and colleagues found that compared with patients with IFP, those with cHP and honeycombing on HRCT had a greater decline in FVC and similar median survival.8

Idiopathic NSIP
The estimated prevalence of iNSIP is 1-9 cases per 100 000.46 In a retrospective cohort study of patients with fibrotic iNSIP, 13% had progression of radiologic findings on HRCT, 36% had radiologic improvement, and 23% had stable findings.47 The prognosis of fibrotic iNSIP is generally better than that of IFP, with a five year survival rate ranging from 45% to 90%.48-49

Sarcoidosis
In the US, the prevalence of sarcoidosis is 141.4 per 100 000 in people identifying as Black or African-American, 49.8 in those identifying as white, 21.7 in those identifying as Hispanic, and 18.9 in those identifying as Asian.50 Fibrotic (stage IV) lung disease is estimated to occur in less than 20% of people with pulmonary sarcoidosis.51-52 In a retrospective cohort study of patients with stage IV sarcoid, 24.8% had worse lung function after a mean 6.2 years of follow-up, whereas lung function was improved in 39.3% and stable in 35.9%.53

Unclassifiable ILD
The proportion of patients with new onset ILD who are deemed to have unclassifiable ILD after multidisciplinary discussion was 10% in one single center retrospective study.54 In this study,
Fig 2 | Mechanisms and signals involved in the development of pulmonary fibrosis and therapeutic targets. During normal repair after lung injury, tissue resident alveolar macrophages interact with other cells in the alveolar epithelium to clear apoptotic cells, particulates, and pathogens without disrupting the normal gas exchanging functions of the alveolus. Alveolar type 2 (AT2) cells differentiate into alveolar type 1 (AT1) cells, passing through a transitional state characterized by expression of keratin-17, thereby restoring the normal alveolar epithelium. During disordered repair, recurring injuries to alveolar epithelium, by either environmental insults or antigen stimulation, cause AT1 cell death as well as aberrant activation of AT2 cells. The process of AT2 cells differentiating into AT1 cells is impaired in regions of lung fibrosis. Partially differentiated keratin-17 positive (KRT17+) epithelial cells accumulate, where they are associated with fibrosis. These KRT17+ cells produce large amounts of connective tissue growth factor (CTGF) and express αvβ6 integrin, which has been shown to activate latent transforming growth factor β (TGF-β), both of which promote differentiation of fibroblasts into myofibroblasts. The abnormally activated alveolar epithelial cells also contribute to fibroblast and myofibroblast proliferation through the production of platelet derived growth factor (PDGF), TGF-β, and CTGF. In response to this failed attempt at epithelial repair, circulating monocytes are recruited into the alveolar space and differentiate into profibrotic alveolar macrophages. These monocyte derived alveolar macrophages (Mo-AM) secrete PDGF and other growth factors that promote the activation and proliferation of fibroblasts as well as their differentiation into myofibroblasts. In a reciprocal positive feed-forward loop, fibroblasts secrete macrophage colony stimulating factor (M-CSF), which maintains alveolar macrophages at the site of injury. Myofibroblasts secrete excessive extracellular matrix (ECM) proteins, leading to stiffening of lung tissue. Myofibroblasts over time produce TGF-β in an autocrine manner and lose their need for macrophages in order to proliferate. The stiff matrix inhibits fibroblast apoptosis in another positive feed-forward loop that contributes to self-sustaining fibrosis. Recombinant human pentraxin (rhPTX)-2 has been proposed to inhibit the recruitment of alveolar macrophages to areas of fibrosis, which in turn inhibits myofibroblast activation. Nintedanib (NTB) likely inhibits fibroblasts by blocking PDGF signaling, among other profibrotic signaling pathways. The exact mechanisms by which pirfenidone (PFD) slows the progression of interstitial pulmonary fibrosis remain incompletely understood. Pamrevlumab (Pmab) is an anti-CTGF antibody that also likely inhibits fibroblasts.
52% of patients had significant progressive decline in lung function or death. Additionally, patients with unclassifiable ILD had longer survival rates compared with IPF and similar survival compared with other ILDs with progressive fibrosis.64

**Pathophysiology**

Pulmonary fibrosis is increasingly recognized to begin with damage to the epithelium, possibly induced by environmental insults including cigarette smoke, viruses, environmental dusts (for example, silica or asbestos), or, perhaps, autoimmune injury (fig 2).75 76 In support of this hypothesis, some genetic mutations associated with pulmonary fibrosis involve genes that are exclusively expressed in the lung epithelium. These include a mutation in the promoter region of MUC5B that enhances its expression and mutations in SFTPC that lead to production of a misfolded protein.57-59 Furthermore, genetic studies in mice localize the fibrotic effects of mutations in genes associated with pulmonary fibrosis that are expressed in all cells to the lung epithelium. Important examples include deficiency in genes that maintain telomere length and genes associated with the Hermansky-Pudlak syndrome.60-62

The advent of single cell RNA sequencing and its application to animal models of lung fibrosis and clinical samples from patients with pulmonary fibrosis have brought the multicellular nature of pulmonary fibrosis into focus.63-68 Repair of the injured alveolar epithelium requires the asymmetric division followed by differentiation of alveolar type 2 cells into alveolar type 1 cells.59 70 During the process of alveolar type 2 to type 1 cell differentiation, a transitional cell population characterized by expression of keratin-8 in mice and keratin-17 in humans forms.68 71-73 These keratin-8 or keratin-17 positive epithelial cells are found at low concentrations in the normal mouse or human lung, but they increase during pulmonary fibrosis and are specifically localized to fibrotic lung regions in mice and humans.64 65 68 72 74 These results suggest that normal epithelial repair is disrupted in regions of lung fibrosis. In response to this failed repair, circulating monocytes are recruited to the alveolar space where they rapidly differentiate into profibrotic monocyte derivative alveolar macrophages.62 75-77 These alveolar macrophages form reciprocal circuits with matrix fibroblasts in which fibroblasts secrete macrophage colony stimulating factor (M-CSF) to maintain alveolar macrophages at the site of injury and alveolar macrophages secrete platelet derived growth factor (PDGF) and other growth factors that drive the differentiation of fibroblasts into myofibroblasts, which excrete excessive matrix proteins.66 78 In addition, alveolar epithelial injury induces the activation of latent transforming growth factor β (TGF-β) in the matrix.79 TGF-β is a cytokine that modulates cellular differentiation, proliferation, and apoptosis, as well as extracellular matrix production.80 It also maintains alveolar macrophages and activates myofibroblasts.81 82 Over time, myofibroblasts lose their requirement for alveolar macrophages for proliferation and matrix secretion, in part through autocrine production and activation of TGF-β,83 84 resulting in spatially restricted regions of progressive fibrosis.76 This model of pulmonary fibrosis suggests a multimodal strategy for treatment. Such a strategy might include therapies to accelerate the differentiation of alveolar type 2 into alveolar type 1 cells through inhibition of the integrated stress response,68 85 therapies that reduce the recruitment or prevent the maintenance of profibrotic monocyte derived alveolar macrophages in the alveolar space,86 and therapies that target signaling through TGF-β, PDGF, and other growth factors in myofibroblasts (for example, nintedanib).11

**Management of IPF**

**Currently approved treatment**

The most recent ATS/ERS/JRS/ALAT clinical practice guideline on the treatment of IPF recommends only two drugs for the treatment of IPF—pirfenidone and nintedanib.4 The 2015 ATS/ERS/JRS/ALAT guideline also included a conditional recommendation for antacid therapy, and therefore its evidence is also discussed here.67 Table 1 lists the major clinical trials that examined the use of pirfenidone and nintedanib in the treatment of IPF and PPF.

**Pirfenidone**

The US Food and Drug Administration (FDA) approved pirfenidone for the treatment of IPF in October 2014. The approval was based on data from three phase 3 clinical trials—CAPACITY I, CAPACITY II, and ASCEND. With pooled data from the CAPACITY I and II trials, primary endpoint analysis found that pirfenidone reduced the mean decline in FVC in per cent predicted over 72 weeks compared with placebo (−8.5% v −11.0%; P=0.005).88 The ASCEND trial found that pirfenidone led to a 47.9% reduction in the proportion of participants who had an absolute decline of 10% or more in the FVC per cent predicted or who died after 52 weeks (16.5% v 31.8%; P<0.001).89 Prespecified secondary analyses that pooled data with the two CAPACITY trials found that treatment with pirfenidone was associated with decreased all cause mortality (3.5% v 6.7%; P=0.01) and IPF specific mortality (1.1% v 3.5%; P=0.006), compared with placebo.89 Separate post hoc analysis of pooled data from the CAPACITY and ASCEND trials also found that participants receiving pirfenidone had a lower risk of respiratory related hospital admissions (7% v 12%; P=0.001).91 The exact mechanisms by which pirfenidone slows the progression of IPF are not known, although several have been proposed.92

**Nintedanib**

The US FDA also approved nintedanib for the treatment of IPF in October 2014. This was based on two INPULSIS phase 2 clinical trials, which both found that nintedanib reduced the annual rate of
<table>
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<tr>
<th>Date</th>
<th>Intervention</th>
<th>Characteristics</th>
<th>Study cohort</th>
<th>Primary outcome(s)</th>
<th>Key secondary outcome(s)</th>
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<tr>
<td>2011 (CAPACITY I) 88</td>
<td>Pirfenidone 2403 mg daily v pirfenidone 1197 mg daily v placebo</td>
<td>Phase 3 RCT, 72 weeks, n=435</td>
<td>IPF patients, FVC ≥50%, DLCO ≥35%, FVC or DLCO ≥90%</td>
<td>Mean decline in FVC –8.9% v –12.4% (pirfenidone 2403 mg/ day v placebo, P=0.001)</td>
<td>Categorical change in FVC ≥10%: 20% (95% CI 0.47 to 1.86)</td>
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<tr>
<td>2011 (CAPACITY II) 88</td>
<td>Pirfenidone 2403 mg daily v placebo</td>
<td>Phase 3 RCT, 72 weeks, n=344</td>
<td>IPF patients, FVC ≥50%, DLCO ≥35%, FVC or DLCO ≥90%</td>
<td>Mean decline in FVC –9.0% v –9.6% (pirfenidone v placebo, P=0.501)</td>
<td>Mean change in 6MWD –45.1 m v –76.9 m (pirfenidone v placebo, P=0.0009)</td>
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<tr>
<td>2014 (ASCEND) 11</td>
<td>Pirfenidone 2403 mg daily v placebo</td>
<td>Phase 3 RCT, 52 weeks, n=555</td>
<td>IPF patients, FVC 50-90%, DLCO 30-90%</td>
<td>Proportion of patients with FVC decline ≥10% or death 16.5% v 31.8% (pirfenidone v placebo, P=0.001)</td>
<td>Mean change in 6MWD absolute difference 26.7 m (P=0.04). Increased progression-free survival time: HR 0.57 (0.43 to 0.77)</td>
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<td>202015</td>
<td>Pirfenidone 2403 mg daily v placebo</td>
<td>Phase 2 RCT, 24 weeks, n=253</td>
<td>Progressive fibrosing° unclassifiable ILD patients, FVC ≥45%, DLCO ≥30%</td>
<td>Median change in FVC measured by home spirometry –87.7 mL v –157.1 mL (pirfenidone v placebo; statistical analysis could not be applied owing to intra-individual variability)</td>
<td>Mean decline in FVC measured by site spirometry –17.8 mL v –113 mL (pirfenidone v placebo). Proportion of patients with &gt;15% decline in DLCO v 9% (pirfenidone v placebo, P=0.039)</td>
</tr>
<tr>
<td>2021 (RELIEF, study ended prematurely)10</td>
<td>Pirfenidone 2403 mg daily v placebo</td>
<td>Phase 2b RCT, 48 weeks, n=127</td>
<td>Progressive non-IPF lung fibrosis (PPF)° patients, FVC ≥40-90%, DLCO 10-90%</td>
<td>Absolute decline in FVC % predicted lower in pirfenidone group than placebo group (P=0.043). Median difference in change in FVC % predicted 1.69-3.53, depending on test. Results non-significant with sensitivity analyses</td>
<td>Difference in DLCO change from baseline 0.4 (95% CI 0.1 to 0.7)</td>
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| Nintedanib | 2014 (INPULSIS I) 11 | Nintedanib 105 mg twice daily v placebo | Phase 3 RCT, 52 weeks, n=515 | IPF patients, FVC ≥50%, DLCO 30-79% | Annual rate of change in FVC −115 mL/year v −240 mL/year (pirfenidone v placebo, P=0.001) | No significant difference in time to first acute exacerbation or change in SGRQ score |
| 2014 (INPULSIS II) 11 | Nintedanib 105 mg twice daily v placebo | Phase 3 RCT, 52 weeks, n=551 | IPF patients, FVC ≥50%, DLCO 30-79% | Annual rate of change in FVC −114 mL/year v −207 mL/year (pirfenidone v placebo, P=0.001) | Increased time to first acute exacerbation: HR 0.38 (0.19 to 0.77; P=0.005). Mean change in 6MWD score 2.80 points v 5.48 points (nintedanib v placebo, P=0.02) |
| 2019 (SENSICS) 10 | Nintedanib 105 mg twice daily v placebo | Phase 3 RCT, 52 weeks, n=580 | SSC-ILD patients, FVC ≥40%, DLCO 30-89% | Annual rate of change in FVC −52 mL/year v −93 mL/year (nintedanib v placebo, P=0.64) | No significant difference in change in modified Rodnan skin score change or change in SGRQ score (nintedanib v placebo) |
| 2019 (INBUILD) 12 | Nintedanib 105 mg twice daily v placebo | Phase 3 RCT, 52 weeks, n=663 | PF-ILD (PPF) patients, FVC ≥45%, DLCO 30-79% | Annual rate of change in FVC −81 mL/year v −188 mL/year (nintedanib v placebo, P=0.001) | Proportion of patients with acute exacerbation: HR 0.80 (0.48 to 1.34). Proportion of patients who died: HR 0.94 (0.47 to 1.86) |

6MWD=6 minute walk distance; CI=confidence interval; DLCO=diffusing capacity of the lung for carbon monoxide; FVC=forced vital capacity; HR=hazard ratio; IPF=idiopathic pulmonary fibrosis; PPF=progressive pulmonary fibrosis; RCT=randomized controlled trial; SGRQ=St George’s Respiratory Questionnaire; SSc-ILD=scleroderma associated interstitial lung disease. °Progressive fibrosis defined as either ≥5% absolute decline in FVC % predicted or significant symptomatic worsening not due to other causes. †Progressive non-IPF lung fibrosis defined in RELIEF study by patients with diagnosis of connective tissue disease associated ILD, fibrotic non-specific interstitial pneumonia, chronic hypersensitivity pneumonitis, or asbestos induced lung fibrosis with disease progression despite conventional therapy (annual FVC decline ≥5%). ‡SSc-ILD patients, FVC ≥50%, DLCO ≥35%, FVC or DLCO ≥90% ‡‡Progressive non-IPF lung fibrosis with disease progression despite conventional therapy (annual FVC decline ≥5%). §PPF defined in INBUILD study as physician diagnosed fibrosing interstitial lung disease other than IPF with relative decline in FVC ≥10% predicted, relative decline of ≥5% predicted and worsening respiratory symptoms or increased extent of fibrosis on high resolution computed tomography, or worsening of respiratory symptoms and increased extent of fibrosis.

In INPULSIS 1, the difference in annual rate of decline in FVC was 125.3 (95% confidence interval 77.7 to 172.8) mL/year (P<0.001); in INPULSIS 2, the difference was 93.7 (44.8 to 142.7) mL/year (P<0.001). In pre-specified pooled analyses, no significant difference was seen between nintedanib and placebo groups in the time to first investigator reported acute exacerbation, death from any cause, or death from a respiratory cause. Nintedanib is a tyrosine kinase inhibitor that was originally developed as an anti-angiogenic cancer drug designed to bind and block platelet derived growth factor receptor (PDGFR), fibroblast growth factor receptor 1 (FGFR-1), and vascular endothelial growth factor receptor 2.3,4 PDGF is made by alveolar macrophages in response to injury and inflammation and contributes to the proliferation, survival, and migration of myofibroblasts, which deposit extracellular matrix proteins in the interstitial matrix.9 95 FGF/FGFR signaling also contributes to lung fibrosis, specifically through FGF-2 which induces fibroblast proliferation and collagen synthesis in lung fibroblasts and myofibroblasts.9 97 Through its inhibition of growth factor signaling, nintedanib is thought to reduce the proliferation and migration of lung fibroblasts, the transdifferentiation of fibroblasts to myofibroblasts, and the deposition of extracellular matrix.9 94

**Antacid therapy**
Abnormal gastroesophageal reflux is common in patients with IPF and is a known risk factor
for aspiration and microaspiration.\textsuperscript{98} Regular use of antacid therapy, either with proton pump inhibitors or histamine-2 blockers, is believed to decrease the lung injury induced by microaspiration of acidic gastric juices.\textsuperscript{99} Although the 2015 ATS/ERS/JRS/ALAT IPF treatment guidelines give a conditional recommendation for the use of antacid therapy, even in patients without symptoms of gastroesophageal reflux, the 2022 updated guideline makes a conditional recommendation against its use for the purpose of improving respiratory outcomes.\textsuperscript{8} The TSANZ/LFA guidelines state that antacid therapy has unclear benefit and do not make a recommendation for or against its use.\textsuperscript{101} When examining IPF patients in the placebo arms of RCTs, one study that used the IPFnet trails found that antacid use at baseline was associated with reduced decline in FVC\textsuperscript{102}; however, a more recent study using the CAPACITY and ASCEND trials found that antacid therapy did not improve outcomes and was associated with an increased risk of infection in patients with advanced lung disease.\textsuperscript{103} Similarly, the WRAP-IPF trial, a phase II randomized, unblinded, controlled trial, found that laparoscopic antireflux surgery in patients with IPF and abnormal gastroesophageal reflux did not significantly reduce the decline in FVC over 48 weeks.\textsuperscript{104} However, in a pilot randomized, placebo controlled trial of participants with IPF and a history of cough, omeprazole use was associated with a reduction in cough frequency of 39.1% (−66.0% to 9.3%), although it was not statistically significant owing to small sample size.\textsuperscript{105}

### Non-drug management

The most recent guidelines from leading international societies of pulmonary medicine recommend long term oxygen therapy for IPF patients with resting hypoxemia, as well as referrals for pulmonary rehabilitation and lung transplant evaluation in appropriate patients.\textsuperscript{106} The current recommendation for supplemental oxygen therapy in IPF is largely based on indirect evidence from two landmark RCTs in obstructive lung disease that showed a survival benefit with long term oxygen therapy in patients with resting hypoxemia (PaO\textsubscript{2} 55-65 mm Hg).\textsuperscript{108} Evidence to directly support the use of supplemental oxygen in people with IPF and resting or exertional hypoxemia is limited. A 2016 Cochrane review that included three RCTs found no evidence to support or refute the use of ambulatory or short burst oxygen in patients with IPF and exertional hypoxemia owing to the limited data.\textsuperscript{110} However, a subsequent systematic review that included studies examining the use of oxygen during exercise or exercise training found that ambulatory oxygen was associated with a consistent increase in exercise capacity.\textsuperscript{111}

Pulmonary rehabilitation is a comprehensive intervention that includes exercise training, education, and behavior change.\textsuperscript{112} A Cochrane review that included five randomized or quasi-randomized controlled trials found that among people with ILD, and IPF specifically, significant improvements in exercise capacity, dyspnea, and quality of life were seen immediately after pulmonary rehabilitation, with the quality of evidence rated

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### Table 2 | Recent active phase 3 clinical trials of treatments for idiopathic pulmonary fibrosis and phase 2/3 trials supporting their study

<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Intervention</th>
<th>Study characteristics</th>
<th>Antibiotic* use allowed?</th>
<th>Primary outcome(s)</th>
<th>Key secondary outcome(s)</th>
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<tr>
<td><strong>Active clinical trials</strong></td>
<td></td>
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<tr>
<td>NCTG04552899</td>
<td>rhPTX-2 v placebo</td>
<td>Phase 3 RCT, 52 weeks, n=658</td>
<td>Yes</td>
<td>Absolute change in FVC</td>
<td>Change in 6MWD, progression-free survival</td>
</tr>
<tr>
<td>NCT03955146</td>
<td>Pamrevlumab v placebo</td>
<td>Phase 3 RCT, 48 weeks, n=340</td>
<td>No</td>
<td>Absolute change in FVC</td>
<td>Time to disease progression or death</td>
</tr>
<tr>
<td>NCT04708782</td>
<td>Inhaled treprostinil v placebo</td>
<td>Phase 3 RCT, 52 weeks, n=396</td>
<td>Yes</td>
<td>Absolute change in FVC</td>
<td>Time to clinical worsening</td>
</tr>
<tr>
<td>NCT04300920</td>
<td>N-acetylcysteine v placebo</td>
<td>Phase 3 RCT, 24 months, n=200</td>
<td>Yes</td>
<td>Time to composite endpoint: 10% decline in FVC, first respiratory hospital admission, lung transplant, or death</td>
<td>Change in FVC</td>
</tr>
</tbody>
</table>

| **Completed clinical trials** |
| NCT02550873\textsuperscript{106} | rhPTX-2 v placebo | Phase 2 RCT, 28 weeks, n=117 | Yes | Mean change in FVC % predicted difference 2.3 (90% CI 1.1 to 3.5) | Decline in 6MWD less with rhPTX than placebo |
| NCT02550873\textsuperscript{119} | rhPTX-2 | Open label extension trial, 76 weeks, n=116 | Yes | Adverse events consistent with long term IPF sequelae | Persistent treatment effect seen on continuation of rhPTX and positive effect seen in patients who crossed over from placebo |
| NCT01890265 (PRAISE)\textsuperscript{120} | Pamrevlumab v placebo | Phase 2 RCT, 48 weeks, n=103 | No | Mean change in FVC % predicted difference 4.4% (90% CI 0.4% to 8.3%) | Progression-free survival improved with pamrevlumab |
| NCT02630316 (INCREASE)\textsuperscript{121,122} | Treprostinil v placebo (for treatment of pulmonary hypertension in patients with ILD) | Phase 2/3 RCT, 16 weeks, n=326 | Yes | Mean difference in 6MWD 31.12 (95% CI 16.85 to 45.39) | FVC % predicted improved and fewer acute exacerbations of ILD with treprostinil |

6MWD=6 minute walk distance; CI=confidence interval; FVC=forced vital capacity; ILD=interstitial lung disease; IPF=idiopathic pulmonary fibrosis; RCT=randomized controlled trial; rhPTX-2=recombinant human pentraxin 2.

*Pirenidone or nintedanib.

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as low to moderate. A subsequent meta-analysis of four RCTs found that, in patients with IPF, pulmonary rehabilitation had no detectable benefit at long term follow-up. The current ATS/ERS/JRS/ALAT guidelines recommend that most patients with IPF be treated with pulmonary rehabilitation (weak recommendation, low quality of evidence).

Given the progressive natural history of IPF, with a median survival time of 3.8 years after diagnosis, guidelines recommend that appropriate patients undergo lung transplantation and that discussion of transplantation should occur at the time of diagnosis or soon after. In North America, the percentage of lung transplants performed in patients with IPF has been increasing over the past three decades, and from 2010 to 2018 IPF was the most common indication for lung transplantation. Although post-transplant survival is worse for patients with IPF than for those with COPD and other matched non-IPF patients, lung transplantation is associated with a 75% reduction in risk of death. From 1992 to 2017 median survival time for patients with IPF was 5.2 years post-transplant, which increased to 7.3 years among those who survived at least one year post-transplant.

Therapies in the pipeline for treatment of IPF
Several drugs for the treatment of IPF—recombinant human pentraxin 2, pamrevlumab, treprostinil, and N-acetylcysteine—have recent phase 3 clinical trials. Table 2 lists these trials along with the data from the phase 2 and 3 trials that support the potential role of these drugs as treatment for IPF.

Recombinant human pentraxin 2 (rhPTX-2; PRM-151)
PRM-151 is a recombinant human pentraxin 2 protein (rhPTX-2). Pentraxin 2, also known as serum amyloid P, inhibits the recruitment of profibrotic monocyte derived alveolar macrophages to areas of fibrosis. This is predicted to limit signaling by macrophages that drive matrix remodeling and myofibroblast activation.

The effect of rhPTX-2 was studied in a phase 2 double blind, randomized, placebo controlled trial of patients with mild to moderate IPF. Concurrent therapy with pirfenidone or nintedanib was permitted. For the primary efficacy endpoint, the least squares mean change in FVC per cent predicted at week 28 in participants treated with rhPTX-2 was −2.5, compared with −4.8 in those given placebo (difference of 2.3, 90% confidence interval 1.1 to 3.5; P=0.001). An open label extension study found a persistent treatment effect in participants who continued taking rhPTX-2, with a decline in the FVC per cent predicted of −3.6% per year. In participants who started taking rhPTX-2, FVC decline improved from −8.7 per cent predicted per year in weeks 0-28 (while taking placebo) to −0.9 per cent predicted per year in weeks 28-52. Thirteen (12%) of 111 participants had adverse events that led to discontinuation of rhPTX-2. Four participants had events that were considered by investigators to be related to rhPTX-2, including IPF exacerbation, tendinitis, dysgeusia, and cardiomyopathy. A phase 3 randomized, double blind, placebo controlled trial to study the efficacy and safety of rhPTX-2 began recruitment in March 2021, with an estimated study completion date in March 2023 (NCT04552899).

Pamrevlumab
Pamrevlumab is an anti-connective tissue growth factor (CTGF) antibody under investigation for the treatment of IPF. CTGF is a mediator of tissue remodeling, acting downstream of TGF-β on connective tissue cells and functioning to stimulate fibroblast proliferation and the production of extracellular matrix. CTGF is produced at high concentrations by airway and epithelial cells, as well as by activated fibroblasts in the lung tissue of patients with IPF.

The effect of pamrevlumab in patients with IPF was investigated in the phase 2 randomized, double blind, placebo controlled PRAISE trial. Patients included had mild to moderate IPF and were not permitted to be on treatment with pirfenidone or nintedanib. Patients treated with pamrevlumab had a decline in FVC of 2.9 per cent predicted per year compared with 7.2 per cent predicted per year with placebo (difference of 4.3 (0.4 to 8.3) per cent predicted per year; P=0.033). The proportion of patients with disease progression, as defined by decline from baseline FVC per cent predicted ≥10% or death at week 48, was also reduced in the pamrevlumab group compared with the placebo group (10.0% v 31.4%; P=0.013). The frequency of adverse events was similar in the pamrevlumab and placebo groups, and the events were generally mild or moderate in severity and typical of participants’ underlying medical conditions. ZEPHYRUS 1 and 2 are ongoing phase 3 randomized, placebo controlled trials to further evaluate the use of pamrevlumab in patients with IPF and are estimated to complete in 2023 (NCT03955146; NCT04419558).

Inhaled treprostinil
Treprostinil is a prostacyclin analog that is approved by the US FDA as an inhaled solution (Tyvaso) for treatment of pulmonary arterial hypertension and pulmonary hypertension associated with ILD. Inhaled treprostinil causes vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. It has also been shown to reduce collagen deposition in a bleomycin induced mouse model of pulmonary fibrosis, in part by inhibiting TGF-β1 induced expression of collagen mRNA and protein.

INCREASE was a randomized, double blind trial that examined the use of inhaled treprostinil in the treatment of pulmonary hypertension in people with ILD. The trial met its primary efficacy endpoint in finding that the least squares mean difference between the inhaled treprostinil group and placebo group in the change from baseline six minute walk distance was 31.12 (16.85 to 45.39) m; P<0.001.
Serious adverse events were similar in the inhaled treprostinil and placebo groups. Post hoc analysis found a difference in change in FVC per cent predicted of 1.8% (0.2% to 3.4%; P=0.028), favoring inhaled treprostinil over placebo, by week 16.128 Notably, this study also found that the largest treatment effect occurred in patients with IPF. Based on these data, a phase 3 randomized, double blind, placebo controlled study began in April 2021 to evaluate the safety and efficacy of inhaled treprostinil in people with IPF, with change in FVC as the primary outcome measure (NCT04708782).

N-acetylcysteine is a tripeptide precursor of glutathione that has antioxidant effects in the lung.129 130 Three randomized, placebo controlled trials have examined the use of N-acetylcysteine monotherapy in the treatment of IPF.131-133 The primary outcome in each of these studies was change in FVC, and none found a significant difference between N-acetylcysteine and placebo groups. Similarly, after the results of these three RCTs were pooled, no significant benefit on mortality, change in FVC, quality of life, or adverse outcomes was seen.87 Two randomized, placebo controlled studies, including the PANORAMA study, then examined N-acetylcysteine in combination with pirfenidone in patients with IPF.134 135 Although neither found a significant difference in the incidence of adverse events, both studies found a greater decline in FVC in patients receiving N-acetylcysteine; however, both were limited by small sample size.

However, a post hoc analysis of the PANThER-IPF trial, which randomized participants with IPF to receive N-acetylcysteine monotherapy, combined prednisone, azathioprine, and N-acetylcysteine, or placebo, identified a subgroup of patients with the TOLLIP TT genotype in which N-acetylcysteine monotherapy was associated with a significant decrease in the composite endpoint of lung disease progression, hospital admission, transplantation, or death (hazard ratio 0.14, 95% confidence interval 0.02 to 0.83; P=0.03).136 The TOLLIP CC genotype was associated with a non-significant increase in risk of the composite endpoint (hazard ratio 3.23, 0.79 to 13.16; P=0.019), which was significant in replication cohorts. Based on these data, the PRECISIONS trial is a phase 3 clinical trial comparing the effect of N-acetylcysteine plus standard care in patients with IPF who have the TOLLIP TT genotype (NCT04300920).

### Treatment of inflammatory ILDs

The currently accepted treatment for inflammatory ILDs, including CTD-ILD, cHP, iNSIP, and unclassifiable ILD, is immunosuppression. However, the only RCT data supporting this approach come from studies in patients with SSC-ILD.137-139 Additionally, the only immunosuppressive drug that is approved by the FDA for the treatment of SSC-ILD is tocilizumab. FaSScinate, a phase 2/3 RCT, and focuSSced, a phase 3 RCT, were the basis for the FDA approval of tocilizumab for the treatment of SSc-ILD.139 140 The focuSSced trial randomly assigned 210 people with diffuse cutaneous systemic sclerosis to receive tocilizumab or placebo.139 People with severe ILD were excluded, and the cohort had a mean baseline FVC per cent predicted of 82% and evidence of SSC-ILD on HRCT in 65% of cases. Although the primary endpoint of change in the modified Rodman skin score was not met, on analysis of secondary outcomes participants who received tocilizumab had less decline in FVC per cent predicted than did those who received placebo (absolute difference in least square mean of 4.2%, 2.0% to 6.4%; P=0.0002).

Although cyclophosphamide and mycophenolate mofetil are not approved by the FDA for the treatment of SSC-ILD, their use is supported by the Scleroderma Lung Studies I and II. In the Scleroderma Lung Study I, which randomized 158 patients with SSC-ILD to receive cyclophosphamide or placebo, the mean absolute difference in adjusted FVC per cent predicted at 12 months was 2.53% (0.28% to 4.79%; P<0.03), favoring cyclophosphamide.138 The Scleroderma Lung Study II subsequently randomized 126 patients with SSC-ILD to receive either cyclophosphamide or mycophenolate mofetil.137 No significant difference was seen in the primary outcome of FVC per cent predicted at 24 months, but mycophenolate mofetil was associated with fewer toxicities and was better tolerated.

The evidence to support the use of immunotherapies such as steroids, mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, and rituximab for the treatment of other inflammatory ILDs is limited to observational studies and case series. Despite this, immunosuppression remains the standard of care for CTD-ILD and cHP and should be considered as first line therapy. The RECITAL trial is ongoing and has randomized patients with severe and/or progressive CTD-ILD to receive either cyclophosphamide (as standard of care) or rituximab as first line therapy and may further clarify the role of rituximab in CTD-ILD.141

Despite the use of immunosuppressive treatment, high morbidity and mortality associated with these ILDs remain. Thus, a clear mandate exists for better treatment strategies that may be informed by understanding the progressive fibrosing phenotype and the role of antifibrotics in its treatment.

### Treatment of PPF

Although the non-uniformity of the interstitial lung diseases that manifest PPF poses a challenge to designing and conducting clinical trials, several studies have established a role for antifibrotic therapy in PPF (table 1).10 12 15 90

**Nintedanib**

Strong evidence supports the use of nintedanib for PPF. The SENSIC trial was a phase 3 RCT that investigated the efficacy of nintedanib versus placebo in 576 people with SSC-ILD.10 Enrollment did not require evidence of disease progression but included...
only people who had fibrosis affecting at least 10% of the lungs on baseline HRCT. The primary endpoint, annual rate of decline in FVC over 52 weeks, was lower in the nintedanib arm (difference 41.0 (2.9 to 69.0) mL/year). INBUILD, another phase 3 RCT of nintedanib versus placebo, expanded inclusion criteria to any non-IPF progressive fibrosing ILD.\textsuperscript{12} Enrollment required meeting the study criteria for progressive fibrosis, based on FVC decline, or a combination of worsening FVC, symptoms, or imaging findings. The primary endpoint of annual rate of decline in FVC over 52 weeks was again lower in the nintedanib arm (difference 107 (65.4 to 148.5) mL/year). The difference was greater for the nearly two thirds of participants with a radiographic pattern of UIP (difference 128.2 (70.8 to 185.6) mL); however, a definitive treatment effect could not be inferred for other radiographic patterns of fibrosis.

Nearly half of the participants in the SENSCIS trial (48.5%) were concurrently taking mycophenolate mofetil, and subgroup analysis found no heterogeneity in nintedanib’s treatment effect according to baseline mycophenolate mofetil use.\textsuperscript{10} \textsuperscript{142} Although the absolute reduction in FVC decline associated with nintedanib use was less in participants taking mycophenolate mofetil, the relative reduction in FVC decline was similar in those taking and those not taking mycophenolate mofetil (40% v 46%). Notably, participants receiving mycophenolate mofetil and placebo had a similar adjusted mean annual rate of FVC decline to those receiving nintedanib alone (−66.5 v −63.9 mL/year); however, the authors note that this comparison was out of the scope of the trial. The INBUILD trial excluded people who were receiving concomitant immunosuppression for ILD.

Pirfenidone

The data supporting pirfenidone in PPF are less robust. Pirfenidone was studied in two completed phase 2/2b RCTs. The first enrolled 253 people with unclassifiable ILD, including those with dermatomyositis with autoimmune features, and evidence of progressive loss of lung function.\textsuperscript{15} The primary endpoint used home spirometry and provided unreliable results that could not be analyzed. The secondary outcome, using on-site spirometry, compared the mean decline in FVC over 24 weeks and showed a treatment difference favoring pirfenidone over placebo (difference 95.3 (35.9 to 154) mL; \textit{P}=0.002). The RELIEF study enrolled only 127 of the planned 374 people with PPF, including those with CTD-ILD, cHP, iNSIP, and asbestos induced lung fibrosis.\textsuperscript{90} The trial was terminated early owing to slow enrollment and for futility. The result was that 47% of participants, in both arms, had imputed data. Despite being underpowered by early termination, when imputed data were included, the primary endpoint of absolute change in FVC in per cent predicted from baseline to 48 weeks was lower in participants taking pirfenidone (\textit{P}=0.049). The median difference in change in FVC per cent predicted per year ranged from 1.69% to 3.53%, depending on the test used. The finding remained significant on multiple sensitivity analyses. Although the analysis of the primary outcome performed without imputation was not statistically significant, these findings may be clinically relevant. Clinical trials of both pirfenidone and nintedanib that are ongoing in a variety of PPF subsets are noted in table 3.

Gaps in knowledge in management of PPF

Identifying and treating PPF

Recognition of a progressive fibrosing phenotype of ILD is important to both treatment strategies and prognosis. However, before May 2022, the diagnosis of PPF had been hampered by the lack of established clinical criteria and biomarkers. Additionally, the proposed criteria do not account for time from disease onset and may identify early inflammatory
disease without a progressive fibrosing phenotype. Early decline in FVC in inflammatory ILDs may be remediated with immunosuppressive treatment, and a progressive fibrosing phenotype may never occur despite the proposed criteria being met early in the course of disease. Nevertheless, this needs to be balanced with the consideration that earlier treatment directed toward fibrosis may help to preserve lung function in patients who ultimately develop a progressive phenotype.

When immunosuppressive treatment is efficacious in inflammatory ILDs, it is continued. When an inflammatory ILD has progressive fibrosis despite immunosuppression, the question is whether to escalate immunosuppressive therapy or to start treatment with an antifibrotic drug such as nintedanib. Treatment decisions should consider the time from disease onset, as immunosuppressive therapies may be more likely to be effective early in the disease course. The prospective trials of immunosuppressive treatments for SSc-ILD recruited people early in the disease course and showed stabilization of lung function with cyclophosphamide, mycophenolate, or tocilizumab. Acute and subacute cases of hypersensitivity pneumonitis may resolve with antigen avoidance with or without a short course of corticosteroids. However, once cHP develops and fibrotic features are present on imaging, five year mortality is similar to that of IPF at 50%. In this setting, immunosuppressive therapy is unlikely to be beneficial and treatment with antifibrotics should be offered. Similarly, in CTD-ILD, antifibrotics should be strongly considered once progressive fibrosis has been established. Whether immunosuppression should continue when antifibrotic therapy is introduced also remains unclear. Although it is associated with worse outcomes in IPF, data in SSc-ILD from the SENSCIS trial suggest that treatment with combined immunosuppression and antifibrotic therapy may be advantageous.

### Biomarkers

Given the complex and multicellular pathobiology of pulmonary fibrosis, defining disease endotypes that can be identified by patterns of clinical characteristics, radiologic features, and biomarkers is important. These endotypes can then be used to guide initial therapy and to modify treatment over time. The recognition of PPF creates a further need to develop biomarkers of progressive disease. A comprehensive review of diagnostic and prognostic biomarkers was recently published. Of the many studies examining biomarkers, most are observational and retrospective in design and few have been validated in separate prospective cohorts. For these reasons, biomarkers are infrequently used in clinical practice. Single cell RNA sequencing and spatial transcriptomic studies conducted on explanted lungs obtained at the time of transplant when fibrosis is well established suggest relatively little heterogeneity between pulmonary fibrosis with differing initiating factors. These findings suggest the need to obtain samples from patients with early disease to guide the selection of initial therapy and monitor the response to therapy over time.

The first large prospective study to evaluate biomarkers in IPF examined serum specimens from the PROFILE cohort, a longitudinal cohort of treatment-naive patients with IPF. After measuring 123 serum proteins, the investigators focused on surfactant protein D (SFTPDP), matrix metalloproteinase-7 (MMP7), CA19-9 (ST6GALNAC6), and CA-125 (MUC16). Including the discovery and validation phases of the trial, the study included 312 participants with IPF (145 with stable disease and 155 with progressive disease at follow-up) and 50 healthy controls. Although MMP7 was higher in patients with IPF compared with controls, it did not predict disease progression or mortality. SFTPDP had higher discriminatory power for distinguishing IPF from healthy controls and identifying patients at high risk of progression. Although neither CA19-9 nor CA-125 could distinguish disease from controls, CA19-9 was most highly predictive of progressive fibrosis, and increasing concentrations of CA-125 predicted both disease progression and overall survival. As CA19-9 and CA-125 are relatively new markers in IPF, immunohistochemical localization of these markers was done in control and fibrotic lung tissue to ensure relevance to lung disease. CA19-9 and CA-125 were present in the apical bronchial epithelium in normal lungs, whereas in the fibrotic lung these markers were seen throughout the metastatic epithelium in fibrotic lesions.

The largest study to examine biomarkers in non-IPF ILD is a retrospective study in 148 people with CTD-ILD, 98 with cHP, and 159 with unclassifiable ILD. Six biomarkers of interest were evaluated with the primary endpoint of progression-free survival defined as survival without lung transplant or ≥10% decline in FVC over two years. The investigators found that increased serum concentrations of CXCL13 were associated with decreased survival in all three disease subgroups, but the optimal threshold concentration varied substantially between subgroups. CXCL13 is a chemokine that is chemotactic for B lymphocyte migration, and increased concentrations have been associated with ectopic germinal centers in autoimmune disease. The authors speculate that the CXCL13 threshold variability may reflect different underlying biology, with inflammatory phenotypes of ILD having a higher baseline concentration overall, and therefore may indicate that CXCL13 could be useful in identifying a population of patients responsive to immunosuppression.

Genetic biomarkers may identify patients at increased risk for pulmonary fibrosis and predict disease progression. Patients with heterozygous mutations of either the TERT gene or the TERC gene, which are part of the telomerase complex genes, are at increased risk of IPF, as are those with shortened
telomeres. Although the use of telomere length testing in patients with suspected familial forms of idiopathic ILD varies in clinical practice, no formal recommendations on its use exist. A single nucleotide polymorphism (SNP) in the promoter region of the MUC5B gene (rs35705950) that increases the expression of the gene is associated with the development of IPF but has unclear effects on disease severity and survival. Three SNPs in the TOLLIP gene have also been associated with IPF. TOLLIP encodes toll interacting proteins that are linked to the lung’s immune responses, including modulation of TGF-β signaling. Post hoc genotyping of TOLLIP and MUC5B was performed on previously collected samples from people enrolled in the PANTHER trial and identified polymorphisms within these genes were suggested to modify the effect of treatment with N-acetylcysteine or immunosuppression. The results of this analysis were used to support further investigation of N-acetylcysteine in IPF patients with the TOLLIP rs3750920 TT genotype through the PRECISION trial (NCT04300920).

**Emerging therapies and diagnostics**

**Advanced diagnostics**

Newer methods that exploit advances in transcriptomics and proteomics may not only advance our understanding of the pathology of fibrosing lung diseases but may also serve to improve the utility of biomarkers. They offer a personalized approach to the management of PPF by eliciting the specific biologic pathways that are active at a given point in time and thereby might facilitate targeted therapy. Machine learning tools offer promise to iteratively improve the predictive power of these information-rich multi-omics data by incorporating detailed clinical and imaging metadata, including the response to therapy.

Currently available for clinical use, the Envisia Genomic Classifier (EGC) was developed using machine learning methods applied to eXome enriched RNA sequencing data from whole lung biopsies (bulk RNA) in combination with histologically confirmed diagnoses. The product of this is an algorithm that differentiates UIP from non-UIP histologic patterns by recognizing the transcriptomic signature of UIP. This classifier was validated using an independent dataset in the BRAVE studies. In these studies, samples were obtained from 84 people with suspected ILD undergoing planned, clinically indicated lung biopsy procedures. The transcriptome analysis showed that biopsy samples histologically classified as UIP were enriched for gene expression pathways associated with cellular metabolism, adhesion, and developmental processes. However, samples histologically classified as non-UIP showed gene expression pathways associated with immune activities, lipid metabolism, stress response, and cell death. Using the developed algorithm and a single transbronchial lung biopsy sample to distinguish UIP from non-UIP histologic patterns, the EGC had a sensitivity of 63% (95% confidence interval 51% to 74%) and a specificity of 86% (71% to 95%). If three to five samples were used, the sensitivity improved to 74% (51% to 90%) and specificity improved to 93% (68% to 100%). The EGC has now been validated in an additional study using the BRAVE cohort, which found that it had a negative predictive value of 60.3% (46.6% to 73.0%) and a positive predictive value of 92.1% (78.6% to 98.3%) for histology proven UIP.

The EGC identifies a transcriptomic pattern associated with histologic UIP in patients with indeterminate radiographic patterns. This does not equate to a diagnosis of IPF. Rather, the results from EGC are an additional piece of data that can be incorporated into a multidisciplinary discussion to achieve a consensus diagnosis. The ECG has also not yet been studied in PPF. However, future studies to evaluate the use of transcriptomic tools to identify or predict progressive fibrosis and predict response to antifibrotics in this patient population may be instrumental in developing precise therapeutic targets.

Bulk RNA sequencing like that used in the EGC provides an average measure of gene expression across the heterogeneous cell populations that make up the lung. This creates a problem of averaging in which a change in cellular composition (for example, an increased number of inflammatory cells) can drive changes in average gene expression and biologically important signals in cell populations or subpopulations can be missed. Single cell RNA sequencing avoids these problems by measuring gene expression within each individual cell, allowing one to compare cell populations—for example, alveolar type 2 cells—in health and disease. In addition to identifying biomarkers, single cell RNA sequencing allows one to generate hypotheses about which cellular interactions drive fibrosis and can be targeted pharmacologically. Although still too costly and time consuming for clinical practice, single cell RNA sequencing has become an invaluable discovery tool, particularly when applied to small samples from patients with early disease, including those obtained by bronchoscopic lavage or biopsy.

**Registries**

Along with improved tools for exploring the pathology of IPF and PPF, several national and international ILD registries are enrolling people. Registries differ from clinical trials in that they are large, they allow for prolonged follow-up time, and enrollment is inclusive and thus more reflective of the general population of patients with a given disease. Participants should be well characterized as to important clinical features of their disease. Insights derived from registries complement clinical trials and may answer questions about the long term effectiveness of treatments. Current registries will need to be expanded to accommodate digitized images and genomic data that will facilitate the training of multimodal machine learning classifiers to predict disease endotypes and responsiveness to therapy.
Resolution of fibrosis

IPF and PPF are characterized by self-sustaining fibrosis and progressive decline in lung function. The therapies approved and undergoing phase 3 clinical trials for the treatment of IPF and PPF have been shown only to slow decline in lung function, and none has shown resolution of fibrosis. However, growing evidence suggests that fibrosis may be reversible, particularly with removal of the underlying cause of injury. A recent review covered the biology of self-sustaining fibrosis and emphasized three processes necessary for resolution of fibrosis—elimination of matrix producing cells, clearance of excess matrix, and regeneration of normal tissue constituents.

Metformin has been found to ameliorate pulmonary fibrosis in bleomycin induced mouse models of lung fibrosis. Metformin inhibits mitochondrial complex 1 to activate adenosine monophosphate activated protein kinase (AMPK), which subsequently inhibits TGF-β. Metformin is able to normalize myofibroblast sensitivity to apoptosis and stimulate turnover of collagen via AMPK dependent activation of autophagy. By eliminating matrix producing myofibroblasts and promoting the clearance of excess matrix, metformin, or other AMPK activators, may be able to reverse established fibrosis. Notably, however, when patients who were randomized to placebo in the CAPACITY and ASCEND trials of pirfenidone were stratified by baseline metformin use, no significant difference in disease progression associated with metformin use was seen. One potential reason for the discrepancy between these findings and experimental studies may be the high doses (65-300 mg/kg) of metformin and intraperitoneal route used in the mouse models.

The resolution of fibrosis requires not only breaking the positive feed-forward loops that sustain and amplify fibrosis but also regenerating normal tissue to occupy the area of former fibrosis. Alveolar type 2 cells are a partially committed stem cell population in the adult lung that undergo asymmetric division and differentiation to replace damaged alveolar type 1 cells; however, when alveolar type 2 cells are isolated from IPF lung tissue they have impaired regenerative ability compared with healthy tissue. In single cell RNA sequencing data from lung explants from patients with pulmonary fibrosis, investigators have noted the emergence of a population of epithelial cells characterized by expression of high concentrations of keratin-5 and increased levels of keratin-17. These cells also express high levels of genes associated with senescence, including p16 (CDKN2A), p21 (CDKN1A), and plasminogen activator inhibitor 1 (SERPINE1), among others. A transcriptionally similar population of cells has been observed in murine models of pulmonary fibrosis and in a murine model of alveolar regeneration after pneumonectomy. All of these studies, these cells are characterized by increased expression of keratin-8, along with similar senescence associated genes. All three initial reports of these cells showed them to be a transitional cell population that forms during the differentiation of alveolar type 2 to type 1 cells. Strunz and colleagues showed that, during bleomycin induced fibrosis, these cells develop a transcriptomic signature suggestive of activation of the integrated stress response during their differentiation. This is of interest because inhibitors of the integrated stress response have been shown to reduce fibrosis in animal models.

Watanabe and colleagues followed up on these results, showing that a small molecule inhibitor of the integrated stress response, ISRIB, accelerated the differentiation of alveolar type 2 cells into alveolar type 1 cells during fibrosis, reducing the number of keratin-8 positive cells. This suggests that a decline in the function of the proteostasis network, as occurs during aging in model organisms, might impair the differentiation of alveolar type 2 cells, predisposing to the development of fibrosis. Future studies are needed to determine whether the emergence of keratin-17 cells explains some of the increase in senescence markers observed in lung fibrosis.

Guidelines

Table 4 summarizes the most recent guidelines from the leading international societies on the management of idiopathic pulmonary fibrosis and highlights some of the key commonalities and differences between the recommendations. The ATS/ERS/JRS/ALAT clinical practice guidelines published in 2011 were updated in 2015 and 2022. The JRS published a separate clinical practice guideline in 2018, which provided additional recommendations not previously included in the 2015 joint guidelines. Specifically, for patients experiencing an acute exacerbation of IPF, they recommend against the use of polymyxin B (weak recommendation, low quality of evidence), neutrophil elastase inhibitors (weak recommendation, very low quality of evidence), and recombinant thrombomodulin (weak recommendation, low quality of evidence) and recommend the use of immunosuppressant drug therapy (weak recommendation, low quality of evidence).

NICE guidelines on the diagnosis and management of IPF were published in 2013 and last updated in 2017. As seen in table 4, NICE guidelines have minor differences from the ATS/ERS/JRS/ALAT guidelines, which may reflect the fact the NICE Guideline Development Group is required to make decisions based on the best available evidence of both clinical effectiveness and cost effectiveness. The TSANZ and the LFA published a position statement on the treatment of IPF in 2017, which differs from the ATS/ERS/JRS/ALAT guidelines in its recommendation to use disease severity to guide decisions on antifibrotic therapy and its neutral stance on antacid therapy.

The first international guidelines on the treatment of PPF came in May 2022 with the ATS/ERS/JRS/ALAT clinical practice guideline. This guideline suggested nintedanib for the treatment of PPF in patients who have not responded to standard management for...
A comparison of guideline recommendations from ATS/ERS/JRS/ALAT, JRS, NICE, and TSANZ/LFA for treatment of idiopathic pulmonary fibrosis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Overall consensus</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirfenidone, nintedanib</td>
<td>For</td>
<td>The ATS/ERS/JRS/ALAT 2015 updated guidelines and JRS updated 2018 guidelines recommend the use of pirfenidone and nintedanib. The ATS/ERS/JRS/ALAT recommendations note that available evidence focuses on patients with mild to moderate impairment in FVC and that whether whether patients with more severe impairment benefit is unknown. NICE and TSANZ/LFA specifically recommend the use of pirfenidone and nintedanib only in patients with mild to moderate IPF. NICE also specifies that these therapies are recommended only if the manufacturing company provides a discounted price and that treatment should be stopped if evidence of disease progression exists (absolute decline of ≥10% in FVC % predicted within a 12 month period). TSANZ/LFA guidelines recommend that patients with severe IPF (FVC &lt;50%) should consider clinical trials rather than pirfenidone or nintedanib.</td>
</tr>
<tr>
<td>Steroids for acute exacerbations of IPF</td>
<td>For/neutral</td>
<td>The ATS/ERS/JRS/ALAT 2011 guidelines make a weak recommendation for the use of steroids in AE-IPF and the question was not re-addressed in the 2015 update. The JRS 2018 guidelines also recommend the use of steroids in AE-IPF. TSANZ/LFA guidelines state that no controlled trial data support the use of steroids for AE-IPF. NICE recommendations do not consider the use of steroids in this context.</td>
</tr>
<tr>
<td>Antacid therapy</td>
<td>Against/neutral</td>
<td>The ATS/ERS/JRS/ALAT 2022 updated guidelines make a conditional recommendation against the use of antacid therapy for the purpose of improving respiratory outcomes. The TSANZ/LFA guidelines state that the benefit of antacid therapy is unclear and do not make a recommendation for or against its use. NICE recommends management of GERD according to normal best practice.</td>
</tr>
<tr>
<td>Steroid monotherapy to modify disease</td>
<td>Against</td>
<td>ATS/ERS/JRS/ALAT and NICE guidelines recommend against the use of steroid monotherapy. TSANZ/LFA guidelines do not consider the use of steroids in this context.</td>
</tr>
<tr>
<td>Combination of prednisone, azathioprine, and</td>
<td>Against</td>
<td>ATS/ERS/JRS/ALAT, NICE, and TSANZ/LFA guidelines all recommend against the use of combination prednisone, azathioprine, and N-acetylcysteine.</td>
</tr>
<tr>
<td>N-acetylcysteine monotherapy</td>
<td>Against/neutral</td>
<td>ATS/ERS/JRS/ALAT and TSANZ/LFA guidelines recommend against the use of N-acetylcysteine. NICE guidelines state that it has unclear benefit.</td>
</tr>
<tr>
<td>Anticoagulation (warfarin)</td>
<td>Against</td>
<td>ATS/ERS/JRS/ALAT, NICE, and TSANZ/LFA guidelines all recommend against the use of warfarin, unless otherwise indicated.</td>
</tr>
<tr>
<td>Vasodilator therapy (ambisentan, bosentan,</td>
<td>Against</td>
<td>ATS/ERS/JRS/ALAT, NICE, and TSANZ/LFA guidelines all recommend against the use of ambisentan, bosentan, macitentan, and sildenafil in IPF patients with or without pulmonary hypertension. ATS/ERS/JRS/ALAT guidelines make a strong recommendation against the use of imatinib. The NICE and TSANZ/LFA guidelines do not make any recommendations for or against its use.</td>
</tr>
<tr>
<td>Immunomodulatory therapy</td>
<td>Against</td>
<td>The ATS/ERS/JRS/ALAT 2011 guidelines make a strong recommendation against the use of combination steroids and immunomodulatory therapy (eg, azathioprine or cyclophosphamide). NICE also recommends against the use of azathioprine and mycophenolate mofetil. TSANZ/LFA does not make a recommendation for or against the use of immunomodulatory therapies. JRS 2018 guidelines recommend the use of immunomodulatory agents for the treatment of AE-IPF.</td>
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<tr>
<td>Non-drug management</td>
<td></td>
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<tr>
<td>Long term oxygen therapy</td>
<td>For</td>
<td>ATS/ERS/JRS/ALAT, NICE, and TSANZ/LFA guidelines all recommend long term oxygen therapy in patients with IPF who have significant resting hypoxemia.</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>For</td>
<td>ATS/ERS/JRS/ALAT, NICE, and TSANZ/LFA guidelines all recommend referral to pulmonary rehabilitation programs for most patients with IPF. NICE specifies that the decision to refer to pulmonary rehabilitation should be based on 6 minute walk test parameters and quality of life assessment.</td>
</tr>
<tr>
<td>Lung transplant referral</td>
<td>For</td>
<td>ATS/ERS/JRS/ALAT, NICE, and TSANZ/LFA guidelines all recommend referral for lung transplant evaluation based on patient preference and clinical appropriateness.</td>
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</table>

**Conclusion**

Tremendous advances have been made in elucidating the biologic processes that promote and sustain pulmonary fibrosis. The recognition that ILDs other than IPF may also have a progressive fibrosing phenotype has also been instrumental in moving forward the treatment options for patients with PPF and conceptualizing how to best manage these patients in the future. Importantly, nintedanib has been shown to slow progression of disease in patients with PPF, and several ongoing clinical trials are examining whether pirfenidone may also be beneficial. Several promising therapies are in the pipeline that may offer novel ways of treating IPF that could potentially be used instead of or in addition to the currently available antifibrotics. However, significant gaps in knowledge surrounding the treatment of IPF and PPF remain. Notably, we lack biomarkers and other diagnostic tests that can be used early in the disease course (before functional decline is present) to determine when patients with PPF may benefit from antifibrotics. Additionally, more studies are necessary to examine whether antifibrotics should be used in lieu of or in addition to immunosuppression when no extrapulmonary indications for immunosuppressive therapy are present. The essential question of whether and how established fibrotic disease can actually be reversed and normal lung tissue and function restored also remains. Future research must consider these questions to continue advancing the care for patients with these devastating diseases.
STATE OF THE ART REVIEW

GLOSSARY OF ABBREVIATIONS

- ALAT—Latin American Thoracic Association
- AMPK—adenosine monophosphate activated protein kinase
- ATS—American Thoracic Society
- cHP—chronic hypersensitivity pneumonitis
- CTD-ILD—connective tissue disease associated ILD
- CGF—connective tissue growth factor
- DlCO—diffusing capacity for carbon monoxide
- EGC—Envisia Genomic Classifier
- ERS—European Respiratory Society
- FDA—Food and Drug Administration
- FGFR—fibroblast growth factor receptor
- FVC—forced vital capacity
- HRCT—high resolution computed tomography
- ILD—interstitial lung disease
- iNSIP—idiopathic nonspecific interstitial pneumonia
- iPF—idiopathic pulmonary fibrosis
- IJS—Japanese Respiratory Society
- LFA—Lung Foundation of Australia
- M-CSF—macrophage colony stimulating factor
- MMP7—matrix metalloproteinase-7
- NICe—National Institute for Health and Care Excellence
- NSIP—nonspecific interstitial pneumonia
- PDGF—platelet derived growth factor
- PDGFR—platelet derived growth factor receptor
- PF-ILD—progressive fibrosing interstitial lung disease
- PPF—progressive fibrosing interstitial lung disease
- RA-ILD—rheumatoid arthritis associated ILD
- RCTs—randomized controlled trials
- rhPTX-2—recombinant human pentraxin 2
- SFTP-D—surfactant protein D
- SNP—single nucleotide polymorphism
- SSCS-ILD—systemic sclerosis associated ILD
- TGF-β—transforming growth factor
- TSANZ—Thoracic Society of Australia and New Zealand
- UIP—usual interstitial pneumonia

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RESEARCH QUESTIONS

- What drives progressive pulmonary fibrosis in patients with interstitial lung disease (ILD)?
- Do biomarkers exist that can predict which patients with ILD will develop progressive pulmonary fibrosis before they have lung function decline?
- What is the optimal timing for starting antifibrotics in patients with non-idiopathic pulmonary fibrosis fibrotic? Should antifibrotics be started only after patients have shown progression on immunosuppression?
- Should immunosuppression be continued in patients with progressive pulmonary fibrosis who start treatment with antifibrotics?
- Do therapies exist that can reverse or resolve pulmonary fibrosis?

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Pirfenidone in patients with idiopathic pulmonary fibrosis (IPF) remains a cornerstone treatment, but its exact role in the pathogenesis of IPF is not fully clarified. Here, we review the current understanding of the cellular and molecular mechanisms that underlie disease progression in IPF, and discuss the potential for novel therapeutic strategies to further improve outcomes for these patients. 

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Antioxidative and clinical effects of high-dose N-acetylcysteine


STATE OF THE ART REVIEW


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