

Therapeutic Approach to Adult Fibrotic Lung Diseases



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Among the interstitial lung diseases (ILDs), idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonitis, and fibrotic connective tissue disease-related ILD are associated with a worse prognosis, with death occurring as a result of both respiratory failure and serious associated comorbidities. The recent development and approval of the antifibrotic agents nintedanib and pirfenidone, both of which reduced the rate of decline in lung function in patients with IPF in clinical trials, offer hope that it may be possible to alter the increased mortality associated with IPF. Although chronic hypersensitivity pneumonitis and connective tissue disease-related-ILD may be associated with an inflammatory component, the evidence for the use of immunosuppressive agents in their treatment is largely limited to retrospective studies. The lack of benefit of immunosuppressive therapy in advanced fibrosis argues for rigorous clinical trials using antifibrotic therapies in these types of ILD as well. Patients with fibrotic ILD may benefit from identification and management of associated comorbid conditions such as pulmonary hypertension, gastroesophageal reflux, and OSA, which may improve the quality of life and, in some cases, survival in affected individuals. Because early assessment may optimize posttransplantation outcomes, lung transplant evaluation should occur early in patients with IPF and those with other forms of fibrotic ILD. CHEST 2016; 150(6):1371-1386

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Interstitial lung diseases (ILDs) are a diverse group of parenchymal pulmonary disorders characterized by varying degrees of inflammation and fibrosis. When pulmonary fibrosis predominates, ILDs are especially challenging to manage and treat.

Idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonitis (cHP), and connective tissue disease-related ILD

(CTD-ILD) are associated with significant mortality.¹⁻³ Other less well-characterized types of fibrotic ILD include fibrotic nonspecific interstitial pneumonia and interstitial pneumonia with autoimmune features, with a usual interstitial pneumonia (UIP) pattern. Although a conservative approach to management has been advocated in early or mild ILD,

ABBREVIATIONS: cHP = chronic hypersensitivity pneumonitis; CTD-ILD = connective tissue disease-related ILD; DLCO = diffusion capacity of the lung for carbon monoxide; FDA = US Food and Drug Administration; HR = hazard ratio; HRCT = high-resolution CT; IIM = idiopathic inflammatory myopathy; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MSC = mesenchymal stem cells; NAC = N-acetylcysteine; PH = pulmonary hypertension; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; SGRQ = St. George's Respiratory Questionnaire; SSC-ILD = systemic sclerosis-associated interstitial lung disease; TGF- β = transforming growth factor- β ; UIP = usual interstitial pneumonia

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antiinflammatory and immunosuppressive therapies are considered and often prescribed when progression of CTD-ILD and cHP occurs despite the largely unproven efficacy in these disorders. A recently completed trial comparing mycophenolate mofetil with oral cyclophosphamide in systemic sclerosis-associated interstitial lung disease (SSc-ILD) showed noninferiority with mycophenolate mofetil.⁴ Two novel antifibrotic agents, nintedanib and pirfenidone, which slowed lung function decline and disease progression in patients with IPF and mild to moderate lung disease, are now approved for the treatment of IPF, a generally progressive and fatal disorder. No strong recommendations can be made regarding the use of nintedanib or pirfenidone in cHP or fibrotic CTD-ILD until the safety and efficacy of these agents are formally evaluated in such populations. Adjunct therapies for patients with fibrotic ILD include oxygen to correct hypoxemia and the identification and treatment of comorbidities.

The present article reviews the most recent advances in the clinical management and medical therapy for the three common fibrotic ILDs: IPF, cHP, and CTD-ILD.

Idiopathic Pulmonary Fibrosis

IPF, the most prevalent idiopathic interstitial pneumonia, has a median survival of 3 to 5 years from diagnosis.^{1,5,6} Although its etiology remains unknown, potential risk factors for IPF include cigarette smoking, gastroesophageal reflux, and certain environmental exposures.⁷ Its pathophysiology is currently believed to involve epithelial injury with abnormal wound healing. The initial conception of the pathogenic process in IPF as partially inflammatory resulted in consideration of broad immunosuppression as a potential therapy. However, the Prednisone, Azathioprine and N-Acetylcysteine: A Study That Evaluates Response in IPF (PANTHER) trial showed that prednisone, azathioprine, and N-acetylcysteine (NAC) resulted in increased mortality compared with placebo.⁸ In addition, NAC alone was not beneficial in patients with IPF who had mild to moderate impairment of lung function.⁹ These studies demonstrated the necessity and ability of well-designed clinical trials to elucidate the safety and efficacy of therapy in IPF. More recently, clinical trials have focused on therapies that attenuate fibrosis.

Pirfenidone

Pirfenidone is an oral agent recently approved by the US Food and Drug Administration (FDA) for the treatment

of IPF (Table 1). It is a pyridone analogue with multiple potential mechanisms of action, including the inhibition of cytokines that play key roles in fibrosis and inflammation such as transforming growth factor- β (TGF- β) and tumor necrosis factor- α .¹⁰⁻¹³ Oral administration results in peak serum concentrations at 30 min in fasting older adults or approximately 4 h when taken with food; its mean elimination half-life approaches 2.4 h.^{14,15}

Five randomized, double-blind, placebo-controlled trials have evaluated the clinical efficacy and safety of pirfenidone in patients with IPF. The first such Phase 2 trial showed that patients treated with pirfenidone 1,800 mg/d experienced a significant reduction in the decline of their vital capacity at 9 months and were free of IPF exacerbations.¹⁶ These findings prompted a Phase 3 clinical trial¹⁷ using different doses of pirfenidone that reported a significantly reduced decline in the vital capacity of patients taking the highest dose of pirfenidone compared with placebo. Progression-free survival defined as time until death and/or $\geq 10\%$ decline in vital capacity was greater in the pirfenidone group. These studies led to the approval of pirfenidone for the treatment of IPF in Japan in 2008.¹⁸

Two similarly designed international Phase 3 trials (Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes) [CAPACITY] 004 and 006) were conducted in North America, Europe, and Australia (Table 2).^{19,20} In CAPACITY-004, patients treated with pirfenidone 2,403 mg/d had a significantly reduced decline in percent predicted FVC of -8.0% vs -12.4% in the placebo group at 72 weeks. CAPACITY-006 found no significant difference in change in FVC between these groups. The decline in the 6-min walk test was significantly reduced in patients taking 2,403 mg/d in the pooled analysis of both trials. Assessment of data from both CAPACITY and the Japanese trials led to the approval of pirfenidone in the European Union in 2011.²¹

The FDA requested an additional study to support the approval of pirfenidone for use in IPF, which led to the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) trial²² (Table 2). This trial used a modified study design with a centralized confirmation of diagnosis that included review of all high-resolution CT (HRCT) scans and a lung biopsy if the CT scan showed possible rather than definite UIP. The eligibility criteria were also modified to enroll patients at a higher risk of disease

TABLE 1] Potential Therapies for Fibrotic Interstitial Lung Disease

Disease	Medication	Dose	Mechanism of Action
Idiopathic pulmonary fibrosis	Nintedanib	150 mg bid	Kinase inhibitor; inhibition of VEGFR 1-3, FGFR 1-3, PDGFR α and β
	Pirfenidone	801 mg tid	Possible inhibition of transforming growth factor- β and tumor necrosis factor- α
Chronic hypersensitivity pneumonitis	Prednisone	0.5-1 mg/kg/d up to 60 mg/d, then tapered to lowest effective dose	Inhibition of multiple inflammatory cytokines
Connective tissue disease-associated	Prednisone	0.5-1 mg/kg/d up to 60 mg/d Doses > 20 mg/d are not advised in SSc	Inhibition of multiple inflammatory cytokines
	Azathioprine	1.5-2 mg/kg/d	Purine antagonist; inhibition of cellular and humoral immunity
	Cyclophosphamide	1-2 mg/kg/d po or 500-1,000 mg IV every 4 wk	Alkylating agent; crosslinks DNA
	Mycophenolate mofetil	1,000 mg bid up to 3,000 mg/d	Inhibition of B- and T-lymphocyte proliferation
	Rituximab	1,000 mg IV, repeat in 2 wk	Monoclonal antibody which binds and depletes B-lymphocyte CD20
	Tacrolimus	1 mg bid titrated by 1 mg based on trough levels	Calcineurin inhibitor; inhibits activation of T-lymphocytes

All these medications are given by mouth unless otherwise indicated. FGFR = fibroblast growth factor receptor; PDGFR = platelet-derived growth factor receptor; SSc = systemic sclerosis; VEGFR = vascular endothelial growth factor receptor.

progression than those in the CAPACITY trials by allowing a lower diffusion capacity of the lung for carbon monoxide (DLCO) of 30% rather than 35% predicted and requiring a FEV₁/FVC ratio > 0.80. This study reported a smaller mean decline from baseline in FVC of -235 mL in those receiving pirfenidone compared with -428 mL in the placebo group ($P < .001$) at 52 weeks. A reduction was noted in the proportion of patients with a $\geq 10\%$ decline in the percent predicted FVC or death in the pirfenidone vs placebo groups. Patients in the pirfenidone group also had a significantly improved progression-free survival (defined as time to first occurrence of a $\geq 10\%$ reduction in the percent predicted FVC, decrease in the 6-min walk test of ≥ 50 m, or occurrence of death) and a significantly smaller decline in their 6-min walk test over the 1-year period compared with placebo. There were no significant differences in dyspnea, all-cause mortality, or IPF-related mortality. Major side effects of pirfenidone compared with placebo included nausea, vomiting, dyspepsia, anorexia, and skin rash.

A pooled population of 1,247 patients enrolled in the ASCEND and both CAPACITY trials was analyzed for all-cause mortality by using prespecified criteria. A significant reduction in IPF-related mortality (hazard

ratio [HR], 0.35 [95% CI, 0.17 to 0.72]; $P = .0029$) and all-cause mortality (HR, 0.52 [95% CI, 0.21 to 0.87]; $P = .0107$) was noted at 52 weeks with the use of pirfenidone compared with placebo.²³ Utilizing data from the same cohort, Nathan et al²⁴ evaluated the effect of continued treatment with pirfenidone in those patients who had experienced a $\geq 10\%$ decline in FVC by month 6. Analysis of longitudinal FVC data and mortality during the subsequent 6 months demonstrated that the pirfenidone group had fewer patients with a $\geq 10\%$ decline in FVC or death compared with the placebo group (5.9% vs 27.9%; $P = .009$; relative difference, 78.9%). Their findings suggest that patients with IPF, who exhibit meaningful disease progression despite treatment, may benefit from continued treatment with pirfenidone. In the PANORAMA study, Behr et al²⁵ assessed the safety and tolerability of combination therapy with pirfenidone and NAC in patients with IPF. This randomized, double-blind, multicenter trial evaluated 123 patients with IPF who were established on pirfenidone therapy and assessed the effect of concomitant therapy with oral NAC or placebo. The investigators found that the occurrence of adverse events related to study treatment, the number of patients experiencing severe adverse events, and the number of life-threatening adverse

TABLE 2] Recent Trials in Fibrotic Interstitial Lung Disease

Disease	Trial/Medication	Primary End Point/Objective	Outcomes
Idiopathic pulmonary fibrosis	CAPACITY-004 (PIPF004) ¹⁹ [Pirfenidone 2,403 mg/d vs 1,197 mg/d vs placebo]	Change in FVC at 72 wk	Pirfenidone 2,403 mg/d significantly reduced decline in FVC
	CAPACITY-006 (PIPF006) ¹⁹ [Pirfenidone 2,403 mg/d vs placebo]	Change in FVC at 72 wk	No significant difference between groups
	ASCEND ²² [Pirfenidone 2,403 mg/d vs placebo]	Change in FVC at 52 wk	Pirfenidone significantly reduced decline in FVC, significantly improved progression-free survival
	RECAP ²⁶ [Pirfenidone 2,403 mg/d]	Long-term safety and tolerability	Pirfenidone was safe and generally well tolerated
	Loeh et al ²⁰ [Retrospective comparison of pirfenidone vs historical control subjects]	Treatment-elicited changes in lung function	Reduction in annual decline in FVC after initiation of pirfenidone
	TOMORROW ³² [Nintedanib 50 mg/d vs 50 mg bid vs 100 mg bid vs 150 mg bid vs placebo]	Rate of decline in FVC at 12 mo	Trend toward a reduced decline in lung function and fewer acute exacerbations with 150 mg bid
	INPULSIS-1 ^{33,34} [Nintedanib 150 mg bid vs placebo]	Rate of decline in FVC at 52 wk	Reduced FVC decline with nintedanib
Connective tissue disease-interstitial lung disease	INPULSIS-2 ^{33,34} [Nintedanib 150 mg bid vs placebo]	Rate of decline in FVC at 52 wk	Reduced FVC decline; increased time to first acute exacerbation
	Costabel et al. ³⁶ [Prespecified subgroup analyses of pooled data from INPULSIS-1 and -2]	Treatment effect of nintedanib	Nintedanib had a consistent effect on slowing disease progression across several prespecified subgroups
	SLS ^{68,69} [Cyclophosphamide ≤ 2 mg/kg/d vs placebo]	Percent predicted FVC at 12 mo, after adjusting for baseline FVC	Modest benefit on FVC, dyspnea, skin thickening, and quality of life with cyclophosphamide
	EUSTAR Rituximab study ⁷⁶ [Retrospective comparison of rituximab with control subjects]	Change in skin fibrosis	Rituximab improved skin fibrosis and prevented worsening of lung fibrosis
	LOTUSS SSc-ILD study ^{72,73} [Pirfenidone 2,403 mg/d]	Evaluation of adverse events	Pirfenidone was safe and generally well tolerated
Chronic hypersensitivity pneumonitis	Tacrolimus in polymyositis and dermatomyositis ^{84,85} [Retrospective comparison of tacrolimus vs conventional therapy]	Time to relapse or death from respiratory cause or serious adverse event	Event-free survival and disease-free survival significantly longer with tacrolimus
	Keir et al ⁶⁰ [Rituximab, pre-to-post]	Change in predicted percentage of FVC and DLco	Median improvement in FVC; stable DLco

ASCEND = Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis; CAPACITY = Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes; DLco = diffusion capacity of the lung for carbon monoxide; EUSTAR = European Scleroderma Trial and Research; LOTUSS = Safety and Tolerability of Pirfenidone in Patients With Systemic Sclerosis–Related Interstitial Lung Disease; SLS = Scleroderma Lung Study; TOMORROW = To Improve Pulmonary Fibrosis With BIBF 1120.

events or death was similar between patients receiving pirfenidone with NAC and those receiving pirfenidone with placebo. However, exploratory analysis revealed

that the addition of NAC to pirfenidone led to a decrease in FVC (−91.3 mL/6 months [95% CI, −174.4 to −8.3]; *P* = .031).

The long-term safety of pirfenidone was evaluated in an open-label extension study (RECAP) of patients who completed either the CAPACITY or ASCEND studies; patients were treated for up to 7.7 years.²⁶ Patients starting pirfenidone at 2,403 mg/d in the RECAP trial who had previously been given placebo in the CAPACITY trial reported a mean change of -5.9% in the percent predicted FVC at 60 weeks, similar to results of previous randomized clinical trials.¹⁹ Rash and photosensitivity occurred in 16% and 9% of treated patients, respectively. Since drug approval, agranulocytosis and angioedema have been identified as rare drug-related adverse events.

Nintedanib

Nintedanib ethanesulfonate is an orally available intracellular tyrosine kinase inhibitor that targets several growth factor receptors (Table 1).²⁷ Its action on the adenosine 5'-triphosphate-binding site of the vascular endothelial growth factor receptor 2 kinase domain results in the inhibition of vascular endothelial growth factor receptor 1 to 3, fibroblast growth factor receptor 1 to 3, and platelet-derived growth factor receptor- α and - β .²⁸⁻³⁰ Recent studies of nintedanib reported inhibitory activity against the proliferation of human endothelial cells stimulated by vascular endothelial growth factor and fibroblast growth factor and vascular smooth muscle cells stimulated by platelet-derived growth factor. In myofibroblasts from patients with IPF, nintedanib counteracted the profibrotic effects of TGF- β 1, thereby increasing expression of matrix metalloproteinase and reducing cell proliferation and collagen secretion.³¹

In the To Improve Pulmonary Fibrosis With BIBF 1120 (TOMORROW) Phase 2 trial, the efficacy and safety of four oral doses of nintedanib were compared vs placebo in patients with IPF³² (Table 2). Nintedanib 150 mg bid revealed a reduction in the primary end point of annual rate of decline in FVC compared with placebo (-0.06 vs -0.19 L/y [$P = .06$ for the multiplicity testing procedure]) with a significantly reduced incidence of acute exacerbations and improved quality of life as assessed by using St. George's Respiratory Questionnaire (SGRQ) score compared with placebo at this dose.

These promising findings led to two randomized, double-blind, placebo-controlled Phase 3 trials (INPULSIS-1 and INPULSIS-2).^{33,34} These multinational trials evaluated the efficacy of nintedanib 150 mg bid over a 52-week period in patients ≥ 40 years old diagnosed with IPF during the past 5 years, with percent predicted FVC $> 50\%$ and percent predicted

DLCO 30% to 79% (Table 2). Patients taking a low dose of prednisone were included. The primary end point for both trials was the annual rate of FVC decline; secondary end points were quality of life, time to first exacerbation, all-cause mortality, and occurrence of adverse effects. In INPULSIS-1 and INPULSIS-2, 23.7% and 25.2% of patients, respectively, discontinued nintedanib prematurely and 17.5% and 20.1% discontinued placebo prematurely. The adjusted annual rate of FVC decline was lower in the nintedanib group compared with the placebo group (INPULSIS-1, -114.7 mL vs -239.9 mL [$P < .001$]; INPULSIS-2, -113.6 mL vs -207.3 mL [$P < .001$]).³⁴ INPULSIS-2 recorded a significant delay in the time to first exacerbation (HR, 0.38 [95% CI, 0.19 to 0.77]; $P = .005$), a result not observed with INPULSIS-1 (HR, 1.15 [95% CI, 0.54 to 2.42 [$P = .67$)]). Prespecified pooled analysis of both studies revealed no significant differences between the nintedanib and placebo groups in the adjusted mean change of SGRQ score or death from any cause (5.5% vs 7.8%; $P = .14$). Patients treated with nintedanib demonstrated more frequent adverse events compared with those receiving placebo. These adverse events included elevated liver enzyme levels (4.9%-5.2% vs 0.5%-0.9%) and myocardial infarction (1.5%-1.6% vs 0.5%). Diarrhea was experienced by 62% of patients who received nintedanib but was associated with medication discontinuation in $< 5\%$ of patients. These results led to FDA approval in 2014 of nintedanib for the treatment of patients with IPF, with subsequent European Union approval in 2015.³⁵

A recent study analyzed the treatment effects of nintedanib in patient subgroups by using pooled data from the INPULSIS trials.³⁶ There were no differences in the prespecified primary end point of yearly FVC decline or key secondary end points of SGRQ change from baseline and time to first acute exacerbation in patients treated with nintedanib when grouped according to age, sex, race, baseline predicted FVC ($< 70\%$ vs $> 70\%$), and baseline SGRQ. Although the studies were not designed to assess the treatment effect of nintedanib in these populations, the findings confirm equivalent efficacy of nintedanib across these different subgroups of patients with IPF.

Recommended Approach to Therapy in IPF

A diagnosis of IPF requires a multidisciplinary assessment according to established guidelines.⁷ The recently updated American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin

American Thoracic Association clinical practice guidelines for the treatment of IPF recommend against the use of warfarin, imatinib, ambrisentan, or a combination of prednisone, azathioprine, and NAC.³⁷ Due to moderate confidence in the effect estimates associated with the use of pirfenidone or nintedanib, these guidelines provide a conditional recommendation for their use in IPF treatment. Based on data from clinical trials of nintedanib or pirfenidone, patients can anticipate a slowing in disease progression (as assessed according to FVC) and may note some improvement in symptoms. There are no data to guide initiation of therapy in elderly patients or in those with very mild or severely reduced lung function or significant comorbidities (these patients did not fit the inclusion criteria of the pivotal trials).

A recent meta-analysis evaluating pharmacotherapies across multiple IPF studies demonstrated similar effects of nintedanib and pirfenidone on FVC decline and respiratory- and all-cause mortality.³⁸ The decision regarding which of the two agents to start should be based on data from the clinical trials validating these therapies, the practitioner's assessment of patient comorbidities and preferences, and the likelihood of potential adverse events given their relative equivalence in efficacy.

The observed difference in the relative reduction in FVC decline between nintedanib (52.2%) and pirfenidone (45.1%) may be attributable to the different statistical methods used to analyze the data. Because the pathogenesis of IPF seems to involve distinct pathways, the safety and efficacy of combination therapy with nintedanib and pirfenidone warrant further study.³⁹ A multinational, randomized, open-label, parallel-group study was initiated to evaluate nintedanib in patients with IPF when administered in combination with pirfenidone, compared with nintedanib therapy alone.⁴⁰

Patients prescribed nintedanib or pirfenidone should be educated on potential adverse effects, need for dose adjustments, behavioral modifications, and therapies to improve tolerability and the need for regular monitoring of hepatic function (Table 3). Results of liver function tests ≥ 3 times the upper limit of normal, severe gastrointestinal disturbance, and hypersensitivity reactions are indications for stopping these medications. After exclusion of other causes, if liver function test results have normalized, nintedanib or pirfenidone may be restarted with careful

monitoring. Dose reduction to improve tolerability and reduce adverse drug reactions may decrease efficacy.

Nintedanib is started at the maximum recommended dose of 150 mg bid. Diarrhea, the most prominent and predictable side effect, should be managed by maintenance of adequate hydration and use of antimotility drugs such as loperamide. Dose reduction to 100 mg bid or temporary interruption until resolution of the adverse reaction may be necessary in some cases. Nintedanib may be reinitiated at 100 mg bid. Coadministration with rifampin, carbamazepine, or phenytoin should be avoided when possible because they may reduce drug exposure. Patients receiving concomitant anticoagulant or antiplatelet therapy should be monitored due to the potential increased risk of bleeding in this setting.

At initiation of pirfenidone, dosage should be titrated starting with one pill (267 mg) three times daily for 1 week, then two pills thrice daily for 1 week, then three pills thrice daily. Gastrointestinal complaints such as nausea, vomiting and dyspepsia, and skin rash are the most common adverse effects; dizziness, fatigue, and anorexia may also be noted. Adverse effects have been associated with peak plasma concentration and tend to develop early during therapy with the exception of phototoxicity, which can develop at any time. Taking pirfenidone with meals may reduce gastrointestinal symptoms. Dermatologic reactions, which occurred in 28% of patients in the ASCEND trial, are most often due to phototoxicity.^{15,22} Avoiding exposure to sunlight and routine use of sunscreen may prevent this reaction. Phototoxicity may be managed by temporary dose reduction or cessation and resumption of full-dose therapy after resolution of the rash. Pirfenidone is metabolized by hepatic enzyme cytochrome P450 1A2; thus, other drugs also metabolized by this enzyme such as fluvoxamine should be used with caution because they may increase blood levels of pirfenidone.²² Prescribing guidelines recommend decreasing the dose in the setting of coadministration with moderate cytochrome P450 1A2 inhibitors such as ciprofloxacin.

Stem Cells and Cell-based Therapies

An increasing number of clinical trials highlight the role of mesenchymal stem cells (MSC) as a potential therapeutic agent for fibrotic lung disease. These multipotent cells of stromal origin, which may be isolated from umbilical cord blood, placenta, adipose

TABLE 3] Adverse Effects Associated With Medications and Response

Drug	Adverse Effect	Dose Modification	Additional Measures/Therapy
Nintedanib	Diarrhea	Reduce dose	Imodium
	Nausea, vomiting, abdominal pain	Reduce dose, take with food	PPI, histamine ₂ -blocker
	Elevated liver enzyme levels	Reduce or interrupt dose	Monitor liver function monthly for 3 mo, then every 3 mo
Pirfenidone	Nausea, vomiting, anorexia	Reduce dose, take with food	PPI, histamine ₂ -blocker, metoclopramide
	Photosensitivity reaction, rash	Reduce or interrupt dose	Sunscreen, avoid sunlight
	Elevated liver enzyme levels	Reduce or interrupt dose	Monitor liver function monthly for 6 mo, then every 3 mo
Prednisone	Glucose intolerance	Reduce to lowest effective dose ^a	Glycemic monitoring
	Osteoporosis, myopathy, weight gain	Reduce to lowest effective dose ^a	Bisphosphonates, teriparatide, bone mineral density monitoring
	Immunosuppression, Infection	Reduce to lowest effective dose ^a	PJP prophylaxis, monitor for infection
Azathioprine	Cytopenias	Split or interrupt dose	Thiopurine S-methyltransferase level
	Infection	Reduce to lowest effective dose	PJP prophylaxis, monitor for infection
Cyclophosphamide	Nausea, vomiting	Reduce dose, take with food	PPI, histamine ₂ -blocker
	Hemorrhagic cystitis	Stop medication Adequate hydration	Prophylactic mesna
Mycophenolate mofetil	Diarrhea	Stop dosing, change to mycophenolic acid	Adequate hydration
	Leukopenia	Dose reduction	
Rituximab	Infusion reactions	Interrupt or reduce rate	Acetaminophen, antihistamine, corticosteroid pretreatment
	Cytopenias		Avoid myelosuppressive agents
	Infection		PJP prophylaxis, monitor for infection
Tacrolimus	Hypertension, nephrotoxicity	Adjust dose to keep trough level < 10 µg/L	Control blood pressure, monitor renal function and electrolytes

PJP = *Pneumocystis jirovecii* pneumonia; PPI = proton pump inhibitor.

^aConsider glucocorticoid-sparing agents.

tissue, Wharton's jelly, or lung tissue, have the ability to self-renew and give rise to progeny that can differentiate into various cell lineages.⁴¹⁻⁴³

The AETHER study, a Phase 1, randomized, double-blinded trial, evaluated the safety and tolerability of IV bone marrow-derived human MSC for patients with IPF in a pilot study.⁴⁴ The interim safety analysis of this 60-week study demonstrated no treatment-emergent adverse events in nine subjects with mild to moderate IPF, randomized into three treatment groups.⁴⁵ Chambers et al⁴⁶ performed a Phase 1B study of placenta-derived MSC in eight patients with moderately severe IPF. This single-center, nonrandomized, dose escalation trial demonstrated no change in the measured FVC, DLCO, 6-min walk test, or CT fibrosis score of the

study participants at 6 months compared with baseline. In this study, MSC administration was well tolerated and only resulted in minor adverse effects such as a transient decrease in arterial oxygen saturation of $\leq 2\%$. Tzouveleki et al⁴⁷ evaluated the safety of endobronchial infusions of adipose-derived stromal cells/stromal vascular fraction in 14 patients with IPF who had mild to moderate disease severity. There were no significant differences in FVC, DLCO, or 6-min walk test, or serious or clinically meaningful treatment-emergent adverse events during the 12-month study period demonstrating an acceptable safety profile.

Unsubstantiated claims of the efficacy of cell-based therapies in diverse lung diseases have led to increased regulatory efforts by the FDA, in collaboration with

TABLE 4] Diagnosis and Management of Comorbid Conditions in Fibrotic Interstitial Lung Disease

Comorbidity	Diagnostic and Screening Tests	Management Considerations
Combined pulmonary fibrosis and emphysema	Disproportionate reduction in DLco compared with FVC	Smoking cessation, supplemental oxygen, pulmonary rehabilitation trial of bronchodilator therapy
Lung cancer	May be incidental finding on chest radiography	Increased risk of pulmonary toxicity or ILD exacerbation in setting of surgical resection, chemotherapy, or radiotherapy
Venous thromboembolism	Consider venous Doppler scan and/or PE protocol CT scans for acute respiratory decompensation	Unchanged from non-ILD except consider drug interactions (nintedanib) PE may exclude patient from lung transplantation
Depression, deconditioning, and sedentariness	Screening and regular assessment in clinic	Cognitive behavioral therapy and antidepressant therapy Pulmonary rehabilitation
Coronary artery disease	Cardiac evaluation ± catheterization	Caution with drug-eluting stents and long-term antiplatelet therapy if candidate for lung transplant Assess for bleeding risk in patients taking nintedanib
Gastroesophageal reflux disease	Esophageal pH evaluation ± manometry	Lifestyle modification Histamine ₂ -blocker, PPI
Hypoxemia	Pulse oximetry at rest and during exercise	Supplemental oxygen if oxygen saturation < 89%
Sleep-disordered breathing	Overnight oximetry Polysomnography	CPAP
Pulmonary Hypertension	Echocardiography, BNP Right-heart catheterization	Exclude other potential treatable causes of pulmonary hypertension Avoid endothelin receptor antagonists in IPF

BNP = B-type natriuretic peptide; ILD = interstitial lung disease; PE = pulmonary embolism. See Table 2, 3, and 4 legends for expansion of other abbreviations.

other governmental agencies, while prominent nonprofit organizations such as the American Thoracic Society, the American Lung Association, and the International Society for Stem Cell Research have issued strong statements that caution against stem cell medical tourism.⁴⁸

Chronic Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is a complex, immunologically mediated diffuse parenchymal lung disease that results from exposure to inhaled chemical or organic antigens, especially avian antigens and environmental mold^{49,50}; cHP is commonly characterized by fibrosis, which may mimic IPF in advanced disease.^{51,52} In a cohort of 20 patients with cHP, Garcia de Alba et al⁵³ demonstrated a significant increase in circulating fibrocytes compared with healthy individuals (5.3% ± 3.4% vs 0.8% ± 0.7%; $P = .00004$). Several studies have shown that the presence of fibrosis on HRCT scans or pathologic specimens is associated with a reduction in survival from approximately 20 years to 5 to 8 years.^{49,54,55} Mooney et al² showed that quantification of lung fibrosis by using the HRCT fibrosis score independently predicted

mortality, suggesting that fibrosis may exert a dose-response effect on mortality in cHP. In a recent analysis of 16 patients with cHP and a histopathologic UIP-like pattern, patients with more fibroblastic foci had increased radiographic reticulation, traction bronchiectasis, and honeycombing; the extent of fibroblastic foci predicted survival (HR, 2.36 [95% CI, 1.02 to 5.48]; $P = .04$).⁵⁶

Studies have confirmed that antigen identification remains difficult, requires a comprehensive assessment, and is correlated with improved outcome. Ryerson et al⁵⁷ studied 206 patients with HP and found that 60% had no identifiable antigen exposure. In a case-cohort study by Morell et al,⁵² 43% of patients meeting 2011 IPF criteria were subsequently diagnosed with cHP attributable to occult antigen exposure after completing a standardized questionnaire and undergoing an inhalational challenge, testing for serum precipitins, BAL, and, in some cases, surgical biopsies. Fernandez Perez et al⁴⁹ studied a cohort of 142 cases of cHP, of which only 47% had an identifiable antigen. After multivariable analysis, patients with an identifiable antigen had a median survival of 8.75 years compared with 4.88 years ($P = .047$) in those with an unidentified antigen. In a recent study evaluating 120 patients with fibrotic cHP, Adegunsoye et al⁵⁸

TABLE 5] Potential Future Therapies in Fibrotic Lung Diseases

Medication	Mechanism of Action	Fibrotic Lung Disease	Current Trial Status	Clinical Trial Identifier
Cotrimoxazole	Antimicrobial	IPF	Phase 3	NCT01777737
FG-3019	Antibody to connective tissue growth factor that blocks TGF- β -mediated pulmonary fibrosis	IPF	Phase 2	NCT01262001
GSK2126458	Phosphoinositol kinase PI3K inhibitor	IPF	Phase 2	NCT01725139
Inhaled carbon monoxide	Potential reduction in the circulating levels of the enzyme matrix metalloproteinase 7	IPF	Phase 2	NCT01214187
IW001	Targets anti-Col (V)-mediated autoimmune processes	IPF	Phase 1	NCT01199887
Lebrikizumab	Anti-IL-13 antibody that antagonizes fibroblast collagen production and differentiation of fibroblasts to myofibroblasts	IPF	Phase 2	NCT01872689
Nandrolone decanoate	Targets the androgen receptors in telomere-related IPF	IPF	Phase 2	NCT02055456
PRM-151	Recombinant pentraxin-2	IPF	Phase 2	NCT02550873
Rituximab	Reduction of autoantibody levels by B-lymphocyte depletion	IPF	Phase 2	NCT01969409
Sirolimus	Reduction of circulating fibrocytes by inhibiting the mechanistic target of rapamycin	IPF	Phase 2	NCT01462006
STX-100	Humanized monoclonal antibody that targets TGF- β_1 pathway	IPF	Phase 2	NCT01371305
TD139	Galectin-3 inhibition	IPF	Phase 1/2	NCT02257177
Thalidomide	Antiangiogenic and immunomodulatory effects may attenuate pulmonary fibrosis	IPF	Phase 2	NCT00162760
Mesenchymal stem cells (placental/ allogeneic/ autologous)	Antiproliferative, immunomodulatory, and antiinflammatory effect of mesenchymal stem cells	IPF	Phase 1/2	NCT01385644/ NCT02135380
Pirfenidone	Possible inhibition of TGF- β and TNF- α	cHP	Phase 2/3	NCT02496182
Bone marrow mesenchymal stem cells	Immunomodulatory effect of intravenously transplanted allogeneic bone marrow mesenchymal stem cells	CTD-ILD/IPF	Phase 1/2	NCT02594839/ NCT02013700
Nintedanib	Kinase inhibitor; inhibition of VEGFR 1-3, FGFR 1-3, PDGFR α and β	SSc-ILD	Phase 3	NCT02597933
Pirfenidone	Possible inhibition of TGF- β and TNF- α	SSc-ILD	Phase 2	NCT01933334
Pomalidomide (CC-4047)	Antiangiogenic and immunomodulatory effects may attenuate pulmonary fibrosis	SSc-ILD	Phase 2	NCT01559129

Ongoing clinical trial information from Clinicaltrials.gov, correct as of May 2016. cHP = chronic hypersensitivity pneumonitis; CTD-ILD = connective tissue disease interstitial lung disease; IPF = idiopathic pulmonary fibrosis; SSc-ILD = systemic sclerosis-associated interstitial lung disease; TGF- β = transforming growth factor- β ; TNF- α = tumor necrosis factor- α . See Table 1 legend for expansion of other abbreviations.

showed that 15% of these patients had autoimmune features, which independently predicted mortality (HR, 4.45 [95% CI, 1.43 to 13.88]; $P = .01$).

Although systemic corticosteroids are often used in the treatment of cHP based on expert opinion, the long-term efficacy of these agents has not been validated by

large, randomized, prospective clinical trials.^{50,59} An empiric regimen of 0.5 to 1 mg/kg/d of prednisone (Table 1) over 4 to 6 weeks followed by a slow taper to 10 mg/d is commonly implemented for cases that progress despite antigen avoidance. The efficacy of immunomodulatory agents such as azathioprine or mycophenolate mofetil in patients with cHP who fail to respond to or who require chronic corticosteroid therapy remains unproven.⁵⁰ A retrospective study by Keir et al⁶⁰ in 50 non-IPF patients demonstrated improvement in FVC and stabilization of DLCO with rituximab in six patients with cHP. Kern et al⁶¹ described a cohort of 31 patients with cHP who underwent lung transplantation for progression of fibrosis with a subsequent 5-year survival of 89% ($P = .005$). The role of nintedanib and pirfenidone in cHP requires further study before either agent can be recommended for use.

Connective Tissue Disease-related ILDs

Connective tissue diseases are frequently complicated by ILDs, which when fibrotic and progressive, are a major contributor to mortality. The heterogeneous nature of CTD-ILDs and lack of coordinated care networks have limited the performance of rigorous clinical trials; thus, evidence regarding the safety and efficacy data of most therapy prescribed for patients with CTD-ILD are either of poor quality or lacking.⁶² Hu et al⁶³ and Fischer et al⁶⁴ retrospectively evaluated 1,044 patients with CTD-ILD, including patients with the recently proposed “interstitial pneumonia with autoimmune features.” Although diagnosis was delayed in 32%, overall prognosis was favorable, and most deaths were attributed to acute exacerbation of CTD-ILD. Disease remission occurred in > 75% with the use of glucocorticoid, antirheumatic, and antifibrotic therapy. Recent guidelines by the Outcome Measures in Rheumatology CTD-ILD working group, defining clinically meaningful disease progression and response to therapy, aim to facilitate the development of well-designed, multicenter, randomized clinical trials.⁶⁵

Systemic Sclerosis-associated Interstitial Lung Disease

In patients with SSc-ILD, radiographic fibrosis is common.^{66,67} Two landmark studies, the Fibrosing Alveolitis in Scleroderma Trial (FAST) and the Scleroderma Lung Study (SLS), have suggested benefit with immunosuppressive treatment.^{68,69} The FAST study demonstrated a favorable change in the FVC in

patients treated with low-dose prednisolone and IV cyclophosphamide followed by azathioprine.

The SLS found a reduced decline in FVC and improved quality of life in patients with SSc-ILD when treated with oral cyclophosphamide for 12 months; benefits were absent at 24 months^{68,70} (Table 2). Preliminary data from a subsequent study comparing the use of oral mycophenolate mofetil vs oral cyclophosphamide in patients with SSc-ILD found that mycophenolate mofetil had comparable efficacy, fewer adverse events, and a lower incidence of treatment failures than cyclophosphamide.⁷¹ Results from the recently completed Safety and Tolerability of Pirfenidone in Patients With Systemic Sclerosis-Related Interstitial Lung Disease (LOTUSS) study⁷² showed that pirfenidone was generally well tolerated in patients with SSc-ILD.⁷³ Khanna et al^{73,74} evaluated the safety and tolerability of pirfenidone in an open-label, 16-week study of 63 patients with SSc-ILD. At study termination, the median change from baseline in percent predicted FVC was -0.5%, whereas the median change from baseline in percent predicted DLCO was 1.5%. Their study found that pirfenidone was generally well tolerated in patients with SSc-ILD. The association of scleroderma renal crisis with the use of moderate to high doses of corticosteroids limits their utility in systemic sclerosis.⁷⁵ A nested case-control study by the European Scleroderma Trial and Research (EUSTAR) group showed that in patients with SSc-ILD, rituximab prevented progressive decline in FVC compared with matched control subjects ($0.4\% \pm 4.4\%$ vs $-7.7\% \pm 3.6\%$; $P = .02$).⁷⁶ A randomized, double-blind, placebo-controlled Phase 3 trial evaluating the efficacy and safety of nintedanib 150 mg bid in treating patients with SSc-ILD is currently active and recruiting participants as of June 27, 2016.⁷⁷

Rheumatoid Arthritis-associated ILD

A study of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) in the United Kingdom by the British Rheumatoid Interstitial Lung network is currently evaluating all-cause mortality with the use of rituximab compared with anti-TNF medications in patients with RA-ILD.^{78,79} A randomized, double-blind, placebo-controlled Phase 2 study evaluating the safety, tolerability, and efficacy of pirfenidone in patients with RA-ILD is not yet open for participant recruitment (as of June 17, 2016).⁸⁰

ILD Associated With Other Connective Tissue Diseases

Retrospective studies in patients with ILD associated with the idiopathic inflammatory myopathies (IIMs)

have demonstrated lung function improvement with oral cyclophosphamide and the ability to taper corticosteroid treatment with mycophenolate mofetil^{70,81,82} (Table 2). Cyclosporine has been shown to have efficacy in small retrospective studies of patients with antisynthetase syndrome associated-ILD refractory to corticosteroids.^{83,84} There is evidence of benefit associated with the use of tacrolimus in patients with IIM or antisynthetase syndrome-ILD.^{84,85} In the aforementioned study by Keir et al,⁶⁰ rituximab was associated with improved FVC and stabilization of DLCO in patients with IIM-associated ILD. However, the treatment effects suggested by these small retrospective studies require validation in larger, prospective randomized clinical trials.

Determining whether and when to start therapy in CTD-ILD is challenging for multiple reasons. Some patients have mild, stable ILD that does not benefit from therapy, whereas ILD in the setting of an IIM may be rapidly progressive and improve with the early use of multimodality therapy.⁶² Immunosuppression with corticosteroids (Table 1) has historically been the mainstay of therapy in CTD-ILD, with expert opinion increasingly favoring adding an immunosuppressive agent when ILD is progressive or severe. Because CTD-ILD can be associated with a UIP pattern on HRCT, it is important to obtain an accurate etiologic diagnosis for prognostic purposes and because immunomodulatory therapy may be detrimental in UIP/IPF. In SSc-ILD, a reduced FVC or advanced fibrosis on HRCT scan are associated with risk of death.⁸⁶ The efficacy of immunomodulatory agents in advanced fibrosis among patients with CTD-ILD remains unclear and should be carefully weighed against their potential for adverse effects. Guidelines have been formulated for monitoring patients with diffuse interstitial and inflammatory ILD (including CTD-ILD) who are undergoing immunosuppressive therapy.⁸⁷ Patients taking prednisone \geq 20 mg/d or other immunosuppressive medication should receive prophylactic therapy for *Pneumocystis jirovecii* pneumonia⁸⁸ and undergo periodic bone health evaluations.⁸⁹ In patients with CTD-ILD, the therapeutic effect of the newer antifibrotic agents, nintedanib and pirfenidone, remains unknown. Those with very advanced fibrosis may be candidates for lung transplantation.

Assessment and Treatment of Comorbidities in Fibrotic Lung Disease

Identification and treatment of the comorbidities that occur with fibrotic ILD may improve quality of life and

outcomes (Table 4).⁹⁰ Many patients with IPF, and some patients with CTD-ILD, have radiographic evidence of coexisting emphysema referred to as combined pulmonary fibrosis and emphysema.^{91,92} These patients often demonstrate a disproportionate decrease in DLCO compared with lung volumes, with flow rates that are relatively preserved. Smoking cessation is imperative. Inhaled bronchodilators and inhaled corticosteroids may be beneficial in individual cases.

The risk of lung cancer is increased in IPF and is reported in patients with other forms of fibrotic lung disease, especially systemic sclerosis-associated and rheumatoid arthritis.⁹³ It is associated with a further reduction in life expectancy.⁹³⁻⁹⁵ Although these patients may be asymptomatic, weight loss and hemoptysis should heighten suspicion and prompt further evaluation. Surgical resection, chemotherapy, and/or radiation therapy may be poorly tolerated and associated with a more rapid decline in lung function.

Patients with fibrotic ILD have an increased risk for VTE. Therefore, acute or subacute worsening should prompt a pulmonary embolism protocol contrast CT scan to evaluate for VTE.^{96,97} Coronary artery disease is prevalent in IPF and RA-ILD and is associated with worse outcomes. The risk of prolonged antiplatelet therapy should be considered when choosing whether to insert a drug-eluting stent because this approach may complicate the management of patients who are candidates for lung transplantation and those undergoing nintedanib therapy.⁹⁸⁻¹⁰⁰

Chronic fibrotic lung diseases are complicated by depression and anxiety,^{101,102} which have been associated with symptom severity and are key predictors of the quality of life. Screening for depression to determine the need for cognitive behavioral therapy or antidepressant medication may be helpful. Data suggest supplemental oxygen and pulmonary rehabilitation may ameliorate dyspnea and depression in patients with ILD.¹⁰³ Pulmonary rehabilitation is also useful in the treatment of comorbidities such as skeletal muscle dysfunction and deconditioning, frequently associated with chronic inflammatory states and sedentariness.^{104,105} In patients with IPF and hypoxemia, exercise training may maintain oxygen uptake while improving quality of life.^{106,107} Current guidelines support regular assessment for hypoxemia with prescription of oxygen for those with oxygen saturation $<$ 89% at rest or with exercise.⁷

Microaspiration from gastroesophageal reflux may constitute a preventable source of repetitive lung injury

in patients with fibrotic ILD. Assessment of BAL fluid from patients with IPF revealed increased markers of aspiration.¹⁰⁸ Objective measures of gastroesophageal reflux were more severe in patients with SSc-ILD than in those with SSc and no ILD.¹⁰⁹ Although the use of proton pump inhibitors and lifestyle modifications to prevent reflux have been associated with improved survival in IPF, a recent pooled analysis evaluating IPF patients in the placebo groups of the CAPACITY-004, CAPACITY-006, and ASCEND trials showed no improvement in outcomes with use of antacid therapy.^{110,111} Although studies suggest antireflux measures may be beneficial in some patients with fibrotic ILD, recommendations for the use of proton pump inhibitors must be balanced against the increasing evidence for adverse effects, including alteration of the gut microbiome, coronary events, and chronic kidney disease.¹¹¹⁻¹¹⁵ Several trials evaluating the association between microaspiration in IPF¹¹⁶ and the role of gastroesophageal reflux and microaspiration in patients with SSc-ILD are ongoing.^{117,118} Also in progress is the WRAP-IPF study, which tests whether treatment of patients with IPF who have gastroesophageal reflux by using laparoscopic antireflux surgery will reduce FVC decline over a 48-week period.¹¹⁹

Sleep-disordered breathing is prevalent in fibrotic ILD, and moderate to severe OSA has been reported in more than two-thirds of patients with IPF.^{120,121} The impact of this disrupted sleep architecture and associated nocturnal hypoxemia on quality of life suggest that screening for OSA may be beneficial. CPAP has been shown to improve quality of sleep and life in patients with IPF and may also confer survival benefits.¹²²

At referral for lung transplantation, almost one-half of patients with IPF have evidence of pulmonary hypertension (PH).¹²³ Patients with CTD-ILD may develop treatment-responsive pulmonary arterial hypertension. PH should be suspected in patients with dyspnea or exercise limitation disproportionate to the severity of their fibrosis or DLCO reduction disproportionate to their FVC.^{124,125} Transthoracic echocardiography and elevation in serum markers of cardiac dysfunction such as N-terminal pro-B-type natriuretic peptide may be used to screen for PH. Echocardiographic estimation of pulmonary arterial pressures is less accurate than right-heart catheterization, which remains the gold standard and may identify patients with treatable concomitant left-heart dysfunction or pulmonary arterial hypertension. In patients with IPF, the use of ambrisentan should be

avoided because it may be detrimental.¹²⁶ Notably, two nonselective endothelin receptor antagonists, bosentan and macitentan, have shown no harm and have yet to be adequately studied in the subpopulation of patients with both ILD and PH. The Riociguat in Patients with Symptomatic Pulmonary Hypertension associated with Idiopathic Interstitial Pneumonias (RISE-IIP) study, which evaluated the use of riociguat (a soluble guanylate cyclase stimulator) in patients with PH associated with idiopathic ILD, was recently terminated following concern for increased mortality in the treatment group.¹²⁷

Currently, the majority of patients with end-stage lung disease awaiting lung transplantation have IPF, but this procedure is an option for all patients with fibrotic ILD. The poor prognosis associated with IPF or other types of fibrotic ILD should prompt an early discussion regarding transplantation and its potential benefits. Although the proportion of patients with IPF receiving bilateral lung transplants has increased over the last decade, a systematic review evaluating posttransplant survival in IPF showed no difference in mortality between single and bilateral lung transplantation.¹²⁸ There is limited evidence regarding the use of nintedanib or pirfenidone in lung transplant recipients who develop posttransplant fibrosis or chronic lung allograft dysfunction. Some lung transplant centers are concerned that antifibrotic agents may interfere with the posttransplant healing process, and they therefore recommend cessation of pirfenidone or nintedanib 1 or 2 months prior to lung transplantation. A randomized controlled trial in this population is in progress.¹²⁹ There are few data on the perioperative use of these medications in patients undergoing lung transplantation.

Conclusions

The symptom burden and high mortality associated with fibrotic ILD have inspired the search for novel and effective treatment options (Table 5). The recent approval of nintedanib and pirfenidone for the treatment of IPF potentially heralds the onset of an era in which effective therapies become available for patients with IPF. Although cell-based therapies with MSCs have been safely administered in Phase 1 clinical trials in IPF, to date there is no evidence of therapeutic benefit.^{42,46,47} As newer agents are studied, either as stand-alone treatment or in combination for their efficacy in halting and potentially reversing the progression of fibrotic ILD, continued attention should be paid to adjunct therapies

that may significantly improve quality of life and clinical outcomes in these patients.

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