REPORT

Overview of Idiopathic Pulmonary Fibrosis, Evidence-Based Guidelines, and Recent Developments in the Treatment Landscape

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Overview of Idiopathic Pulmonary Fibrosis and Evidence-Based Guidelines

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive-fibrosing interstitial lung disease (ILD) of unknown origin characterized by progressive lung scarring and the histologic picture of usual interstitial pneumonia.[1,2] Disorders belonging to the ILD category cause damage to the lung interstitium through various mechanisms, including inflammation, edema, and/or fibrosis.[3] Despite sharing common clinical and pathophysiologic features, ILDs are a group of heterogenous diseases with diverse etiologies and prognoses.[4] Accounting for 55% of all ILDs, IPF results in dilation of the bronchi, alveolar remodeling, and bibasilar parenchymal fibrosis, all of which contribute to scarring that leads to impaired gas exchange, particularly oxygenation, as shown in **Figure 1**.[5]

The disease course of IPF is highly variable; most patients progress more slowly while others experience rapid lung decline.[6] In addition, patients with IPF may have periods of relatively stable disease interspersed with acute deteriorations in lung function.[7] Therefore, the clinical course of an individual patient is difficult to predict; however, the median survival for patients with IPF before the era of antifibrotics has been 3 to 5 years following diagnosis.[8]

The incidence of IPF increases with age, and diagnosis before age 50 is rare.[9,10] Among adults aged 18 to 64 years, the annual incidence is approximately 6 cases per 100,000 person-years,[11] yet in adults 65 years and older, this incidence climbs to 94 cases per 100,000 person-years.[12] Similarly, the prevalence of IPF is 18 cases per 100,000 adults aged 18 to 64 years,[11] whereas in individuals 65 years and older, the prevalence is 495 cases per 100,000.[12] Incidence and prevalence data vary widely due to fundamental differences in data collection methods and definitions of IPF. Collectively, it has been estimated that 130,000 people in the United States have been diagnosed with IPF.[3] A claims analysis of US Medicare beneficiaries from 2000 to 2011 found that older age and male sex were significantly associated with a higher incidence of IPF and shorter survival time following diagnosis.[12] In addition, thyroid disease, diabetes, coronary artery disease (CAD), and lung cancer have been associated with shorter survival in patients with IPF.[13,14]

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive-fibrosing interstitial lung disease of unknown origin that affects 3 million people worldwide and imparts substantial burdens to patients, their families, and the healthcare system. The IPF disease course is highly variable and presents several diagnostic and management-related challenges. Two therapies, nintedanib and pirfenidone, are FDA approved and are recommended by clinical practice guidelines for the treatment of IPF. Although neither of these treatments is curative, both slow disease progression and impact survival of patients with IPF. To ensure optimal management, this supplement will provide an overview of the epidemiology, pathophysiology, and diagnosis of IPF, along with management-based considerations including evidence-based guideline recommendations, in-depth reviews of nintedanib and pirfenidone, and outcomes from other completed clinical trials.

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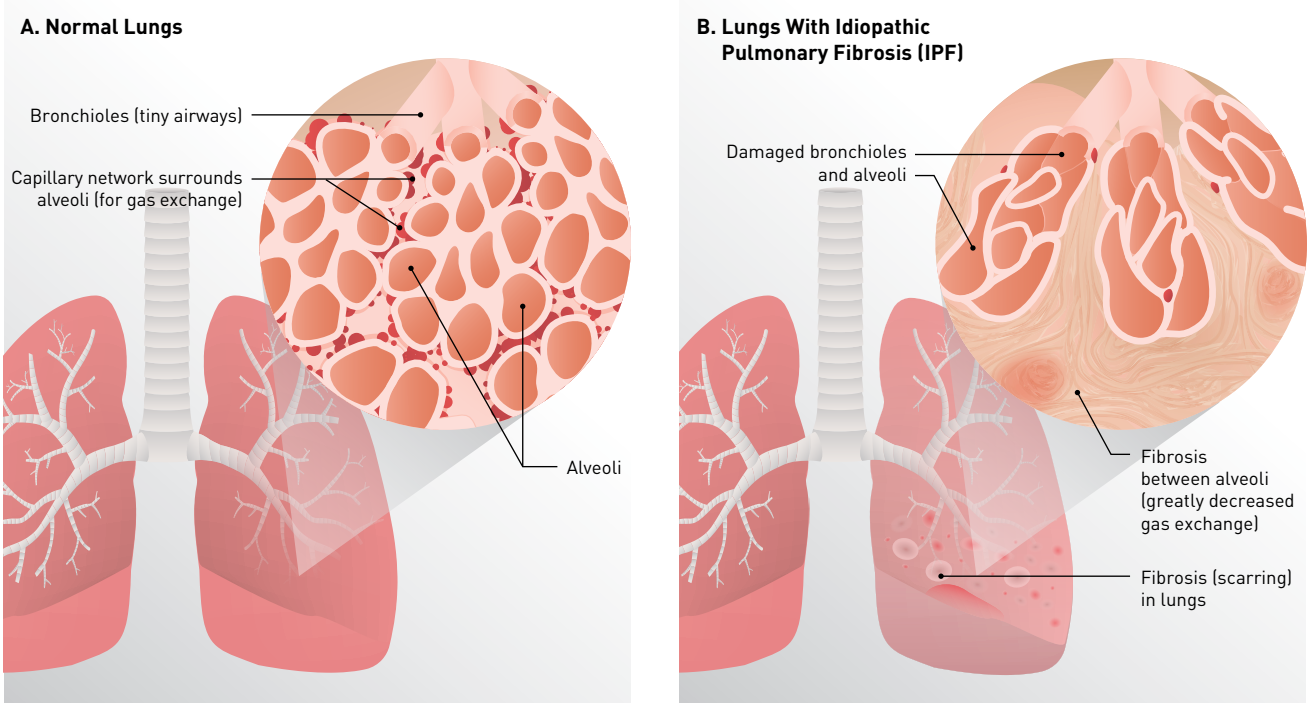
Along with increasing age and male sex, potential risk factors for IPF include cigarette smoking, environmental exposures, microbial pathogens, and genetic factors.[1] Anyone with a smoking history has a 60% higher risk of developing IPF.[15] A retrospective analysis found that current smokers are 13 to 14 years younger at diagnosis compared with nonsmokers and former smokers (58.1, 71.4, and 72.5 years, respectively).[13] Occupational exposures that may contribute to IPF include agriculture and farming; livestock; silica; and wood, metal, or stone dust.[16] Some viruses, such as the Epstein-Barr virus, may also play a part in IPF development.[3] The lung microbiota has a much higher bacterial load in patients with IPF than those without; understanding the possible role of bacteria in IPF pathogenesis is the focus of the current trial Clean-UP IPF for the Pulmonary Clinical Trials Cooperative (NCT02759120).[17]

A cohort study by Adegunsoye et al investigated survival rates in African American patients diagnosed with IPF. Despite being diagnosed at an earlier age, having poor measures of lung function and similar rates of hospitalizations as the cohort population, African Americans exhibited longer survival times. These findings suggest that race and genetics may play a role in the survival advantage exhibited by African American patients.[18] A recent study has identified American Indians/Alaska Natives as the racial group with the highest IPF-related mortality rate.[19] The interracial differences observed may support a genetic basis for predisposition to disease. Other factors to explore are whether behavioral or environmental risk factors differ by race. For instance, it is known that smoking rates differ by race, with the highest rates observed among American Indians.[20]

Comorbidities are substantial among patients with IPF and include hypertension, pulmonary hypertension (PH), obstructive sleep apnea, lung cancer, chronic obstructive pulmonary disease, CAD, vascular disease, diabetes, and gastroesophageal reflux disease (GERD).[13] Effective management of comorbidities contributes to survival and may positively impact the IPF disease course.[21] Microaspirations of gastric content may be involved in the lung injury leading to IPF[3]; however, the relationship between GERD and IPF may be confounded by smoking. A recent meta-analysis reported that a significant association between GERD and IPF (odds ratio, 2.94; $P < .0001$) was found when 18 case-control studies (3206 cases of IPF and 9368 controls) were pooled, but this association disappeared when investigators controlled for smoking status.[22]

The pathogenesis of IPF is multifactorial and involves the convergence of 3 elements: (1) epithelial damage, (2) lung tissue destruction, and (3) accelerated aging-associated changes.[3] The combination of these elements leads to the release of mediators that induce migration, proliferation, and activation of fibroblasts and myofibroblasts that resist apoptosis and secrete extracellular matrix. Growth factors are released that contribute to the relentless progression of the disease.[3]

FIGURE 1. Alveolar Damage in Idiopathic Pulmonary Fibrosis[5]



The hallmark clinical signs of IPF are nonproductive cough and progressive exertional dyspnea, and approximately one-third of patients with IPF will have digital clubbing. Scalene muscle hypertrophy and bibasilar fine crackles should also raise suspicion of IPF.[23] The diagnosis of IPF in suspected cases involves an in-depth review of both medication and environmental exposure histories followed by a high-resolution computed tomography scan (HRCT). Depending on the results of the HRCT, an analysis of the bronchoalveolar lavage fluid or surgical lung biopsy may be performed.[8] An evaluation of the HRCT results combined with a histopathology pattern confirms a diagnosis of IPF.[8] Other conditions, such as systemic sclerosis ILD (SSc-ILD, a type of connective tissue disease [CTD]) and rheumatoid arthritis-associated ILD (RA-ILD), have a similar pathophysiology as IPF and should be considered in a differential diagnosis.[23] Findings that are suggestive of an alternative diagnosis include pleural plaques (consider asbestosis), dilated esophagus (consider CTD including SSc), distal clavicular erosions (consider RA), extensive lymph node enlargement (consider other etiologies), and pleural effusions and/or thickening (consider CTD/drugs).[8]

As a result of overlapping comorbidities and lack of specific symptoms, delays in the diagnosis of IPF are common. Lamas et al found a median delay of 2.2 years (interquartile range [IQR], 1.1-3.8 years) between the onset of dyspnea and the date of the initial evaluation for IPF. As shown in **Figure 2**,[24] a longer delay was associated with shortened survival following initial evaluation (hazard ratio [HR], 1.3; 95% CI, 1.03-1.6; $P = .03$). Patients who waited 4 years or longer for a diagnosis had higher rates of CAD, diabetes, and GERD at baseline.[24] Therefore, any efforts to improve the early recognition and diagnosis of patients with IPF can greatly impact outcomes.

Evaluating Treatment Options

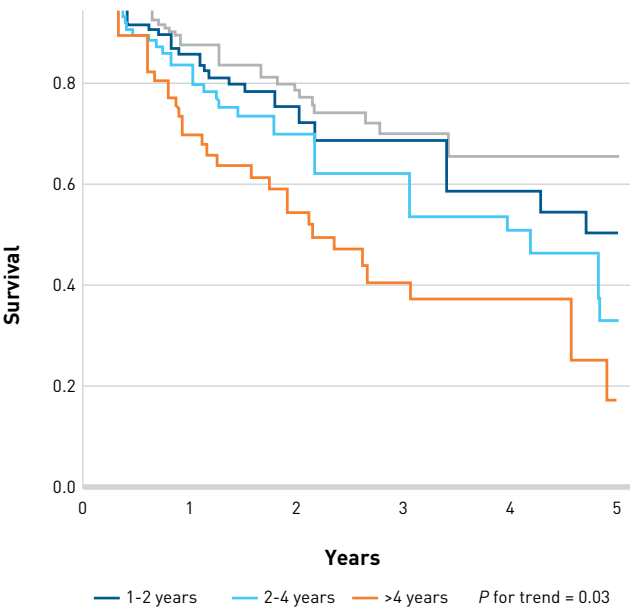
The goals of IPF management are to ameliorate symptoms, improve health status, preserve lung function, maintain adequate oxygenation with supplemental oxygen (when needed), minimize adverse events (AEs) of therapy, reduce the frequency of acute exacerbations and, ideally, improve survival.[3] Disease progression is monitored through the use of pulmonary function tests, particularly forced vital capacity (FVC) and the 6-minute walk test (6MWT).[23] There is currently no cure for IPF but the antifibrotic agents, nintedanib and pirfenidone, have been shown to slow the decline of FVC, prevent acute exacerbations, and slow disease progression.[23] Given the progressive nature of the disease, lung transplantation is a common consideration among patients with advanced IPF. Early referral for lung transplant is recommended in light of the variable disease course and occurrence of acute exacerbations.[25,26]

The management of IPF is multifaceted and involves various members of the healthcare team collaborating to provide patient education and support, vaccinations, and management of symptoms, comorbidities, and palliative care.[27] According to the CDC, patients with lung disease should receive influenza, pneumococcal, zoster, and tetanus-diphtheria-and-pertussis (Tdap) vaccines.[28] Smoking cessation counseling should be a high priority in patients with IPF.

Education and support should focus on 4 areas that have been identified as topics of concern for patients: (1) the physical problem, (2) family support, (3) interactions with the healthcare system, and (4) hope for research.[29] Along with individual counseling, pharmacists can assist patients by recommending resources for accurate information, patient support groups, pulmonary rehabilitation, and community-based conferences.[27] Patient education should begin at the time of diagnosis and continue throughout the disease progression.

Acute exacerbations can occur at any time and are associated with a 50% mortality rate.[30] Among 225 patients with a first hospitalization for acute respiratory deterioration, 30% of cases were attributable to acute exacerbations related to IPF, which were independently associated with poor survival.[31] Some risk factors for acute exacerbations include low or worsening FVC, GERD, new ground-glass opacities on the HRCT, and air pollution.[27] Once an exacerbation occurs, the patient may likely be hospitalized and receive supplemental oxygen and broad-spectrum antibiotics. No single algorithm is accepted as standard-of-care management for

FIGURE 2. Survival From Time of Evaluation for Idiopathic Pulmonary Fibrosis[24]



patients with acute exacerbations; however, acceptable and expected management can include corticosteroids and immunosuppressants.[1] A recent retrospective investigation compared the postexacerbation 90-day survival rates in patients treated with corticosteroids alone or corticosteroids plus immunotherapy with cyclophosphamide. Compared with corticosteroids alone, combination therapy did not significantly improve survival in patients after an acute exacerbation.[32] The use of antifibrotic agents and minimal exposure to infectious agents, airborne irritants, and pollutants may minimize the occurrence of exacerbations.[33] Because of the high mortality following acute exacerbations, more trials are needed to focus on optimal management to improve outcomes.

Although diagnostic recommendations were updated in 2018,[8] the 2015 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association (ATS/ERS/JRS/ALAT) international IPF therapy guidelines remain a primary resource for the pharmacologic management of the disease.[34] In 2018, the JRS published updated clinical guidelines for the treatment of IPF.[35] **Table 1** provides a summary of recommendations from the 2015 ATS/ERS/JRS/ALAT and 2018 JRS guidelines, along with strength of recommendation and confidence-in-effect estimates.[34,35] The 2 most recent guidelines agree on recommendations, with the exception of some therapeutic approaches addressed by 1 publication and not the other. The only therapies currently supported by guideline recommendations are nintedanib, pirfenidone, and antireflux medications.[34,35] When selecting between the antifibrotic agents, clinicians should consider patient preference, tolerance, potential AEs, drug interactions, and comorbid conditions.

Nintedanib

Nintedanib, an antifibrotic agent approved for the treatment of IPF, is an intracellular inhibitor that targets multiple tyrosine kinase receptors that have been shown to be involved in lung fibrosis, including the vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor receptors.[36,37] The prescribing information for nintedanib is shown in **Table 2**.[38] Several warnings and precautions should be noted with the use of nintedanib, including the potential of drug-induced liver injury, embryo–fetal toxicity, bleeding and arterial thromboembolic events, and gastrointestinal (GI) perforation.[38] The most common AEs associated with nintedanib use include diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight loss, and hypertension. Notably, smoking can decrease the patient's exposure to nintedanib, which may reduce its efficacy profile.[38]

TABLE 1. Guideline Recommendations for the Treatment of Idiopathic Pulmonary Fibrosis[34,35]

Agent	2015 ATS/ERS/JRS/ALAT Recommendations	Strength, *Confidence* in Effect Estimates	2018 JRS Recommendations	Strength, *Quality* of Evidence
Anticoagulant (warfarin)	Against use	Strong, Moderate	Not addressed	
Combination prednisone + azathioprine + *N*-acetylcysteine	Against use	Strong, Low	Against use (combination steroids + immunosuppressants)	Strong, Low
Selective endothelin receptor antagonist (ambrisentan)	Against use	Strong, Low	Not addressed	
Imatinib, a tyrosine kinase inhibitor with 1 target	Against use	Strong, Moderate	Not addressed	
Nintedanib, a tyrosine kinase inhibitor with multiple targets	For use	Conditional, Moderate	For use	Weak, Moderate
Pirfenidone	For use	Conditional, Moderate	For use	Weak, Moderate
N-acetylcysteine + pirfenidone	Not addressed		Against use[a]	Weak, Low
Nintedanib + pirfenidone	Not addressed		Withholding judgment at this time	
Dual endothelin receptor antagonists (macitentan, bosentan)	Against use	Conditional, Low	Not addressed	
Phosphodiesterase-5 inhibitor (sildenafil)	Against use	Conditional, Moderate	Not addressed	
Antacid therapy	For use	Conditional, Very low	Not addressed	
N-acetylcysteine monotherapy	Against use	Conditional, Low	Against use[a]	Weak, Low
Corticosteroid monotherapy	Not addressed		Against use	Strong, Very Low

ATS/ERS/JRS/ALAT indicates American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association.
[a]May be a reasonable option in a minority of patients.

The approval of nintedanib in patients with IPF and subsequent guideline recommendations for its use are primarily based on outcomes from the INPULSIS-1 and INPULSIS-2 trials, which are summarized in **Table 3**.[37] The data from the INPULSIS trials demonstrated the efficacy of nintedanib in slowing the annual rate of decline of FVC as compared with placebo. Patients (95%) receiving nintedanib experienced at least 1 AE during the two phase 3 trials, 62% experienced diarrhea, and 30% experienced at least 1 serious AE.[39] In post hoc analyses, nintedanib has been shown to significantly reduce the risks of a first acute exacerbation reported as a serious AE (HR, 0.57; 95% CI, 0.32-0.99; $P = .0476$) and a first confirmed/suspected acute exacerbation reported as a serious AE (HR, 0.30; 95% CI, 0.14-0.64; $P = .0019$).[40]

Real-world expectations involving shared decision making necessitates that pharmacists explain to patients the AEs associated with nintedanib use. Recently published data from the long-term follow-up, open-label extension study to the INPULSIS trials, INPULSIS-ON, showed a similar safety profile that was demonstrated in phase 3 trials over a median exposure time of 44.7 months (range, 11.9-68.3 months).[39] Fifteen percent of patients discontinued nintedanib permanently due to diarrhea, which was the most frequent AE (60.1%-71.2%). Other AEs including bronchitis, nasopharyngitis, cough, nausea, and upper respiratory tract infection occurred in fewer than 30% of study participants. Among patients who received nintedanib in each of the INPULSIS-1, INPULSIS-2, and INPULSIS-ON trials, the event rate per 100 patient exposure-years of bleeding was 8.4, which may be related to the known vascular endothelial growth factor antagonism of nintedanib.[38] Cardiac events included major cardiovascular AEs (3.6/100) and myocardial infarction (1.3/100), underscoring the recognition of cardiac comorbidities in patients with IPF.[39]

Pooled results from 5 clinical trials, including the INPULSIS and INPULSIS-ON trials, found no new safety signals in 1126 patients in the pooled nintedanib group compared with the 565 patients in the pooled placebo group.[41] Diarrhea occurred at a lower rate in the pooled nintedanib group than those observed during the INPULSIS trials (76.5 vs 112.6 events per 100 patient exposure-years), and diarrhea was generally well managed for most patients. Median survival was 11.6 (95% CI, 9.6-14.1) and 3.7 (95% CI, 2.5-5.4) years in the pooled nintedanib and placebo groups, respectively.[41]

Given the high rates of AEs associated with nintedanib use in clinical trials, data from real-world observational studies should also be considered. An observational study in Greece found that the most common AE associated with nintedanib use was diarrhea, which occurred in 55.3% of participants. Of 94 patients with IPF, 20 (21.2%) permanently discontinued nintedanib due to serious AEs.[42] In another study, 50.0% and 45.4% of 108 patients with IPF experienced diarrhea and anorexia, respectively, during the course of nintedanib therapy, with 97.2% of patients experiencing at least

TABLE 2. Prescribing Information for Nintedanib[38]

Topic	Prescribing Information
Formulations	Capsules: 100 mg, 150 mg
Dosage and administration	Take with food Recommended: 150 mg bid Mild hepatic impairment or adverse effects: 100 mg bid
Warnings/ precautions	May cause elevated liver enzymes, drug-induced liver injury, GI disorders, embryo–fetal toxicity, arterial thromboembolic events (use caution in CAD or other high cardiovascular risk), bleeding events, GI perforation
Adverse events	Diarrhea (62%), nausea (24%), abdominal pain (15%), vomiting (12%), liver enzyme elevation (14%), decreased appetite (11%), headache (8%), weight decreased (10%), hypertension (5%)
Drug interactions	P-gp and CYP3A4: Coadministration of inhibitors may increase nintedanib exposure. Smoking: May decrease exposure of nintedanib and reduce efficacy of treatment
Hepatic impairment	Not for use in moderate to severe hepatic impairment
Renal impairment	Safety and efficacy in severe renal impairment or ESRD unknown.

bid indicates twice daily; CAD, coronary artery disease; ESRD, end-stage renal disease; GI, gastrointestinal; P-gp, P-glycoprotein.

TABLE 3. Pivotal Phase 3 Clinical Trials of Nintedanib[37]

Study Information or Outcome	INPULSIS-1	INPULSIS-2
Dose of nintedanib	150 mg bid	150 mg bid
Population, treatment group	309	329
Study duration	52 weeks	52 weeks
Adjusted annual rate of change in FVC (mL/year), difference vs placebo (95% CI)	125.3 (77.7-172.8) ***P* <.001**	93.7 (44.8-142.7) ***P* <.001**
Mean observed change from baseline in FVC (mL), difference vs placebo (95% CI)	109.9 (71.3-148.6) ***P* <.001**	109.8 (70.9-148.6) ***P* <.001**
Cumulative incidence of first investigator-reported acute exacerbation, HR (95% CI)	1.15 (0.54-2.42) *P* = .67	0.38 (0.19-0.77) ***P* = .005**
Adjusted mean change in SGRQ (quality of life) from baseline to week 52, difference vs placebo (95% CI)	−0.05 (−2.50 to 2.40) *P* = .97	−2.69 (−4.95 to −0.43) ***P* = .02**
All-cause mortality, HR (95% CI)	0.70 (0.43-1.12) *P* = .14	

bid indicates twice daily; FVC, forced vital capacity; HR, hazard ratio; SGRQ, St George's Respiratory Questionnaire.

TABLE 4. Prescribing Information for Pirfenidone[46]

Topic	Prescribing Information
Formulations	Capsules: 267 mg Tablets: 267 mg, 801 mg
Dosage and administration	Take with food Titration schedule: • Days 1-7: 267 mg tid (801 mg qd) • Days 8-14: 534 mg tid (1602 mg qd) • Days 15 onward: 801 mg tid (2403 mg qd)
Warnings/ precautions	May cause elevated liver enzymes, photosensitivity and rash, and gastrointestinal disorders
Adverse events	Nausea (36%), rash (30%), abdominal pain (24%), upper respiratory tract infection (27%), diarrhea (26%), fatigue (26%), headache (22%), dyspepsia (19%), dizziness (18%), vomiting (13%), anorexia (13%), GERD (11%), sinusitis (11%), insomnia (10%), weight decreased (10%), and arthralgia (10%)
Drug interactions	CYP1A2: Moderate and strong inhibitors increase systemic exposure of pirfenidone and may alter safety profile; pirfenidone dose reduction or discontinuation may be necessary with some agents. Smoking: May decrease exposure of pirfenidone and reduce efficacy of treatment
Hepatic impairment	May need to reduce dose or discontinue. Not for use in severe hepatic impairment.
Renal impairment	May need to reduce dose or discontinue. Not for use in patients with ESRD on dialysis.

ESRD indicates end-stage renal disease; GERD, gastroesophageal reflux disease; qd, daily; tid, 3 times daily.

TABLE 5. Pivotal Phase 3 Trials of Pirfenidone[45,47]

Study Information or Outcome	CAPACITY 004	CAPACITY 006	ASCEND
Dose of pirfenidone	2403 mg/day	2403 mg/day	2403 mg/day
Population, treatment group	174	171	278
Study duration	72 weeks	72 weeks	52 weeks
Adherence to pirfenidone	NR	NR	85.3%
Categorical change in FVC ≥10%, absolute difference (95% CI)	14.4 (7.4-21.3) ***P* = .001**	3.8 (-2.7 to 10.2) *P* = .440	NR
Progression-free survival time, HR (95% CI)	0.64 (0.44-0.95) ***P* = .023**	0.84 (0.58-1.22) ***P* = .355**	0.57 (0.43-0.77) ***P* <.001**
Mean change in 6MWT (meters), absolute difference (95% CI)	16.4 (−10.9 to 43.7) *P* = .171	31.8 (3.2-60.4) ***P* = .0009**	NR ***P* = .04**
All-cause mortality (on-treatment), HR (95% CI)	0.65 (0.36-1.16) *P* = .141		0.55 (0.26-1.15) *P* = .10
IPF-related mortality (on-treatment), HR (95% CI)	0.48 (0.24-0.95) *P* = .03		0.44 (0.11-1.72) *P* = .23
All-cause mortality (overall), HR (95% CI)	0.77 (0.47-1.28) *P* = .315		NA
IPF-related mortality (overall), HR (95% CI)	0.62 (0.35-1.13) *P* = .117		NA

6MWT indicates 6-minute walk test; FVC, forced vital capacity; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; NA, not applicable; NR, not reported.

1 AE and 53.3% discontinuing therapy as the result of an AE.[43] Pharmacists can assist in managing GI complications related to nintedanib use by recommending hydration and use of the recommended over-the-counter antidiarrheals such as loperamide, and/or referring to their physician for potential dose reduction.

Pirfenidone

Pirfenidone is an orally bioavailable antifibrotic agent approved for the treatment of IPF.[44,45] Although its exact mechanism of action is unknown, animal models of lung fibrosis have shown that pirfenidone regulates the activity of transforming growth factor β and tumor necrosis factor α, inhibits fibroblast proliferation and collagen synthesis, and reduces cellular and histologic markers of fibrosis.[45] Prescribing information for pirfenidone is shown in **Table 4**.[46] AEs include GI symptoms, photosensitivity, skin rash, anorexia, and liver toxicity; these effects were generally well tolerated during clinical trials, especially with dose reduction.[3] As with nintedanib, active smokers will experience a reduced exposure of pirfenidone, which may alter the efficacy of the agent in IPF treatment.[46]

The translation of clinical trial data to practice is a necessary component of effective IPF management. Results from the pivotal phase 3 CAPACITY and ASCEND trials are shown in **Table 5**.[45,47] According to outcomes data from the phase 3 CAPACITY and ASCEND trials, 2403 mg/day of pirfenidone significantly reduced the decline in FVC, improved progression-free survival time, and increased the 6MWT distance compared with placebo among patients with IPF.[45,47] The most common AEs in the CAPACITY trial among patients who received pirfenidone versus placebo were nausea (36% vs 17%), rash (32% vs 12%), dyspepsia (19% vs 7%), dizziness (18% vs 10%), and vomiting (14% vs 4%).[45] Patients taking pirfenidone in the ASCEND trial experienced more AEs compared with those taking placebo, with the most common being nausea (36% vs 13.4%) and rash (28.1% vs 8.7%); AEs led to study discontinuation in 14.4% and 10.8% of patients taking pirfenidone and placebo, respectively.[47]

A post hoc analysis of 1247 patients from the CAPACITY and ASCEND trials found a lower risk of respiratory-related hospitalizations with pirfenidone treatment compared with placebo (HR, 0.52; 95% CI, 0.36-0.77; $P = .001$); however, all-cause and nonrespiratory-related hospitalizations were not affected by pirfenidone use. Furthermore, the protective effect of pirfenidone on respiratory-related hospitalizations lost significance after 52 weeks, leaving long-term conclusions uncertain.[48] Another post hoc analysis of the CAPACITY and ASCEND trials found that pirfenidone was associated with significantly fewer progression events compared with placebo (17.0% vs 30.1%; $P < .0001$); additionally, death following a progression event occurred less frequently with pirfenidone than placebo (2.1% vs 6.3%; $P = .0002$).[44] A recent post hoc analysis of the open-label, long-term extension study, RECAP (NCT00662038) found that longer-term pirfenidone treatment resulted in a similar rate of lung function decline and AEs in patients with more advanced versus less advanced IPF, indicating that pirfenidone is safe, efficacious, and well tolerated in patients with IPF regardless of advanced disease.[49]

Alongside clinical trials, observational and retrospective analyses of pirfenidone in IPF must also be considered, as these studies provide real-world expectations for treatment outcomes. During a real-world, long-term follow-up study of 841 patients with IPF, fewer than one-fourth of those who received pirfenidone experienced disease progression (ie, decline of ≥10% FVC and ≥15% diffusing capacity of the lungs for carbon monoxide [DLCO]) by 2 years of follow-up. At 5 years of follow-up, pirfenidone had significantly increased survival compared with no antifibrotic therapy (55.9% vs 31.5%; $P = .002$).[50] A French ancillary study of the 2-year observational PASSPORT trial reported a mean absolute change in percent predicted FVC to be −2.4% and −3.8% and in 6MWT to be 8.6 and 3.1 meters at 12 and 24 months, respectively. The median duration of pirfenidone use was 16.3 months, with a median progression-free survival of 18.4 months. Acute exacerbation and PH occurred in 20.0% and 8.4%, respectively, of patients who received pirfenidone. Reasons for early discontinuation of pirfenidone included AEs (31.3%), death (11.5%), and disease progression (10.9%).[51] Hanta et al also evaluated outcomes in the real-world use of pirfenidone in patients with IPF. After 6 months of treatment, 58.3% of patients experienced less cough, and 55% of patients experienced at least 1 AE, with dyspepsia (36.4%), nausea (27.3%), and rash/photosensitivity (24.2%) being the most common. Notably, 26.7% of patients required a dose adjustment.[52] Results of a retrospective observational intent-to-treat study found that pirfenidone was associated with significantly longer survival compared with an IPF cohort from a tertiary referral center (HR, 0.28; 95% CI, 0.16-0.48; $P < .0001$) after adjusting for age, gender, and FVC, as well as exclusion of severe cases (DLCO <30%).[53] The guidelines highlight that the optimal duration of therapy with either antifibrotic treatment is unknown, as is the endurance of treatment effects with ongoing therapy.[34,35]

New Frontiers for Pirfenidone and Nintedanib

The use of pirfenidone as add-on therapy to nintedanib was compared with the use of nintedanib alone in patients with IPF.[54] After 12 weeks of treatment, patients who received pirfenidone plus nintedanib demonstrated significantly less decline in mean FVC from baseline compared with nintedanib alone (−13.3 mL vs −40.9 mL). GI AEs occurred in 69.8% of patients treated with pirfenidone plus nintedanib and in 52.9% of those treated with nintedanib alone, in line with the safety profiles of each drug.[54] Although this study supports the potential of combination pirfenidone–nintedanib therapy for patients with IPF, more evidence supporting these outcomes is necessary.

Due to the similarities between IPF and other ILDs, pirfenidone and nintedanib are currently undergoing clinical development targeting other fibrotic lung diseases. Both agents are undergoing phase 3 trials for use in SSc-ILD, an ILD found in patients with SSc with no currently approved treatment.[55] Pirfenidone and nintedanib are also being explored in patients with RA-ILD. Despite the availability of drugs with proven articular benefit, none has been demonstrated to affect RA-ILD. Unfortunately, some of the RA-targeted immunotherapies have been implicated in the ex novo occurrence and acceleration of ILDs.[56] The benefits demonstrated by pirfenidone and nintedanib may extend to other fibrotic lung diseases, and pharmacists should bear in mind the potential for expanded use of these agents in the coming years.

Antacid Therapy

Because GERD has been implicated as a potential inciting factor in IPF pathogenesis and worsening, antacid therapy (AAT) with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists may provide benefit to patients with IPF; however, the guidelines note a "very low" confidence in effect estimates for the use of these agents.[3,34] The guideline recommendations are based on outcomes from observational and retrospective studies in which the use of AAT was shown to decrease the decline in FVC and improve survival in patients with IPF.[57,58] More recently, a post hoc analysis of patients with IPF who received pirfenidone in 3 clinical trials evaluated outcomes between those on AAT compared with those not taking AAT (non-AAT). After 52 weeks in the trials, investigators found no significant difference in disease progression, all-cause mortality rate, IPF-related mortality rate, all-cause hospitalization rate, or mean change in percent FVC. Although a relative FVC decline of greater than 10% significantly favored AAT ($P = .03$), severe GI AEs and pulmonary infections were also more frequent with AAT ($P = .015$ and $P = .035$, respectively).[40] Similarly, a post hoc analysis of AAT use in patients with IPF who received nintedanib or placebo found that AAT use at baseline did not impact disease course.[49] Despite evidence to the contrary, a meta-analysis of 8 observational studies found that pharmacologic treatment of GERD in patients with IPF was associated with a significant reduction in IPF-related mortality

compared with no GERD treatment (HR, 0.60; 95% CI, 0.38-0.97; $P = .04$), but all-cause mortality did not differ between groups.[59]

AEs associated with long-term use of PPIs include infection, hypomagnesemia, and myocardial infarction.[3] Clinicians must weigh the potential AEs associated with long-term use of AAT against the outcomes supported by the literature.[27]

Combined ILD/PH: Approaches to treatment

A current clinical trial addresses the use of inhaled nitric oxide in the management of patients with IPF and PH.[60] The INSTAGE trial studied the efficacy and safety of nintedanib plus sildenafil versus nintedanib monotherapy in patients with more advanced IPF and severe impairment in gas exchange (n = 274) (DLCO ≤35% predicted). Subjects did not show significant improvement in change from baseline in St George's Respiratory Questionnaire total score at week 12 (primary end point) compared with nintedanib therapy alone. The change in FVC from baseline to 12 and 24 weeks in patients treated with nintedanib alone was −25.5 mL and −58.2 mL, respectively. These results, although not statistically significant, suggest that nintedanib may also have effects on lung function decline in patients with more advanced disease.[33]

Emerging Therapies

The approvals of pirfenidone and nintedanib substantially altered the treatment landscape of IPF; although these agents slow the decline in lung function, they do not provide a cure for IPF. Several novel agents are currently undergoing clinical development in the hopes that they will provide additional therapeutic options to patients living with this disabling and deadly disease. A multitude of therapeutic targets are currently being explored with hypothesized effects on the clinical course of IPF.[61] Although many of these agents are still in the early phases of development, awareness of emerging therapies is an important component of effective patient care. These agents may offer patients hope of improved outcomes through potential enrollment in clinical trials and/or access to alternative therapeutic options once the agents are FDA approved.

Conclusions

Approximately 3 million people worldwide are living with IPF, a chronic, progressive lung disease with substantial morbidity and mortality burdens. The median survival of patients with IPF is 3 to 5 years, and many patients experience unacceptable delays in recognition, diagnosis, and treatment of the disease, which greatly impacts prognosis. Two antifibrotic agents, pirfenidone and nintedanib, have demonstrated efficacy in slowing the decline of lung function, reducing acute exacerbations, increasing quality of life, and/or improving mortality. The potential for AEs must also be weighed against the benefits of these agents. An in-depth knowledge of the pathogenesis of IPF and outcomes from clinical trials and real-world studies is necessary to understand the role of antifibrotic therapy along with emerging agents in effective IPF management. Ultimately, patient education and counseling are key in the shared decision-making model necessary for the management of a chronic, debilitating disease that has no cure. By applying current guideline recommendations, clinical data, and prescribing information, pharmacists in clinical and managed care positions will be better prepared to improve outcomes for patients with IPF. ■

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