

Pharmacologic Treatments for Idiopathic Pulmonary Fibrosis

This chronic disease has historically lacked an effective treatment option, but the FDA recently approved two: pirfenidone and nintedanib. This discussion of these new drug therapies—including mechanism of action, study results, and adverse effects—could help your patients catch their breath.

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A 64-year-old man has a one-year history of dyspnea on exertion and a nonproductive cough. His symptoms are gradually worsening and increasingly bothersome to him.

His medical history includes mild seasonal allergies and GERD, which is well-controlled by oral antihistamines and proton pump inhibitors. He has spent the past 30 years working a desk job as an accountant. He denies a history of smoking, exposure to secondhand smoke, and initiation of new medication.

He admits to increased fatigue, but denies fever, chills, lymphadenopathy, weight change, chest pain, wheezing, abdominal pain, diarrhea, vomiting, claudication, and swelling in the extremities. The rest of the review of systems is negative.

Lab results—complete blood count, comprehensive metabolic panel, TSH, antinuclear antibodies, erythrocyte sedimentation rate, and C-reactive protein—are within normal limits. Spirometry shows very mild restriction. A chest x-ray is abnormal but nonspecific, showing peripheral opacities. An ECG shows normal sinus rhythm.

The patient is given a trial of an inhaled steroid, which yields no improvement. Six months later, the patient is seen by a pulmonologist. Idiopathic pulmonary fibrosis (IPF) is diagnosed based on high-resolution CT (HRCT) and lung biopsy results.

PF is a chronic, progressive, fibrosing interstitial disease that is limited to lung tissue. It most commonly manifests in older adults with vague symptoms of dyspnea on exertion and nonproductive cough, but symptoms can also include fatigue, muscle and joint aches, clubbing of the fingernails, and weight loss.¹ The average life expectancy following diagnosis of IPF is two to five years, and the mortality rate is estimated at 64.3 per million men and 58.4 per million women per year.^{2,3}

DIAGNOSIS

IPF belongs in the general class of *idiopathic interstitial pneumonias* (IIPs), which are characterized by varying degrees of inflammation and fibrosis of lung interstitium.⁴ All subtypes of IIPs cause dyspnea and diffuse abnormalities on HRCT, and all vary from each other histologically. Table 1 (page 18) outlines the key features of each.⁵⁻⁸

Because of its vague symptomology and the extensive workup needed to rule out other diseases, patients with IPF often have symptoms for one to two years before a diagnosis is made.¹ Physical exam may reveal fine inspiratory rales in both lung bases and digital clubbing; eventual signs of pulmonary hypertension and right-sided heart failure may be appreciated.^{1,9}

There are no specific diagnostic laboratory tests to confirm IPF; however, base-

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line labwork (as outlined in the case presentation) is typically ordered to rule out infection, thyroid disease, or connective tissue disease.¹⁰ Many patients are referred to a cardiologist before being seen by a pulmonologist; cardiac stress testing may be done, and an echocardiogram may be performed to rule out heart failure.

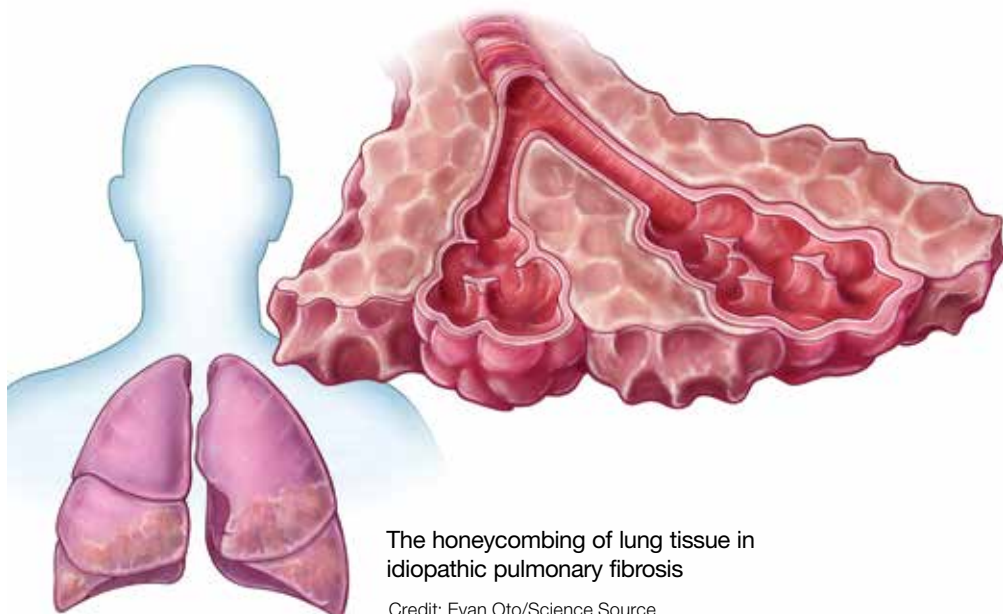
Diagnostic testing may include pulmonary function testing, HRCT of the chest, and lung biopsy.¹⁰ Tissue samples from patients with IPF reveal different stages of disease, including dense fibrosis with honeycombing, subpleural or paraseptal distribution, fibroblast foci, and normal tissue.¹¹ Pulmonary function test results will show a restrictive pattern. Both forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) will be reduced, and the FEV_1/FVC ratio preserved. Due to decreased functional lung volume, diffusing capacity of the lung for carbon monoxide (DL_{CO}) will also be reduced.^{4,12}

The differential is broad and includes allergic asthma, bronchitis, COPD, lung cancer, hypersensitivity pneumonitis, asbestosis, or pulmonary embolism.

TREATMENT HISTORY

IPF has a long history of tried and failed treatment options. The American Thoracic Society (ATS), in concert with other professional organizations, has published comprehensive guidelines and recommendations pertaining to the use of pharmacologic medications to control disease progression. Warfarin and other anticoagulants have been studied, based on the observation that a procoagulant state promotes fibrotic changes in the lung tissue.¹³ However, anticoagulant use is not recommended in patients with IPF due to lack of efficacy and high potential for harm.¹³

Immunosuppressants have also been in the spotlight as possible treatment for IPF, but a clinical study investigating the efficacy



The honeycombing of lung tissue in idiopathic pulmonary fibrosis

Credit: Evan Oto/Science Source

of a three-drug regimen including prednisone, azathioprine, and N-acetylcysteine was stopped early due to increased risk for harm. Endothelin antagonists and potent tyrosine kinase inhibitors are also not recommended in the most recent edition of IPF guidelines, as they lack benefit.¹³

In fact, prior to the 2015 edition of the guidelines, no single medication was routinely recommended for patients with IPF. But this is now changing, following the 2014 FDA approval of two new drugs, nintedanib and pirfenidone, designed specifically to treat IPF.¹⁴ These drugs have shown promise in clinical trials (results of which are summarized in Table 2, page 20).

NEW PHARMACOLOGIC OPTIONS Pirfenidone

In 2008, a study was conducted in Japan to determine the mechanism of action of pirfenidone.¹⁵ Through in vitro studies of healthy adult lung fibroblasts with added pro-fibrotic factor and transforming growth factor ($TGF-\beta 1$), the researchers found that pirfenidone was effective at decreasing the production of a collagen-binding protein called HSP47. This protein is ubiquitous in fibrotic tissue. The study also showed that pirfenidone decreased the production of collagen type 1, which, when uninhibited, increases fibrosis.¹⁵

CAPACITY trials. In the CAPACITY trials, two phase 3 multinational studies conducted from 2006 to 2008, patients were given either pirfenidone or placebo.¹⁶ In the

TABLE 1
Key Characteristics of Idiopathic Interstitial Pneumonias

Disorder	Patient population (most common)	Onset	Chest x-ray findings	HRCT findings	Pharmacologic treatment
Idiopathic pulmonary fibrosis	Men > 50	Chronic (> 12 mo)	Basilar predominant, reticulonodular abnormalities, honeycombing*	Peripheral, subpleural, basilar reticular honeycombing*	Pirfenidone Nintedanib
Nonspecific interstitial pneumonia	Women ages 40-60 (< 40% smoke)	Subacute to chronic (mo to yrs)	Ground-glass and reticular opacity	Peripheral, basilar, symmetric Variable ground-glass opacification	Oral steroids Immunosuppressive therapy
Lymphoid interstitial pneumonia	Women of any age	Chronic (> 12 mo)	Reticular opacities Nodules	Diffuse pattern Ground glass Thin-walled cysts	Corticosteroids**
Cryptogenic organizing pneumonia	Age 40-50 (< 50% smoke)	Subacute (< 3 mo)	Patchy bilateral consolidation	Peribronchial Patchy consolidation, nodules	Corticosteroids** Macrolide antibiotics (anti-inflammatory effects) Immunosuppressive or cytotoxic therapy

* Honeycombing is a coarse, reticular pattern reflecting end-stage fibrosis.¹

**Spontaneous resolution may occur without treatment if mild.

Sources: Cleveland Clinic. 2015⁵; Skandhan & Weerakkody. Radiopaedia⁶; Tatco & Weerakkody. Radiopaedia⁷; King et al. UpToDate.⁸

first study arm, patients were assigned to pirfenidone 2,403 mg/d (n = 174), pirfenidone 1,197 mg/d (n = 87), or placebo (n = 174). In the second study arm, 171 patients received pirfenidone 2,403 mg/d and 173 patients received placebo. Endpoints were measured at baseline and up to week 72.

The first study arm found that the mean rate of decline of FVC—the primary endpoint—was 4.4% less in the treatment group than in the placebo group (p = 0.001), and there was a 36% decrease in risk for death or disease progression in the treatment group

(HR, 0.64; p, 0.023). (Endpoints were defined as: time to confirmed > 10% decline in percentage predicted FVC, > 15% decline in percentage predicted DL_{CO}, or death.) The researchers found no clinically significant change in the six-minute walk test—a secondary endpoint of the study.¹⁶

The second study arm, however, found no statistically significant change in FVC between the treatment and placebo groups (with a 0.6% smaller decrease in FVC in the pirfenidone group), nor did they see a difference in progression-free survival. How-

ever, there was a significant change in the six-minute walk test between the treatment and placebo groups ($p = 0.0009$). Throughout the study, the most common adverse effects included nausea (36%), rash (32%), and dyspepsia (19%).¹⁶

ASCEND trial. The 2014 Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) trial was a phase 3, multinational, randomized, double-blind, placebo-controlled study of the use of pirfenidone 2,403 mg/d.¹⁷ The study was conducted from 2012 to 2013. Of the total number of patients ($N = 522$), half received pirfenidone and half received placebo. After 52 weeks of treatment (the end of the study), the researchers found a smaller decline in FVC—the primary endpoint—in the treatment group compared to placebo (mean decline, 235 mL vs 428 mL, respectively [$p < 0.001$]). Regarding the six-minute walk test, the investigators found that 25.9% of the treatment group exhibited a decrease of ≥ 50 meters, compared to 35.7% of the placebo group ($p = 0.04$). (Progression-free survival was defined as a confirmed $\geq 10\%$ decrease in predicted FVC, a confirmed decrease of 50 meters in the six-minute walk test, or death.)

The pirfenidone group in the ASCEND trial showed a 43% reduced risk for death or disease progression (HR, 0.57; $p < 0.001$).^{16,17} All-cause mortality was lower in the pirfenidone group (4%) than in the placebo group (7.2%), but this was not statistically significant. Deaths from IPF in the pirfenidone group totaled three patients (1.1%) versus seven patients (2.5%) in the placebo group; this was also not statistically significant. The most common adverse effects seen during the study were nausea (36%), rash (28.1%), and headache (25.9%).¹⁷

Recommendations for use. Liver function testing should be performed at baseline, monthly for six months, and every three months afterward, as elevations in liver enzymes have been observed.¹⁸ Pirfenidone is a CYP1A2 substrate; moderate-to-strong CYP1A2 inhibitors should therefore be discontinued prior to initiation, as

they are likely to decrease exposure and efficacy of pirfenidone. There are currently no black box warnings.¹⁸

Nintedanib

Hostettler et al studied lung samples from patients with IPF to determine the mechanism of action of nintedanib.¹⁹ Evaluation of fibroblasts derived from IPF samples revealed that they contained higher levels of platelet-derived growth factor (PDGF) than did nonfibrotic control cells. They also found that nintedanib, a tyrosine kinase inhibitor, significantly inhibited the phosphorylation of fibrotic-inducing growth factors—PDGF as well as vascular endothelial growth factor (VEGF).

INPULSIS trials. A phase 3 replicate of randomized, double-blind, multinational studies, the INPULSIS trials were performed between 2011 and 2012.²⁰ Two study arms were used to evaluate a total of 638 patients who received nintedanib 150 mg bid for 52 weeks. The primary endpoint was annual rate of decline of FVC.

The researchers also evaluated efficacy through two other endpoints: patient-reported quality of life and symptoms via the St. George's Respiratory Questionnaire (SGRQ) and evaluation of time to acute exacerbation. The latter was defined as worsening or new dyspnea, new diffuse pulmonary infiltrates visualized on chest radiography and/or HRCT, or the development of parenchymal abnormalities with no pneumothorax or pleural effusion since the preceding visit; and exclusion of any known causes of acute worsening, including infection, heart failure, pulmonary embolism, and any identifiable cause of acute lung injury.²⁰

INPULSIS 1 (first arm) included 309 patients in the treatment group. Results showed an adjusted annual rate of decline in FVC of 114.7 mL/year, versus 239.9 mL/year in the placebo group ($p < 0.001$). In the treatment group, 52.8% exhibited

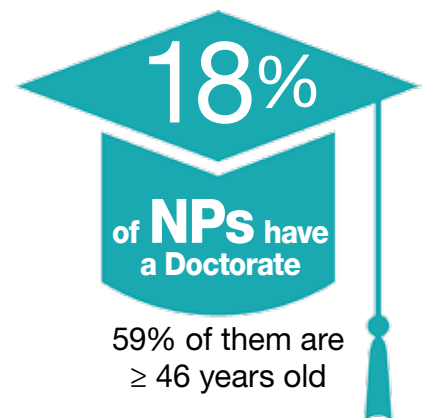


TABLE 2
Annual Rate of Change in FVC:
Comparison of Clinical Trial Endpoints

Clinical Trial	Active Treatment vs Placebo		
	Nintedanib 150 mg bid	Placebo	P value
INPULSIS			
Trial 1	-1,114.7 mL	-239.9 mL	< 0.001
Trial 2	-113.6 mL	-207.3 mL	< 0.001
CAPACITY			
	Pirfenidone 2,403 mg/d	Placebo	P value
Study arm 004	-8%	-12.4%	0.001
Study arm 006	-9%	-9.6%	0.501
ASCEND			
	-235 mL	-428 mL	< 0.001

Abbreviation: FVC, forced vital capacity.

Sources: Noble et al. *Lancet*. 2011¹⁶; King et al. *N Engl J Med*. 2014¹⁷; Richeldi et al. *N Engl J Med*. 2014.²⁰

≤ 5% decline in FVC, compared to 38.2% in the placebo group (p = 0.001). No significant between-group differences were found in SGRQ score or time to acute exacerbation.²⁰

INPULSIS 2 had 329 patients receiving nintedanib. An annual rate of decline in FVC of 113.6 mL/year from baseline was observed in the treatment group, compared to 207.3 mL/year in the placebo group (p < 0.001). In the treatment group, 53.2% showed ≤ 5% decline in FVC, versus 39.3% in the placebo group (p = 0.001). There was also a significantly smaller increase in total SGRQ score (meaning, less deterioration in quality of life) in the nintedanib group versus the placebo group (p = 0.02). A statistically significant increase in time to first acute exacerbation was observed in the nintedanib group (p = 0.005).²⁰

There was no significant difference between groups in death from any cause, death from respiratory causation, or death that occurred between randomization and 28 days post treatment. The most common adverse effects seen throughout the two trials included diarrhea (trial 1, 61.5%; trial 2, 63.2%), nausea (trial 1, 22.7%; trial 2, 26.1%), and nasopharyngitis (trial 1, 12.6%; trial 2, 14.6%).²⁰

Recommendations for use. Liver func-

tion testing should be performed at baseline, at regular intervals during the first three months, then periodically thereafter; patients in the treatment group of both INPULSIS trials had elevated liver enzymes, and cases of drug-induced liver injury have been observed with use of nintedanib.²¹ This medication may increase risk for bleeding due to its mechanism of action (VEGFR inhibition). Coadministration with CYP3A4 inhibitors may increase concentration of nintedanib; therefore, close monitoring is recommended. Avoid coadministration with CYP3A4 inducers, as this may decrease concen-

tration of nintedanib by 50%. There are currently no black box warnings.²¹

Patient monitoring

The ATS recommends measuring FVC and DL_{CO} every three to six months, or sooner if clinically indicated.¹³ Pulse oximetry should be measured at rest and on exertion in all patients, regardless of symptoms, to assure proper saturation and identify the need for supplemental oxygen; this should also be done every three to six months.

The ATS recommends prompt detection and treatment of comorbidities such as pulmonary hypertension, emphysema, airflow obstruction, GERD, sleep apnea, and coronary artery disease.¹³ These recommendations are based on the organization’s 2015 guidelines.

OUTCOME FOR THE CASE PATIENT

The patient was started on pirfenidone (2,403 mg/d). He is continuing treatment and showing improvements in quality of life and slowed deterioration of lung function.

CONCLUSION

IPF causes progressive fibrosis of lung interstitium. The etiology is unknown, the

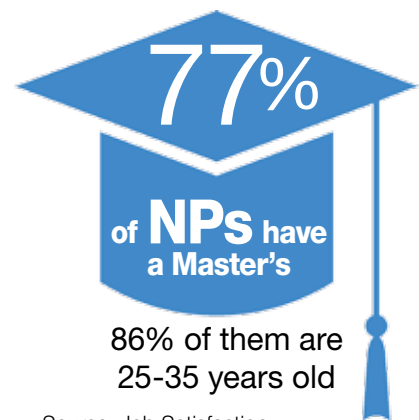
symptoms and signs are vague, and mean life expectancy following diagnosis is two to five years. The most recent IPF guidelines recommend avoiding use of anticoagulants and immunosuppressants (eg, steroids, azathioprine, and N-acetylcysteine), due to their proven ineffectiveness and harm to patients with IPF.

Since the FDA's approval of pirfenidone and nintedanib, the ATS has made recommendations for their use in patients with IPF. Despite mixed results in clinical trials, both drugs have demonstrated the ability to slow the decline in FVC over time, with relatively benign adverse effects. It is difficult to compare pirfenidone and nintedanib, or to recommend use of one drug over the other. However, it is promising that patients with this routinely fatal disease now have treatment options that can potentially modulate their disease progression. **CR**

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Source: Job Satisfaction. *Clinician Reviews.* 2017;27(12):25-30.