

Idiopathic Pulmonary Fibrosis: Exploring the Clinical and Economic Implications of the Evolving Treatment Landscape

Joao A. de Andrade, MD; Gary M. Owens, MD; and Leslie Tolle, MD

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia, a form of interstitial lung disease (ILD) characterized by abnormal wound healing in the lung that leads to progressive scarring and loss of lung function.¹⁻³ Clinically, IPF is heterogenous, often presenting with nonspecific symptoms such as dyspnea and persistent nonproductive cough.¹ It is more commonly found in men, and the frequency increases with age.¹ IPF is limited to the lungs; the presence of nonpulmonary symptoms suggests a need for further evaluation for an alternate diagnosis.¹ A limited number of epidemiologic studies exist for IPF. Literature suggests that the incidence is rising, with an estimated 2.8 to 18 cases per 100,000 people in North America.^{4,5} Prevalence is 13 to 20 cases per 100,000.¹ Although it is unknown if race, ethnicity, or geography are factors in incidence,⁶ rates in Asia and South America are lower (0.5-4.2 cases per 100,000 individuals per year) than in North America and Europe (3-9 new cases per 100,000 each year).⁵

Mutations in a number of genes have been found to confer an increased risk for developing IPF. In particular, a single nucleotide polymorphism (rs35705950) in the *MUC5B* gene, which codes for mucin 5B, a glycoprotein with a functional role in airway clearance and innate immune response to bacteria, has been strongly associated with IPF.⁷ In addition, a number of nongenetic risk factors for IPF have been identified, including cigarette smoking and environmental hazards (eg, exposure to metal and wood dust).⁷ Other factors, such as gastroesophageal reflux and exposure to certain viruses, have been suggested to increase risk, but the evidence to support causal links is inconclusive, and efforts to delineate their contribution to IPF is confounded by their prevalence in the general population.^{3,6} Nevertheless, the growing body of research that has helped to uncover the roles of genetics, aging, and environmental exposures in IPF pathogenesis has caused some to make the case that it should no longer be considered idiopathic.²

Clinical Course and Risk of Mortality by IPF Phenotype

IPF is associated with a poor prognosis, with a median survival of 3 to 5 years from the time of diagnosis.⁸ The most common cause

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia, a form of interstitial lung disease characterized by abnormal wound healing in the lung that leads to progressive scarring and loss of lung function. Comorbidities are highly prevalent in IPF and often lead to further complications and worse outcomes. In fact, undetected and untreated comorbidities are independently associated with poor outcomes. IPF not only affects patient quality of life (QOL) but also requires significant cost for delivering care. Given the potential for rapid progression of IPF and the associated risk for mortality, early diagnosis is critical for retaining the highest lung function and QOL for as long as possible. Delayed diagnosis of IPF is associated with increased costs in terms of investigations performed, and delayed referral can result in lower survival rates independent of disease severity or associated prognostic factors. Significant progress has been made in understanding IPF pathogenesis, which has, in turn, led to the development of novel therapeutic options that improve outcomes, extend life, and minimize disease burden on patients' daily lives. For patients with IPF in the absence of underlying liver disease, pirfenidone and nintedanib are licensed for the treatment of IPF. Additionally, a number of investigational therapeutic options are currently in development. The extent of clinical effectiveness compared with the cost of therapy has led to a lack of consensus on the cost-vs-benefit analyses for the drugs.

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of death among patients with IPF is chronic hypoxemic respiratory failure. Palliative measures are often needed to give patients comfort at the end of life.^{3,9} Ischemic heart disease, heart failure, bronchogenic carcinoma, infection, and pulmonary embolism are also leading causes of mortality in patients with IPF.¹⁰⁻¹³

Estimates suggest that only 20% to 30% of patients survive more than 5 years after receiving a diagnosis of IPF.¹⁰ In general, older age (> 70 years), smoking history, low body mass index, severe physiological impairment, larger radiological extent of disease, and pulmonary hypertension (PH) confer a higher risk of mortality.¹ Data from case series suggest that mortality is nearly universal in patients who develop respiratory failure and are placed on invasive mechanical ventilation.¹⁴

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Radiographic evidence of the disease process may be evident before diagnosis; a portion of patients with IPF have subclinical disease for several years prior to diagnosis.¹⁰ Given the challenges of classifying IPF and predicting prognosis among individual patients, a staging system was developed to help guide management decisions. The multidimensional index includes 4 variables (gender, age, and 2 lung physiology variables) that classify IPF in stages based on predicted mortality.¹⁵ It is unclear what mechanisms may trigger progression from subclinical to active disease, and it is unknown whether screening efforts during the subclinical phase might alter outcomes.¹⁰

About 5% to 20% of patients with IPF are affected by acute exacerbations, which portend worse outcomes.¹ Exacerbations of IPF are characterized by rapid deterioration of symptoms; decline in lung function; and radiographic appearance in the absence of infection, heart failure, pulmonary embolism, or another identifiable cause.¹⁰ As many as 60% of patients with an acute exacerbation of IPF die during hospital admission, and over 90% of those who survive hospitalization die within 6 months after discharge.¹⁶

Comorbidities in IPF

Comorbidities are highly prevalent in IPF and often lead to further complications and worse outcomes. In fact, undetected and untreated comorbidities are independently associated with poor outcomes.¹⁷

IPF is associated with several respiratory comorbidities, notably PH and chronic obstructive pulmonary disorder (COPD), including emphysema. In a systematic review of literature reporting on outcomes from around the world, COPD varied in prevalence based on location, ranging from 6% to 67%;¹⁷ it was also associated with reduced survival in some studies.¹⁷ The prevalence of PH was 3% to 86%, though most estimates were between 30% and 50%.¹⁷ Other respiratory comorbidities of note included obstructive sleep apnea (prevalence, 6%-91%) and lung cancer (prevalence, 3%-48%).¹⁷ Among all respiratory comorbid conditions in patients with IPF, the risk for mortality was highest with lung cancer.¹⁷ PH also commonly conferred an increased risk of mortality, with more severe manifestations portending higher risk.¹⁷

Patients with IPF may also be affected by nonrespiratory comorbidities, including ischemic heart disease (prevalence, 3%-68%) and gastroesophageal reflux disease (prevalence, 0%-94%).¹⁷

Idiopathic Pulmonary Fibrosis and Quality of Life: Impact on Patients and Caregivers

General health, energy level, and amount of independence are typically impaired in patients with IPF.¹⁸ More severe disease appears to have a greater impact on patients' mental and emotional well-being. A retrospective study published in 2001 explored interactions between physical symptoms (eg, cough, reduced exercise capacity, and severity of dyspnea) and quality-of-life (QOL) outcomes (as assessed by Beck Depression Inventory and Children's Depression Inventory scores). It found that, in addition to patients' physical symptoms being significantly more pronounced compared with those of healthy individuals (regardless of treatment status), patients also performed more poorly when it came to psychological characteristics. Patients with IPF were particularly affected in their perception of general health and level of independence compared with matched controls.¹⁹ Additionally, recent findings from a cross-sectional analysis of the Idiopathic Pulmonary Fibrosis-Prospicive Outcomes (IPF-PRO) Registry confirmed that patients with more severe IPF experience greater QOL impairments; this should be considered in the clinical decision-making process.²⁰

Both perceived seriousness of illness and subjective breathlessness correlated with specific aspects of QOL including physical health, level of independence, pain and discomfort, energy and fatigue, dependence on medication or treatments, working capacity, and sexual activity.¹⁹ In a systematic review, pulmonary function scores correlated with QOL measures, though in many of the studies reviewed for the analysis, these associations did not rise to the level of statistical significance. The most consistently identified

clinical parameter found to affect QOL was dyspnea.¹⁸ Elsewhere, researchers have noted that depression in patients with IPF, whether or not directly attributable to their pulmonary disease, impacts responses to the St George's Respiratory Questionnaire, a clinically validated tool used to measure QOL in patients with airway obstruction. Along with dyspnea and exercise capacity, measures of depression more accurately predicted questionnaire scores than other physiologic variables.²¹

Importantly, the emotional and psychological impact of IPF is not limited to patients. In one study, researchers described the emotional devastation felt by loved ones and informal care providers of patients with IPF. Patient mood swings and the caregiver's perception of a confined lifestyle due to the patient's physical limitations exacted a particular toll.²² Feelings of hopelessness over not being able to relieve a loved one's pain were common; in some cases, the obligations of caring for and living with a loved one with IPF led to a sense of burnout or manifested as frustration or resentment.²² Indeed, findings from a number of qualitative research studies have demonstrated the impact of IPF on caregivers, its potential to drive negative mind-sets that impact outcomes, and how the perception of a limited flow of information about the disease and its prognosis creates feelings of anxiety and frustration.²³⁻²⁷

Economic Impact of Idiopathic Pulmonary Fibrosis

The cost of delivering care to patients with IPF is significant. Health care utilization, particularly the requirement for inpatient hospital stays, is a key factor. Data from the IPF-PRO Registry, which was launched in June 2014 in the United States, showed that 27.7% of the IPF population had at least 1 hospitalization and 9.7% had at least 1 emergency department (ED) visit over a one-year period.²⁸ Patients spent an average of 2.2 days in the hospital and 0.8 days in intensive care. Acute-care costs averaged \$14,073; the cost of hospitalizations with an intensive care unit (ICU) stay averaged \$11,438.²⁸ In another study, median length of stay was 5 days and a diagnosis of pneumonia or pneumothorax, need for admittance to the ICU, need for mechanical ventilation, and need for bronchoscopy or lung biopsy were associated with a longer hospital stay.²⁹ Findings from a commercial claims database cohort study estimated total IPF-related hospitalization costs to be approximately \$3.9 million over a 6-year period.³⁰ Possible IPF exacerbation events requiring hospitalization contributed \$3.2 million to the overall cost burden, but despite high occurrence, the majority of these exacerbations did not require hospitalization.³⁰

However, the cost-of-care delivery reported in published studies may actually underestimate the total economic impact of IPF, as study designs may not fully account for cost burden prior to the initiation of treatment. One study reviewed a US Medicare claims database between 2000 and 2011 to assess health care resource use and cost in the year prior to diagnosis (preindex period) and the

year following diagnosis (postindex period).³¹ In the study, patients with IPF had an 82% higher risk of hospitalization (28.8% vs 15.8%) and 72% higher total medical costs (\$10,124 vs \$5888) than matched controls in the preindex period, which may be expected because symptoms precede diagnosis by a median of 1 to 2 years.³¹ Health care utilization and costs increased significantly in the postindex period; patients with IPF had a 134% higher risk of hospitalization (48.7% vs 20.8%), increased risk of ED visits (39.6% vs 17.5%), and 134% higher total medical costs (\$20,887 vs \$8932) compared with matched controls. Based on an assumption of about 158,000 patients with IPF covered by Medicare, authors estimated that total health care costs were approximately \$3 billion per year, \$1.8 billion of which was directly attributable to IPF and associated comorbidities.³¹

Current Treatment Options

Given the poor prognosis, high mortality, and economic burden associated with IPF, the need for effective treatments is high. Among current treatment options, lung transplantation can improve survival among patients with IPF and should be considered in patients with moderate to severe IPF.⁶ Patients should be assessed for lung transplantation at the time of diagnosis. Only highly selected patients would be candidates, given the risk of complications and contraindications associated with transplantation.³

Given the potential for rapid progression of IPF and the associated risk for mortality, early diagnosis is critical for retaining the highest lung function and QOL for as long as possible.

For patients with IPF in the absence of underlying liver disease, pirfenidone and nintedanib are licensed for the treatment of IPF.³² The 2015 update to the American Thoracic Society IPF treatment guidelines included strong recommendations against the use of the following pharmacologic modalities: anticoagulation (warfarin), imatinib, combination prednisone with azathioprine or N-acetylcysteine, and the selective endothelin receptor antagonist ambrisentan.³² Nonpharmacologic options, including supplemental oxygen and/or pulmonary rehabilitation, may be additive in the

care regimen to assist patients with normal function,³ but such measures may add cost burden.

Nintedanib

Nintedanib is an orally administered tyrosine kinase inhibitor that inhibits platelet-derived growth factor receptor α and β , fibroblast growth factor receptor 1 to 3, vascular endothelial growth factor receptor 1 to 3, and FMS-like tyrosine kinase-3; it is administered at a dose of 150 mg twice daily.^{33,34} Liver function tests (ie, alanine transaminase [ALT], aspartate transaminase [AST], and bilirubin) should be performed prior to initiation of nintedanib, as well as every 3 months during therapy and as clinically indicated. Nintedanib is not recommended for use in patients with advanced liver disease (Child-Pugh B or C).

The safety and efficacy of nintedanib in patients with IPF were assessed in 2 replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2). In each study, the adjusted annual rate of change in forced vital capacity (FVC), which was the primary end point, was lower in the nintedanib group vs placebo (-114.7 mL/year vs -239.9 mL/year in INPULSIS-1; -113.6 mL/year vs -207.3 mL/year in INPULSIS-2). Although there was no significant difference in time to the first acute exacerbation in INPULSIS-1, there was a significant benefit with nintedanib vs placebo in INPULSIS-2 (HR, 0.38; 95% CI, 0.19-0.77; $P = .005$).³⁴ A pooled analysis of patients treated with the 150-mg twice-daily dose in the phase 3 studies or the phase 2 TOMORROW study suggested a reduced risk for acute exacerbation events and a reduction in all-cause mortality favoring nintedanib³⁵; it is worth noting, however, that nintedanib is not indicated for these potential benefits. Across clinical trials, diarrhea was the most frequently reported adverse event (AE) after treatment with nintedanib compared with placebo (61.5% vs 18.6% in INPULSIS-1; 63.2% vs 18.3% in INPULSIS-2).³⁴ In the phase 3 studies, a higher proportion of patients in the nintedanib group experienced myocardial infarction compared with the placebo group (2.7% vs 1.2%), while a lower proportion had other ischemic heart disease (1.7% vs 3.1%).^{34,36} Other AEs of note included nausea, vomiting, and increased liver function tests.³⁴

Pirfenidone

The exact mechanism of action of pirfenidone is not entirely clear,³⁷ though the drug is known to have a number of anti-inflammatory and antifibrotic effects including inhibition of collagen synthesis, downregulation of tumor growth factor β and tumor necrosis factor α , and a reduction in fibroblast proliferation.³ The drug is administered orally in an escalating-dose fashion over a 14-day period: It is initiated with one 267-mg capsule 3 times daily (TID), increased to 2 capsules (534 mg) 3 times daily after 1 week, and increased again to 3 capsules (801 mg) 3 times daily after 3 weeks. Liver function tests (ie, ALT, AST, and bilirubin) should be conducted before

initiation, monthly for the first 6 months of treatment, and then every 3 months thereafter as clinically indicated.³ The safety and efficacy of pirfenidone were initially studied in 3 phase 3 trials: a trial in Japan with 275 patients and 2 parallel multinational studies (CAPACITY 004 and 006).³⁸ In the Japanese cohort and in CAPACITY 004, pirfenidone demonstrated reductions in decline of FVC compared with placebo, but the result was not replicated in CAPACITY 006. At the request of the FDA, the drug's sponsor initiated the ASCEND trial to resolve this discrepancy.³⁸ In the latter, the mean decline in FVC after 1 year was -235 mL vs -428 mL in the pirfenidone and placebo groups, respectively. With respect to the study's primary end point, the proportion of patients with a decline of 10 percentage points or more in FVC was reduced by 47.9%, while the proportion of patients with no decline was increased by 132.5% in the pirfenidone group, each compared with placebo.³⁸ Gastrointestinal AEs were common with pirfenidone. In addition, skin-related AEs were more common in the pirfenidone group compared with placebo.³⁸ Additional analyses of pooled data from the phase 3 trials suggested that pirfenidone reduced respiratory-related hospitalization.^{39,40}

Idiopathic Pulmonary Fibrosis Pipeline

A number of investigational, potentially disease-modifying therapeutic options are currently in development. Purified serum amyloid P (pentraxin 2) inhibits monocyte differentiation into profibrotic fibrocytes, which are thought to contribute to the pathogenesis of IPF. In a phase 2 clinical trial that evaluated 117 patients between the ages of 40 and 80 over 24 weeks, the percentage of predicted value from baseline to week 28 was -2.5 in the treatment arm vs -4.8 in placebo (difference, 2.3; 90% CI, 1.1-3.5; $P = .001$).⁴¹ However, there were no significant treatment differences in a number of secondary outcomes, including total lung volume, quantitative parenchymal features on high-resolution CT, and measurement of diffusing capacity for carbon monoxide. There was some suggestion of improved lung function, as the change in 6-minute walk distance was -0.5 m vs -31.8 m in the pentraxin 2 and placebo groups, respectively.⁴¹ Cough, fatigue, and nasopharyngitis were the most commonly reported AEs in the pentraxin 2 group.⁴¹

Pamrevlumab is a fully recombinant monoclonal antibody that targets the secreted glycoprotein connective tissue growth factor that plays an essential role in the fibrotic process.⁴² In the multicenter, phase 2, randomized, double-blind, placebo-controlled PRAISE trial, pamrevlumab reduced the decline in percentage of predicted FVC by 60.3% at week 48, and a lower proportion of patients in the active treatment arm experienced disease progression at that time point.⁴² Treatment-emergent AEs were similar between the study groups. Although more patients in the pamrevlumab group experienced serious treatment-emergent AEs (24%

vs 15%), fewer patients in the pamrevlumab group discontinued treatment compared with the placebo group (6% vs 13%).⁴² A phase 3 trial is currently under way.

Additional pharmacologic agents that have entered clinical trials include PBI-4050, which may improve FVC when administered with nintedanib, and BMS-986020 (NCT01766817), an oral LPA antagonist.³

Challenges, Opportunities, and Future Directions

Given the potential for rapid progression of IPF and the associated risk for mortality, early diagnosis is critical for retaining the highest lung function and QOL for as long as possible. Delayed diagnosis of IPF is associated with increased costs in terms of investigations performed, and delayed referral can result in lower survival rates independent of disease severity or associated prognostic factors.⁴³ However, several questions remain regarding how best to make a diagnosis of IPF, including:

- What CT features should prompt biopsy when the CT is not diagnostic for usual interstitial pneumonia?
- Which type of biopsy should be used (ie, transbronchial lung cryobiopsy vs surgical vs other)?
- Is there a role for genomic classifiers to aid diagnosis?
- How can clinicians best utilize a multidisciplinary discussion process in making a diagnosis?

Often, interstitial lung abnormalities (ILAs) are identified as an incidental finding (usually in the context of investigating potential lung cancer), and the particular etiology and prognosis follow from discovery of relevant clinical features and patient characteristics (by way of patients' environmental exposure history, for example). Results of a 2013 study evaluating a lung cancer screening population showed that approximately 10% of participants were discovered to have ILAs; 5.9% were nonfibrotic and 2.1% were fibrotic.⁴⁴ Among this group, 37% of individuals showed progression over a 2-year period,⁴⁴ suggesting that incidental findings of ILD should not be dismissed. Other studies suggest that ILAs are present in 7% to 8% of patients undergoing lung cancer screening.^{45,46} It is worth noting that, despite radiographic progression, progression to IPF over the next few years appears unlikely.⁴⁷ Results of another study showed a 6.6% prevalence of ILD with CT screening, which had a higher frequency in men.⁴⁸

From the perspective of treatment, the approvals of nintedanib and pirfenidone for IPF were significant breakthroughs. Each has demonstrated an ability to slow disease progression. Also, ongoing research and development efforts on novel pharmacologic options—some with the potential to halt or even reverse the disease process—are encouraging, but unmet needs remain. First, clinicians will need greater insight on the role of supportive, nonpharmacologic treatments, and there is also a need for safe and

effective treatments for IPF sequelae and complications. Second, to date, there have been no direct comparative trials involving approved therapeutic options. Data from randomized clinical trials suggest that nintedanib and pirfenidone have similar efficacy and that each is well tolerated. Therefore, the choice of agent may be tailored to patient preference and potential for AEs. Factors that clinicians may wish to consider include contraindications, potential for adherence, patient preference, and patient lifestyle. Making choices about treatment, including whether to treat at all, should be conducted via shared decision-making between the clinician and patient. This may be particularly true as more treatment options become available, including novel adjunctive, supportive, and palliative options. The latter brings to light third and fourth potential unmet needs: What is the best first-line treatment option, and what is the best course of action to extend the treatment benefit long term?

From a historical perspective, significant progress has been made in understanding IPF pathogenesis, which has, in turn, led to improved treatment paradigms that improve outcomes, extend life, and minimize disease burden on patients' daily lives.

Expanding concerns about health care resource utilization present an additional factor for clinicians to consider. Active management may minimize excess utilization and costs in addition to improving QOL for patients. On the other hand, despite the current high rates of reimbursement, the treatment landscape is rapidly changing, which potentially has implications for the payer-clinician relationship. The IPF drugs currently on the market, nintedanib and pirfenidone, are estimated to cost approximately \$100,000 per year, representing a high cost burden for patients, Medicare, Medicaid, and private insurers.^{3,49} Two economic modeling analyses suggested that both pirfenidone and nintedanib improved treatment effectiveness at a higher cost compared with best supportive care, placebo, or other pharmacologic approaches.^{50,51} Drug acquisition cost was the most significant determinant of overall cost. One of these studies suggested an advantage for nintedanib on cost-effectiveness measures.⁵⁰

However, the extent of clinical effectiveness compared with the cost of therapy has led to a lack of consensus on the cost-vs-benefit analyses for the drugs, particularly because the available data have mostly come from Europe.

With the aforementioned questions and concerns notwithstanding, there is good reason to be cautiously optimistic about the future of IPF treatment and patient care. From a historical perspective, significant progress has been made in understanding IPF pathogenesis, which has, in turn, led to treatment paradigms that improve outcomes, extend life, and minimize disease burden on patients' daily lives. The remaining challenges that are faced in how best to provide care for patients with IPF are welcomed, as answering them provides hope for making additional incremental advances in patient care. ■

Author affiliations: Vanderbilt University Medical Center, Nashville, TN (JAD); Gary Owens Associates, Glen Mills, PA (GMO); Cleveland Clinic Respiratory Institute, Cleveland, OH (LT).

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Address correspondence to: Leslie Tolle, MD. E-mail: tollel@ccf.org.

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