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Keeping Pace With the Evolving Treatment Landscape in Idiopathic Pulmonary Fibrosis

Highlights

- Idiopathic Pulmonary Fibrosis: The Role of Pathobiology in Making a Definitive Diagnosis
- Idiopathic Pulmonary Fibrosis: The Role of Evolving Therapies in Patient Care
- Idiopathic Pulmonary Fibrosis: The Role of the Pharmacy Benefit Manager in Providing Access to Effective, High-Value Care

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Keeping Pace With the Evolving Treatment Landscape in Idiopathic Pulmonary Fibrosis

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Intended Audience

Managed care physicians and pharmacists.

Activity Overview

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease of unknown etiology characterized by progressive respiratory insufficiency and shortened survival. This supplement to *The American Journal of Managed Care* will provide a clinical overview of the emerging pharmacologic treatment options for IPF, describe the intricate drug formulary requirements for disease- and symptom-centered management of patients with IPF, and discuss the role of pharmacy benefits managers in implementing cost-effective ways to provide optimal patient care.

Statement of Educational Need

Over the years, a number of pharmacologic strategies have been used to treat IPF without solid clinical evidence supporting a beneficial impact on the disease course. Notably, treatment guidelines released in 2011 did not recommend any pharmacologic treatment for patients with IPF. However, clinical trials conducted after the release of the 2011 guidelines have been useful in defining harmful and/or ineffective treatments and identifying successful therapies in the management of IPF. Within the last year, 2 therapies were approved by the FDA to treat IPF. In addition, IPF is associated with multiple co-morbidities that affect survival or affect quality of life and require attention and management. Therefore, it is important for healthcare professionals to be aware of new developments in the treatment of IPF so that they can use these emerging options in appropriate patients.

Educational Objectives

At the completion of this activity, the participant will be able to:

- Recognize emerging pharmacologic treatment options for IPF
- Discuss the complex drug formulary requirements for disease- and symptom-centered management of patients with IPF
- Review the role of pharmacy benefit managers in facilitating access to care and reducing cost in the management of IPF

Physician Credit

Accreditation Statement

CME

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- Practice-based learning and improvement
- Professionalism

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Table of Contents

Participating Faculty	S274
Reports	
■ Idiopathic Pulmonary Fibrosis: The Role of Pathobiology in Making a Definitive Diagnosis	S276
Maria Padilla, MD	
■ Idiopathic Pulmonary Fibrosis: The Role of Evolving Therapies in Patient Care	S284
Maria Padilla, MD	
■ Idiopathic Pulmonary Fibrosis: The Role of the Pharmacy Benefit Manager in Providing Access to Effective, High-Value Care	S294
Thomas J. Morrow, MD	
CE/CME Sample Posttest	S302



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Idiopathic Pulmonary Fibrosis: The Role of Pathobiology in Making a Definitive Diagnosis

Maria Padilla, MD

Idiopathic Pulmonary Fibrosis: A Challenging Disease

Interstitial lung disease is characterized by diffuse fibrosis and scarring of the interstitium—the lace-like network of tissue that extends around the air sacs of the lungs.¹ Idiopathic pulmonary fibrosis (IPF) is one of the most common interstitial lung diseases, with an increasing prevalence and high mortality.^{2,3} IPF has a histopathological pattern of usual interstitial pneumonia (UIP), but, as its name suggests, is of unknown etiology.³ It is a chronic, progressive disease characterized by fibrosis and worsening dyspnea and lung function.¹ IPF is a complex disease that is challenging to diagnose and manage due to its nonspecific respiratory symptoms, unknown cause, need to exclude alternative diagnoses, varied clinical course punctuated by episodes of acute exacerbations, and an array of associated comorbidities.³

Epidemiology: Incidence and Mortality on the Rise?

The exact incidence or prevalence of IPF is unknown. The complexity of the diagnosis, variability in course, and evolving definition of the disease have made it difficult to conduct large-scale studies of the incidence or prevalence of IPF in the United States.³ However, a variety of population-based cohort studies have estimated the prevalence to range from 14 to 42.7 cases per 100,000 individuals, using narrow and broad-based criteria to define IPF, respectively. The annual incidence of IPF is estimated at 6.8 and 16.3 per 100,000 people, using narrow and broad-based definitions, respectively.⁴ These numbers have doubled over the past 3 decades.³

IPF primarily affects middle-aged to older adults.^{1,2} In the Medicare population, the annual prevalence of IPF has increased steadily, from 202.2 cases per 100,000 individuals in 2001 to 494.5 cases per 100,000 individuals in 2011.⁵ The majority of patients have a history of cigarette smoking.¹ Among newly diagnosed patients with Medicare, the majority were white (91%) and female (54%).

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease of unknown etiology characterized by fibrosis of the interstitium, resulting in progressive respiratory insufficiency and shortened lifespan. Treatment focus tends to shift from disease-centered to symptom-centered as the disease progresses. Over the years, a number of pharmacologic strategies have been used to treat IPF, albeit without solid evidence demonstrating a beneficial impact on the disease course. The previously held theory that inflammation was the predominant underlying feature of IPF led to the use of corticosteroids and immunosuppressive therapy as the standard of care. However, a greater understanding of the pathogenesis of IPF has evolved and guidelines were developed using evidence-based criteria. Guided by the data, treatment guidelines developed in 2011 stated that no pharmacologic therapy showed a proven benefit for patients with IPF and issued recommendations against the use of most treatments. The treatment landscape changed in October 2014, when the FDA approved pirfenidone and nintedanib for the treatment of IPF. For the first time, clinicians have therapeutic options with demonstrated clinical efficacy to treat patients with IPF. To provide effective high-value care for patients with IPF, healthcare professionals require thorough knowledge and awareness about these medications, including their safety concerns.

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For author information and disclosures, see end of text.

However, male sex was associated with a higher incidence of the disease and a shorter survival time after diagnosis.⁵

IPF is a progressive disease. Progression, however, is highly variable: most patients continue for years with a steady but gradual decline in lung function, while a minority stabilize or undergo a period of rapid decline. Some experience an acute exacerbation—a period of acute deterioration in respiratory function without a known cause or origin. IPF is typically fatal, with median survival estimated to be between 3 and 5 years after diagnosis.⁶ Death rates are estimated at 61.2 deaths/million and 54.5 deaths/million for men and women, respectively.⁷ Mortality, which increases with age, is consistently higher in men than women, and undergoes seasonal variation, even upon exclusion of infectious causes.⁸ Evidence suggests that the incidence of IPF and its associated mortality are increasing, partly as a result of the aging population, and also because of an increased awareness of the disease among patients and physicians, as well as an improved ability to diagnose IPF.^{7,9,10}

Pathobiology

The pathogenesis of IPF is complex. The driving force behind disease progression is hypothesized to be the loss of cellular integrity in the alveolar epithelium, which results from a combination of factors that include injury, aging, genetic and epigenetic influences, and reactivation of developmental signaling pathways.^{8,11} The distortion of the lung's architecture results in vascular remodeling, decreased oxygenation, respiratory failure, and, ultimately, death.⁸

The hallmark histopathologic feature of IPF is a heterogeneous, variegated appearance of the lungs, with alternating areas of healthy lung tissue adjacent to areas of fibrosis, with foci of fibroblastic activity (fibroblastic focus) and remodeled lung architecture manifested by the presence of honeycomb changes (cystic spaces surrounded by fibrous thickened walls that replace the normal lacelike structure of lung parenchyma) and scant interstitial inflammation.¹² These changes are thought to occur due to a relentless fibrotic process itself resulting from an inflammatory response or an epithelial/mesenchymal (fibroblastic) disorder that propels disease progression.^{13,14} The currently accepted paradigm is that unknown endogenous or environmental stimuli disrupt the homeostasis of the alveolar epithelial cells that line most of the lung surface. When the lung is damaged, a key component of normal healing is to reestablish the epithelium. In IPF, there is excess epithelial cell apoptosis, while fibroblasts develop resistance to apoptosis, causing

fibroproliferation. The damaged areas are repopulated by fibroblasts instead of epithelial cells, and these fibroblasts differentiate into myofibroblasts and secrete matrix proteins and collagen, leading to fibrosis.^{12,13}

Another perspective on the pathophysiology of IPF also leads away from the thought that inflammation progressing to fibrosis is a key driver in IPF. IPF has been described as a neoproliferative, neoplastic disorder of the lung. This hypothesis is based on similarities in the pathogenicity of IPF and cancer, including genetic alterations, uncontrolled proliferation, resistance to apoptosis, tissue invasion by myofibroblasts, and altered cellular communications and intracellular signaling pathways.¹⁴ The presence of cytogenetic alterations related to carcinogenesis have been demonstrated in patients with IPF, including the presence of a mutated *p53* gene, a tumor suppressor gene involved in apoptosis and cell proliferation, and the fragile histidine triad gene.^{14,17} Even intracellular signaling pathways, such as Wnt/beta-catenin and the phosphatidylinositol 3-kinase/protein kinase B pathways crucial in the pathogenesis of cancer, are prominent in IPF.¹⁴ If the similarities between the pathogenesis of IPF and cancer translate into a link between these diseases, it may provide researchers greater insight into the etiology of IPF, alter the treatment options and management strategies currently used in IPF, and improve the prognosis of patients with IPF.

Risk Factors

Despite its unknown etiology, there are a number of known risk factors associated with IPF. The most widely accepted is cigarette smoking, which increases the risk of IPF by approximately 2-fold.¹⁸ Smoking is considered a major risk factor in patients regardless of genetic or familial factors, particularly in those with a history of more than 20 pack-years.¹ Other risk factors include occupational exposure (agriculture/farming, hairdressing, and textile manufacturing) and environmental exposure to contaminants, including textiles, coal dust, stone, and sand.^{1,3,19} Metal dust (specifically brass, lead, and steel dust) and wood dust (pine) are also associated with IPF. Autopsy reports have also shown that patients with IPF had higher levels of inorganic particles, such as silicon and aluminum, in their hilar lymph nodes compared with controls.^{1,19,20}

Epidemiologic study results show the prevalence of IPF is greater in industrialized regions versus rural regions within a nation.²¹ Exposure to microbial agents and viral infections, particularly chronic viral infections with the Epstein-Barr virus and hepatitis C, is thought to

Report

be associated with an increased risk of IPF. Due to the confounding factor of patients receiving immunosuppressive therapy, however, definitive conclusions cannot be made, making infection a potential complication of therapy rather than a factor in the presence of IPF.^{1,19}

There is also increasing evidence for a genetic basis for IPF, with family history often indicating increased risk.^{1,19} Although familial forms of IPF account for less than 5% of total patients with IPF, genetic studies have proven to be insightful when it comes to the pathogenesis of the disease.¹ Additionally, the presence of comorbid conditions, such as gastroesophageal reflux disease (GERD) (via microaspiration) and diabetes, may be considered risk factors for IPF.^{1,3} Identification of risk factors and an early diagnosis is critical in developing prevention strategies and prompt treatment initiation.

Diagnosis

The clinical symptoms of IPF, which are cough and dyspnea, are nonspecific and could be readily attributed to other pulmonary diseases. IPF's histologic pattern, although currently defined as UIP, was previously often grouped with diseases now considered separate entities (nonspecific pneumonia and desquamative interstitial pneumonia). As a result, IPF may have been misdiagnosed as nonspecific interstitial pneumonia or desquamative interstitial pneumonia.³ Accurate diagnosis involves a combination of clinical, laboratory, radiologic and/or pathologic data obtained from physical examination, laboratory (exclusionary serologic findings) testing, and diagnostic imaging.⁶ A multidisciplinary approach with close collaboration among an array of health care professionals (ie, clinicians, radiologists, and pathologists) increases the accuracy of diagnosis.

Clinical Presentation

Evidence-based guidelines suggest that any patient presenting with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and finger clubbing be considered for the possible diagnosis of IPF.¹ The most common signs and symptoms include shortness of breath, with breathlessness during exercise, initially and at rest later in the course of the disease, and uncontrolled bouts of a constant dry, hacking cough.² Other signs and symptoms that may develop as the disease progresses include rapid and shallow breathing, gradual but unintended weight loss, fatigue or malaise, muscle aches, and clubbing of the fingers or toes. Progression of IPF has been associated with collapsed lung, lung infec-

tions, blood clots in the lungs, lung cancer, respiratory failure, pulmonary hypertension (PH), and heart failure.² However, around 5% of patients have no symptoms. Other diseases, especially collagen vascular disorders, may have similar pulmonary radiographic and histologic pictures that may precede the rheumatologic manifestations of these diseases, further complicating the diagnosis. The importance of performing serologic testing and eliminating alternative underlying diagnoses cannot be overemphasized.⁴ Combined with the progressive nature of the disease, these factors can make it extremely challenging to obtain a definitive diagnosis of IPF⁴ without the help of a multidisciplinary team.

Diagnostic Criteria

The clinical presentation of IPF is nonspecific and broad. The evaluation of a patient suspected of having IPF begins with the exclusion of other known causes. This includes a careful physical examination and a thorough individual and family history. Evaluations should focus on comorbidities, medication use, and occupational, avocational, and environmental exposures.^{1,2}

Diagnostic tests include a chest x-ray, CT scan of chest along with a variety of lung function tests, such as spirometry, lung volume and diffusing capacity, pulse oximetry, the 6-minute walk test, a skin test to rule out tuberculosis, exercise testing, an electrocardiogram, and blood levels of oxygen and carbon dioxide (arterial blood gas test).²

Although no specific blood tests exist to help diagnose IPF, certain markers or serologic tests have been recommended to exclude connective tissue diseases that may have a similar presentation. Based on symptomatology and physical exam findings, the latter may include an expanded panel of rheumatologic markers to further establish an accurate diagnosis. Bronchoalveolar lavage cellular analysis and transbronchial lung biopsy are not helpful in establishing a diagnosis of IPF due to the small size of specimen, but may be useful in excluding other diagnoses. A surgical lung biopsy is more definitive in establishing the histologic pattern of UIP to support the diagnosis of IPF or an alternative diagnosis.^{1,2} Not all patients are candidates for surgical biopsies due to limited reserve or increased morbidity. However, making a definitive diagnosis of IPF requires confirmation of the presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients who do not undergo a surgical lung biopsy (see [Table 1](#)) or specific combinations of HRCT and surgical lung biopsy patterns (see [Table 2](#)) in patients who undergo a surgical lung biopsy (see [Table 3](#)).¹

Table 1. HRCT Criteria for UIP Pattern¹

UIP Pattern	Possible UIP Pattern	Inconsistent With UIP Pattern
<ul style="list-style-type: none"> • Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis <p>and</p> <ul style="list-style-type: none"> • Absence of features listed as inconsistent with UIP pattern (see third column) 	<ul style="list-style-type: none"> • Subpleural, basal predominance • Reticular abnormality <p>and</p> <ul style="list-style-type: none"> • Absence of features listed as inconsistent with UIP pattern (see third column) 	<ul style="list-style-type: none"> • Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent greater than reticular abnormality) • Profuse bilateral micronodules (predominantly upper lobes) • Discrete multiple, bilateral cysts, away from areas of honeycombing • Diffuse, bilateral mosaic attenuation/air trapping in 3 or more lobes <p>or</p> <ul style="list-style-type: none"> • Consolidation in bronchopulmonary segment(s)/lobe(s)

HRCT indicates high-resolution computed tomography; UIP, usual interstitial pneumonia. Reprinted with permission of the American Thoracic Society. Copyright © 2015 American Thoracic Society. Raghu G, Collard H, Egan J, et al. 2011. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 183(6):788-824. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Histopathological criteria for a UIP pattern includes evidence of marked fibrosis or architectural distortion with or without honeycombing in a predominantly subpleural or paraseptal distribution, the presence of patchy involvement of lung parenchyma by fibrosis, the presence of fibroblast foci, and an absence of features against a diagnosis of UIP, suggesting an alternate diagnosis. Criteria suggesting an alternate diagnosis include hyaline membranes, organizing pneumonia, granulomas, marked interstitial inflammatory cell infiltrate away from areas of honeycombing, predominant airway-centered changes, or other features suggestive of an alternate diagnosis. However, the presence of hyaline membranes and organizing pneumonia may be associated with an acute exacerbation of IPF.¹ Confirmation of a UIP pattern using these criteria ensures that a differential diagnosis is limited to those that present with UIP in other clinical settings, such as connective tissue disease, chronic hypersensitivity pneumonitis, and pneumoconiosis.¹ In instances where a HRCT cannot confirm a diagnosis (see Table 2¹ for criteria inconsistent with a UIP pattern), a surgical lung biopsy is needed to ensure appropriate diagnosis.¹ In these instances, it is important to have a multidisciplinary discussion among experts in interstitial lung diseases that includes the potential for sampling error and re-evaluating the adequacy of the HRCT technique. The accurate diagnosis of IPF requires exclusion of diseases that may have similar radiographic and/or histologic patterns and may be treated differently. The multidisciplinary discussion enhances the accuracy of

diagnosis and facilitates the initiation of appropriate therapy for IPF.¹

Common Comorbidities

IPF is associated with a number of comorbidities that are responsible for a substantial proportion of morbidity and mortality. Among the most significant comorbidities is GERD, which is present in approximately 90% of patients with IPF; it is associated with a worsening or exacerbation of IPF.²² Conversely, stabilization of pulmonary function and improved oxygen saturation levels have been demonstrated with the medical and surgical treatment of GERD. It has been suggested that more than 50% of patients with IPF have asymptomatic GERD.²² Current guidelines recommend treating most patients with asymptomatic GERD.¹

In patients with IPF evaluated for lung transplantation, more than one-third presented with PH at baseline. Over time, about 78% of patients who did not present with PH at baseline developed the condition. In addition, at the time of transplant, 86.4% of patients with IPF also had PH.²³ Concomitant PH tends to increase the incidence of dyspnea and impair exercise capacity.^{6,24} Both of these, along with the diagnosis of PH itself, are known to increase risk of death within 2 years.¹

Depression was observed in about a quarter of patients with IPF, and it is associated with increased dyspnea and pain, poor sleep quality, and reduced forced vital capacity (FVC).²⁵ Obstructive sleep apnea (OSA) was reported in up to 88% of patients with IPF, with 68% diagnosed with moderate to severe OSA. Because of the lack of strong

Table 2. Histopathological Criteria for UIP Pattern: Surgical Lung Biopsy¹

UIP Pattern	Probable UIP Pattern	Possible UIP Pattern	Not a UIP Pattern
<ul style="list-style-type: none"> Evidence of marked fibrosis/architectural distortion with or without honeycombing in a predominantly subpleural/paraseptal distribution Presence of patchy involvement of lung parenchyma by fibrosis Presence of fibroblast foci <p>and</p> <ul style="list-style-type: none"> Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis (see fourth column) 	<ul style="list-style-type: none"> Evidence of marked fibrosis/architectural distortion with or without honeycombing Absence of either patchy involvement or fibroblastic foci, but not both Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis (see fourth column) <p>or</p> <ul style="list-style-type: none"> Honeycomb changes only^a 	<ul style="list-style-type: none"> Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation Absence of other criteria for UIP (see first column) <p>and</p> <ul style="list-style-type: none"> Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis (see fourth column) 	<ul style="list-style-type: none"> Hyaline membranes Organizing pneumonia^b Granulomas^b Marked interstitial inflammatory cell infiltrate away from honeycombing Predominant airway centered changes <p>or</p> <ul style="list-style-type: none"> Other features suggestive of an alternate diagnosis

HRCT indicates high-resolution computed tomography; UIP = usual interstitial pneumonia.

^aAn isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.

^bThis scenario usually represents end-stage fibrotic lung disease in which honeycombed segments have been sampled, but where a pattern of UIP might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by preoperative targeting of biopsy sites away from these areas using HRCT.

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screening tools for OSA in these patients, it is recommended that a formal sleep evaluation and polysomnography or nocturnal oximetry at least be considered in patients with IPF.²⁶

In addition to these comorbidities, several others are seen with IPF. Patients with IPF have a 7-fold increase in the risk of developing lung cancer, with squamous cell carcinoma being most common.^{27,28} The risk of developing lung cancer was independent of the contribution of cigarette smoking on the development of lung cancer or IPF.²⁸ Finally, venous thromboembolism occurs at an incidence 34% higher than in the general population²⁹ and should be considered in patients with IPF who have declining respiratory status. Other common comorbidities include pulmonary infection, bronchitis, asthma, heart disease (including heart failure, myocardial infarction, atrial fibrillation, and coronary artery disease), and cerebrovascular disease. The presence of comorbidities negatively impacts patient outcomes and quality of life. Comprehensive evaluation for these comorbidities and aggressive management of them may lead to improved outcomes in patients with IPF.

Disease Progression: Acute Exacerbations

Although most patients continue for years with a steady but gradual decline in lung function, some patients

with IPF undergo a period of rapid decline or an acute exacerbation. Acute exacerbations can occur at any time, and it remains unclear if they are the result of a respiratory complication or an acceleration of the biological processes underlying IPF. The reported incidence of acute exacerbations varies, but it may be as high as 60%. Patients with acute exacerbations have an especially poor prognosis, with retrospective study results reporting mortality rates between 69% and 96% in patients in intensive care units.³⁰⁻³³ The most commonly reported cause of death in patients with IPF is respiratory complications, usually due to an acute exacerbation.³⁴ The criteria for diagnosing an acute exacerbation are typically unexplained breathing difficulty within the previous month, impaired gas exchange, new alveolar infiltrates on HRCT, and no apparent explanation for worsening symptoms.¹

Disease Progression: Risk of Mortality

There are a variety of suggestions proposed for staging IPF, most based on resting pulmonary function test measurements or the extent of radiologic abnormalities. The process is complicated due to the range of comorbidities associated with IPF and unpredictable acute exacerbations. Clinicians may find staging helpful in framing decisions regarding disease management and transplant timing.

Table 3. Diagnosing IPF Using a Combination of HRCT and Surgical Lung Biopsy¹

		HRCT Pattern		
		UIP	Possible UIP	Inconsistent With UIP
Surgical Lung Biopsy Pattern (when performed)	UIP	Yes	Yes	Possible
	Probable UIP	Yes	Yes	No
	Possible UIP	Yes	Probable	No
	Nonclassifiable fibrosis ^a	Yes	Probable	No
	Not UIP	No	No	No

HRCT indicates high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.
^aNonclassifiable fibrosis: biopsy may reveal a pattern of fibrosis that does not meet the above criteria for a UIP pattern and the other idiopathic interstitial pneumonias.
 Adapted from Raghu G, Collard H, Egan J, et al. *Am J Respir Crit Care Med.* 2011;183(6):788-824.

Identifying patients at risk of death within 2 years is critical in prioritizing patients for lung transplantation.¹ Currently, patients with IPF account for the largest proportion of patients on the lung transplant waiting list, with 46.1% classified as having restrictive lung disease (ie, IPF or re-transplants). Depending on the patient population, the country, and the era (before or after lung allocation score), a total of 14% to 67% of patients with IPF die while on the waiting list for a single or bilateral lung transplant.³⁵ Baseline factors associated with an increased risk of death in patients with IPF include greater levels of dyspnea, diffusion capacity for carbon monoxide (DL_{CO}) less than 40% predicted, oxygen desaturation of 88% or less during the 6-minute walk test, greater extent of honeycombing on HRCT, or PH.¹

Longitudinal factors that increase the risk of death within 2 years include an increase in the level of dyspnea, a decreased FVC by at least 10% of absolute value, a decrease in DL_{CO} by at least 15% absolute value, or worsening of fibrosis on HRCT.¹ Physiologic parameters should be assessed at 3- to 6-month intervals.

Treatment of IPF

Once a diagnosis has been obtained, there are a number of management strategies that can be used; guidelines have also been developed to assist practitioners. Because IPF is a progressive disease, the goal of therapy is to improve the status of patients by slowing the progression of disease, managing comorbidities, and preventing acute exacerbations to optimize quality of life and increase survival. Management strategies are typically disease-centered (using pharmacologic and nonpharmacologic approaches to manage disease progression) or symptom-centered (palliative care that focuses on maximizing quality of life and reducing symptom burden from IPF or

its comorbidities), with the latter increasing over time as IPF progresses.^{1,36}

The recommendation is for patients to be considered for nonpharmacologic and pharmacologic therapies for IPF symptoms and treatment of comorbidities as soon as they are diagnosed, especially in cases of PH (challenging, as no approved pharmacologic therapy exists), OSA, and GERD. Currently, oxygen is the only modality recommended for the treatment of patients with PH who are hypoxemic at rest or with effort. Throughout the course of IPF, patients should be evaluated for their risk of death and suitability for a lung transplant. Lung transplantation remains the final treatment option over the course of the disease. However, not all patients are eligible for lung transplantation. In addition, even among those who undergo a transplant, median survival is only 4.5 years.³⁵

The treatment guidelines for IPF were updated in 2015 to include the first 2 drugs approved for the treatment of IPF: pirfenidone and nintedanib.³⁷ Pirfenidone (Esbriet) is an approved antifibrotic and is an anti-inflammatory drug that has the potential to reduce the risk of disease progression by 30%.^{38,39} In the pirfenidone group, compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC ($P < .001$).⁴⁰ Twenty-three percent of patients on pirfenidone had stable lung function, and pirfenidone reduced the decline in FVC by 193 mL compared with placebo.⁴¹ A second drug, nintedanib (Ofev), is a small molecule tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor.⁴² Nintedanib has demonstrated a

Report

45% to 68% reduction in the annual rate of FVC decline compared with placebo,⁴²⁻⁴⁴ as well as a significant reduction in the time to first acute exacerbation in patients with IPF (but only in 1 of 2 trials conducted in parallel).⁴² Together, these results potentially indicate a slowing of IPF progression.⁴² Both agents require close monitoring due to significant adverse events.

As a result of the varied course of IPF, the presence of comorbidities, the periods of acute exacerbations that may necessitate aggressive treatment, and the lack of updated treatment guidelines, there is no unified IPF treatment strategy. IPF management should continually evolve over the course of the disease in an effort to prevent disease progression and maximize quality of life and health status. Discussion with patients as to goals of therapy, expected benefits, and potential adverse effects and interventions to mitigate these are imperative before initiating treatment with specific therapeutic agents. It is essential, therefore, that all members of the healthcare team, from the primary care physicians to the pharmacy benefits managers, understand the course and evolution of the disease, the range of comorbidities, and the potential for acute exacerbations. All of these factors need to be assessed to develop a comprehensive and effective drug formulary for IPF and ensure a timely shift in management strategy to counter any adverse events or worsening of symptoms. Furthermore, there is a significant potential for drug interactions with increasing polypharmacy as treatment evolves and comorbidities appear. Through drug utilization reviews, prescriptions should be monitored to ensure that old medications that are no longer needed or do not appear to be effective will not continue to be used in error; in addition healthcare professional should ensure compliance with medications to promote optimal well-being.

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Idiopathic Pulmonary Fibrosis: The Role of Evolving Therapies in Patient Care

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Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic lung disease of unknown etiology characterized by progressive respiratory insufficiency and shortened survival. The course of illness is complicated by multiple comorbidities that impact prognosis and quality of life and adversely affect survival. Treatment of IPF is based on disease-centered management (ie, pharmacologic and nonpharmacologic approaches) and symptom-centered management (ie, palliative care to improve quality of life and reduce symptom burden).¹ As the disease progresses, emphasis on disease-centered management decreases and shifts to symptom-centered management. Despite the fact that there is limited evidence demonstrating the efficacy of many of the agents used, both strategies rely on a range of pharmacologic and nonpharmacologic approaches. Therefore, it is important for healthcare professionals to understand the range of therapeutic options, as well as the appropriate use of agents and interventions.

Patients with IPF have a poor prognosis, and until 2014, there were no approved therapies except lung transplantation. Unfortunately, not all patients are eligible for lung transplantation, and while conferring a survival benefit, the median survival of 4.5 years remains a significant obstacle to long-term success of this procedure.² Treatment guidelines from the American Thoracic Society and the European Respiratory Society (ATS/ERS), which were published in 2000, identified IPF as a distinct entity, provided diagnostic criteria (both major and minor), and gave treatment recommendations.³ At the time, the recommended standard of care included corticosteroids and immunosuppressive agents (ie, azathioprine or cyclophosphamide). This recommendation was based on the theory that inflammation was the predominant pathogenic mechanism of IPF, despite the fact that there was minimal supporting evidence.⁴

In the ensuing decades, we have gained a greater understanding of the pathogenesis and course of IPF.

Abstract

Idiopathic pulmonary fibrosis (IPF) is a disease with a poor prognosis. Treatment focuses on both disease- and symptom-centered management with emphasis shifting from disease-centered to symptom-centered, as the disease progresses. In the past, a number of pharmacologic strategies were used to treat IPF, although none demonstrated any solid evidence of beneficial impact on the disease course. The initial theory that inflammation was the predominant characteristic of IPF placed corticosteroids as the standard of care. However, the pathobiology of IPF has evolved, and guidelines are now developed using evidence-based criteria. In the last year, 2 therapies, pirfenidone and nintedanib, were approved for IPF and have quickly become the cornerstone of the standard of care for this disease. For the first time, clinicians have therapeutic options that have demonstrated clinical efficacy in patients with IPF. These treatments however, have safety concerns and should not be administered concurrently with certain medications. In addition, recent clinical trials have shed new light on other treatment approaches. Because of this, healthcare professionals should remain cognizant of the evolving changes in the management of IPF.

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Based on findings and observations, the prevailing concept is one of abnormal reparative response to alveolar epithelial cell injury that results in migration, proliferation, and activation of fibroblasts, and excessive secretion of extracellular matrix components. This results in scarring of the lung, remodeling of the lung architecture, and irreversible loss of function. The search for an effective treatment was directed at compounds targeting the wound-healing cascade and fibrogenesis, but due to the vast number of mediators, growth factors, signaling pathways, and redundancy of systems involved in the process, finding effective treatments has been challenging.⁴

Treatment Guidelines

The strength and extent of accumulating evidence demonstrates the need to change guidelines and management recommendations. When treatment guidelines were first published by the ATS/ERS in 2000, recommendations were based on the minimal evidence available at the time. As was the standard practice, guidelines were developed based on a consensus approach.³ Guidelines are now developed using evidence-based medicine and utilize a standard system called Grading of Recommendations of Assessment, Development and Evaluation (GRADE) to support recommendations.^{5,6} The 2011 guidelines were based on all available data published before May 30, 2010, at a time when there were no therapies shown to improve IPF. Based on the GRADE criteria, the 2011 guidelines stated that no pharmacologic therapy showed definitive, proven benefit for patients with IPF and the committee recommended against most treatments.⁶ A summary of the committee's treatment recommendations is presented in the [Table](#).^{4,6-10}

Prior to 2014, it was recommended that clinicians discuss preferences and prognosis with the patient at the time of diagnosis, assess if the patient was appropriate for lung transplantation, and reserve pharmacologic treatment for patients willing to accept possible adverse events with minimal benefit.¹¹ A review article by Lee and colleagues stated that for most patients, the first-line pharmacologic approach should be participation in a clinical trial, as it allows patients to actively participate in their care, have access to potentially beneficial treatments, and obtain medical care at leading facilities.¹

The 2011 guidelines also provided recommendations for nonpharmacologic treatments, including pulmonary rehabilitation, long-term oxygen therapy, mechanical ventilation, and noninvasive positive-pressure ventilation. According to the guidelines, pulmonary rehabilita-

tion is recommended for the majority of patients with IPF because improvements are generally seen in dyspnea and the 6-minute walk test (6MWT); however, the long-term benefits of this therapy are unclear.¹² Regarding the other treatments, long-term oxygen therapy is recommended for patients with hypoxemia, noninvasive positive pressure is recommended for some patients, and mechanical ventilation was deemed appropriate for a minority of patients as an interim treatment to lung transplantation.⁶

The guidelines stated that lung transplantation should be discussed with appropriate patients at the time of diagnosis, or at the first sign of objective deterioration. Lung transplantation is the only treatment that has shown improved survival in a select patient population despite a median survival of only 4.5 years.²

In summary, in the 2011 guidelines, clinicians were advised to discuss patients' values, preferences, and prognosis and make patients aware of available clinical trials. Patients with a high risk of death should be considered for lung transplantation, while a limited group of patients may be eligible for pharmacologic treatment, as long as they are willing to accept the potential adverse events compared with unknown potential benefits. Patients should be monitored for disease progression and treated with corticosteroids when experiencing acute exacerbations, while palliative should be reserved for symptom management rather than disease treatment.⁶

First Treatments Indicated for IPF

Since publication of the 2011 guidelines, 2 compounds, pirfenidone (Esbriet) and nintedanib (Ofev), have been approved in the United States for the treatment of IPF and have become cornerstones in the standard of care. Given the seriousness of the disease, poor prognosis and lack of proven therapies available for IPF, the FDA granted both therapies fast track, priority review, orphan product, and breakthrough designations.^{13,14}

Pirfenidone

In preclinical models, pirfenidone demonstrated anti-inflammatory, antioxidant, and antifibrotic effects.^{15,16} The safety and efficacy of pirfenidone in IPF was demonstrated in 5 randomized, controlled trials comprising 1710 patients.^{15,17-19} In one double-blind, placebo-controlled Japanese study, pirfenidone demonstrated slower decline of vital capacity in patients receiving pirfenidone; however, the trial was stopped early due to an increased incidence of acute exacerbations in the placebo group.¹⁵ These encouraging results fueled the initiation of 3 ran-

Table. Summary of Treatment Regimens^{4,6-10}

Therapy	2011 ATS/ERS Recommendation	Trials of Note	2015 Updates
Corticosteroid monotherapy	Not recommended. However, the majority of patients experiencing an acute exacerbation should be treated with a corticosteroid. No recommendations about the dose, route, and duration were made.		
Colchicine	Not recommended		
Cyclosporin A	Not recommended		
Corticosteroid/ immunomodulator (eg, azathioprine, cyclophosphamide)	Not recommended		
Corticosteroid/azathioprine/ acetylcysteine	The majority of patients should not be treated; however, it may be an option for a minority of patients. The therapy may be appropriate in patients willing to accept the possible adverse events despite the small benefits.	The 3-drug arm of the PANTHER-IPF study was stopped early due to higher rates of death, hospitalization, and serious adverse events.	Strong recommendation against its use.
Acetylcysteine monotherapy	Not recommended. Treatment may be reasonable for a minority of patients. Therapy may be appropriate in patients willing to accept the possible adverse events despite the small benefits.		
Interferon gamma-1b	Not recommended		
Bosentan	Not recommended. However, the committee was not unanimous in its decision.		Conditional recommendation against its use.
Etanercept	Not recommended. However, the trial was underpowered so no definitive conclusion regarding efficacy could be drawn.		
Anticoagulation therapy	Not recommended. Treatment may be appropriate for a minority of patients.	ACE-IPF was stopped early due to an increased number of deaths in the anticoagulation arm.	Strong recommendation against its use.
Pirfenidone	No. However, it may be appropriate for a minority of patients.	Approved in the United States based on CAPACITY 1, CAPACITY 2, and ASCEND.	Conditional recommendation for its use.
Nintedanib	Not addressed	Approved in the United States based on INPULSIS 1 and INPULSIS 2.	Conditional recommendation for its use.
Sildenafil	Data was published after the formal face-to-face voting so there was insufficient time for the committee to conduct a thorough review. No recommendation was made.	STEP-IPF trial did not meet its primary end point of improvement in 6MWT.	Conditional recommendation against its use.
Imatinib mesylate	Data published after the formal face-to-face voting so there was insufficient time for the committee to conduct a thorough review. No recommendation was made.		Strong recommendation against its use.

ATS/ERS indicates American Thoracic Society and the European Respiratory Society; 6MWT, six-minute walk test.

domized, controlled trials: 1 in Japan and 2 multinationally.^{18,19} The multinational studies termed CAPACITY were 2 concurrent, placebo-controlled, phase 3 trials (CAPACITY 1 and CAPACITY 2) that enrolled a total of 779 patients with mild to moderate IPF. The primary end point was change in the percentage of predicted forced vital capacity (FVC) from baseline to week 72.¹⁹ In CAPACITY 1 (also called study 004), treatment with pirfenidone significantly reduced the mean decline from baseline in FVC compared with placebo at week 72 ($P = .001$) and in the proportion of patients with a FVC decline of at least 10%.¹⁹ In CAPACITY 2 (also called study 006), there was a significant treatment difference in FVC up to week 48 with pirfenidone versus placebo ($P = .005$), but this was not maintained at week 72.¹⁹ Pooled data for the primary end point from both trials showed a significant treatment effect regarding FVC with pirfenidone versus placebo (-8.5% vs -11.0% ; $P = .005$), and a positive treatment effect for pirfenidone for select secondary end points (ie, progression-free survival [PFS], categorical decline in FVC, and 6MWT).²⁰

A 2012 interim analysis of RECAP, an open-label extension study of the CAPACITY trials, reported that 50% of patients initially randomized to pirfenidone in CAPACITY were still alive and remained on treatment almost 4 years later; this suggested that pirfenidone is suitable for long-term treatment.²⁰ Lung function and overall survival were also analyzed in patients originally randomized to placebo in CAPACITY and switched to pirfenidone in RECAP. These patients demonstrated similar FVC and survival outcomes to those who received pirfenidone in the CAPACITY studies.²¹

Because the primary end point of change in predicted FVC was met in CAPACITY 1 and not CAPACITY 2, the FDA requested an additional confirmatory phase 3 study to support approval.¹⁷ The ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in IPF) trial enrolled 555 patients and showed that treatment with pirfenidone led to a 45% relative reduction in mean change in FVC at 52 weeks (the primary end point) and also significant improvements in 6MWT ($P = .04$) and PFS ($P < .001$) (secondary end points).¹⁷ Pooled data from ASCEND and the 2 CAPACITY studies showed a 48% reduction in all-cause mortality and a 68% reduction of IPF-related mortality.⁴

The most common adverse events (AEs) seen in the clinical trials were photosensitivity and gastrointestinal (GI)-related events, such as nausea, dyspepsia, anorexia, and GI reflux. In addition, elevations in levels of alanine

or aspartate aminotransferases to at least 3 times the upper limit of normal were more frequent with pirfenidone than placebo, but these changes were reversible and associated with no clinically significant sequelae.⁴

A long-term analysis of safety that included 789 patients who received at least 1 dose of pirfenidone in the phase 3 studies and the 2 open-label studies with a cumulative total exposure for the population of 2059 patient-exposure years showed that worsening IPF was the leading cause of drug discontinuation along with nausea, rash, and respiratory failure. The most commonly reported treatment-emergent AEs with pirfenidone were GI- and skin-related events, specifically nausea (40%), dyspepsia (21%), vomiting (18%), and rash (26%). However, these events were generally mild to moderate, occurred early in treatment, and rarely led to discontinuation.²²

The recommended dose of pirfenidone is 801 mg three times daily with food for a total of 2403 mg/day. Pirfenidone should be initiated at one 267-mg tablet 3 times daily and titrated to the full dose over a 2-week period. The recommended dosing schedule is 1 capsule (267 mg) 3 times daily with food for week 1; 2 capsules 3 times daily with food for week 2; followed by 3 capsules 3 times daily for week 3 and beyond.¹⁶ Clinical studies have shown that between 70% to 80% of pirfenidone is metabolized via cytochrome P450 (CYP)1A2; therefore, it is recommended that strong CYP1A inhibitors (ie, fluvoxamine, enoxacin) be stopped before the patient begins pirfenidone. If concomitant use occurs, the dose of pirfenidone should be reduced to 1 capsule 3 times a day.¹⁶ In addition, moderate CYP1A2 inhibitors, such as ciprofloxacin (750 mg twice daily) may slightly increase the dose of pirfenidone in the bloodstream, and the dose of pirfenidone should be reduced to 2 capsules 3 times a day. No dose adjustment is recommended for lower doses of ciprofloxacin; however, patients should be monitored.¹⁶ Finally, CYP1A inducers may lower the amount of pirfenidone in the bloodstream and, therefore, should be discontinued.¹⁶ The prescribing information recommends that clinicians be aware of other medications that patients are taking; if they are inhibitors of CYP1A2 or of other CYP isoenzymes involved in the metabolism of pirfenidone, they should be stopped before pirfenidone is started.¹⁶

Nintedanib

Nintedanib is a small molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor, and

platelet-derived growth factor receptor.²³ The efficacy and safety of nintedanib in patients with IPF was examined in a phase 2, dose-finding study (TOMORROW) and in 2 phase 3 placebo-controlled trials (INPULSIS-1 and INPULSIS-2).^{23,24} The primary end point in the 3 trials was the annual rate of decline in FVC.²² In TOMORROW, an analysis of the primary end point showed that the annual rate of FVC did not differ significantly between patients treated with nintedanib and placebo; however, the difference did approach the threshold of significance ($P = 0.01$). An analysis of secondary end points showed that patients who received nintedanib had a significantly smaller mean absolute reduction in FVC ($P = .004$), better resting oxygen saturation ($P = .03$), and improvement in total lung capacity ($P < .001$) compared with those receiving placebo.^{23,24}

Nintedanib was approved on the basis of 2 parallel INPULSIS trials that evaluated the efficacy and safety of the therapeutic in 1066 patients. In both trials, the primary end point was rate of decline in FVC over 1 year.²⁴ Both INPULSIS trials showed that nintedanib was associated with a significantly reduced rate of decline in FVC over the treatment period. In INPULSIS-1, a significantly greater proportion of patients given nintedanib had a response in FVC ($P < .001$).²⁴ INPULSIS-2 showed a significant delay in time to first exacerbation ($P = .005$); however, that same delay was not seen in INPULSIS-1.⁴ While no survival benefit was observed in either study, both trials demonstrated that treatment with nintedanib, over 52 weeks, significantly reduced the rate of FVC decline.²³

The most frequent AEs in the nintedanib arms were GI in nature. The most common was diarrhea, which led to premature discontinuation of study drug in 4.5% of patients given nintedanib in INPULSIS-1 and 4.3% of patients in INPULSIS-2.⁴ Other AEs reported more frequently in the nintedanib arms in the clinical trials were nausea, vomiting, and elevated levels of alanine aminotransferase, aspartate aminotransferase, or both, at 3 times or more the upper limit of normal.⁴ According to the prescribing information, AEs, seen more often in nintedanib versus placebo, included bronchitis (1.2% vs 0.8%) and myocardial infarction (1.5% vs 0.4%).²⁵ The most common AEs leading to death that occurred more frequently in the nintedanib group versus the placebo group were pneumonia (0.7% vs 0.6%), malignant lung neoplasm (0.3% vs 0%), and myocardial infarction (0.3% vs 0.2%).²⁵ Treatment with nintedanib was also associated with arterial thrombotic events. In the clinical trials, 2.5% of patients given nintedanib reported an event compared

with 0.8% of patients given placebo. Caution should be used when treating patients with cardiovascular risk factors and nintedanib should be stopped if the patient develops signs or symptoms of acute myocardial ischemia.²⁵

The recommended dose of nintedanib is 150 mg twice daily. Nintedanib is a substrate of permeability glycoprotein (P-gp) and CYP3A4; therefore, concomitant use of nintedanib and P-gp and CYP3A4 inhibitors (ie, ketoconazole and erythromycin) may increase blood levels of nintedanib. Patients should be monitored closely, and if AEs occur, nintedanib should be temporarily stopped and/or reduced (to 100 mg twice daily).²⁵ If stopped, treatment can be restarted at the full dose of 150 mg twice daily or at 100 mg twice daily and increased back to 150 mg twice daily at a later time. If the patient cannot tolerate the reduced dose, treatment with nintedanib should be discontinued.²⁵ Conversely, coadministration with P-gp and CYP3A4 inducers (ie, rifampicin, carbamazepine, phenytoin, and St. John's wort) decrease blood levels of nintedanib and should be avoided.²⁵ Nintedanib is also a VEGFR inhibitor, which may increase the risk of bleeding, so healthcare professionals should closely monitor patients on anticoagulation therapy and adjust their anticoagulation therapy if needed.²⁵ They should also monitor for possible increased risk of arterial thrombotic events in patients with an already inherent risk due to IPF. It is recommended that liver function tests be performed at periodic intervals to monitor for potential toxicity of both therapies (pirfenidone and nintedanib).

Implications of Additional Trials

Clinical trials have led to FDA approval of the first successful therapeutics in IPF. These therapeutics have been demonstrated to slow the rate of progression of the disease, providing invaluable initial strategies for IPF. They expand the opportunity for additional trials that may lead to more effective therapies and to targeted interventions. Great value has been served by the many well-designed, but negative trials conducted over the past decades. A summary of the trials and their potential impact on the 2011 treatment recommendations is located in the Table.^{4,6-10} The following section will review some of the key clinical trials.

PANTHER-IPF

The use of glucocorticoids or immunosuppressive therapy was traditionally the standard approach to IPF. This was based on the belief that inflammation played a role in pathogenesis.⁴ The 2011 guidelines stated that a

corticosteroid/immunomodulatory combination should not be used in patients; however a corticosteroid/azathioprine/acetylcysteine combination may be an option for a minority of patients, if those patients are willing to accept the possible AEs despite the small benefits.⁶ A 2008 survey of pulmonologists reported that approximately 50% prescribed the 2-drug regimen of azathioprine/prednisone or the 3-drug regimen of azathioprine, prednisone, and *N*-acetylcysteine (NAC) in patients with mild to moderate IPF.²⁶

PANTHER-IPF (Prednisone, Azathioprine, and *N*-Acetylcysteine: a Study that Evaluates Response in Idiopathic Pulmonary Fibrosis) evaluated the 3-drug combination in patients with mild to moderate IPF.⁷ Patients were randomized to 1 of 3 arms: prednisone, azathioprine, NAC (triple combination therapy); NAC alone; or placebo. The pre-specified interim analysis of efficacy and safety showed that the triple combination therapy was associated with an increase in all-cause mortality (8 vs 1, $P = .01$), all-cause hospitalizations (23 vs 7, $P < .001$), and serious treatment-related AEs (24 vs 8, $P = .001$) compared with placebo, and that there was no significant difference in change in FVC (-0.24 liters vs -0.23 liters, $P = .85$).⁷ Therefore, the triple therapy arm was terminated early.⁷

ACE-IPF

Anticoagulation has shown some efficacy in experimentally-induced lung fibrosis when given prophylactically or therapeutically, and a small trial demonstrated benefit in 1-year survival in patients with IPF.⁴ The 2011 treatment guidelines state that anticoagulation therapy may be appropriate in a minority of patients despite the lack of evidence supporting its benefit. The Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) study examined if treatment with recommended doses of warfarin could reduce the composite end point of mortality, hospitalization, and 10% annual rate of FVC decline.⁹ ACE-IPF was the first placebo-controlled, double-blind study with the goal of evaluating anticoagulation therapy in IPF.⁹ In 2011, an unplanned interim analysis was requested by the data safety monitoring board due to excess mortality in the warfarin arm, and the trial was stopped before it reached the time of the pre-specified interim analysis for all-cause mortality.⁹ The interim analysis reported an increased number of deaths associated with warfarin versus placebo (14 vs 3) and that two-thirds of deaths in the warfarin arm were likely due to respiratory worsening.⁹

These negative trials were of immense value in definitively establishing contraindications of treatments previously considered of some merit in the treatment of IPF.

STEP-IPF

Limited evidence suggests that treatment with sildenafil improves exercise tolerance, reduces dyspnea, and improves quality of life in patients with IPF and vascular involvement.¹⁰ Because patients with IPF have abnormalities in lung vasculature, it is thought that sildenafil, a phosphodiesterase-5 inhibitor which has demonstrated a role in pulmonary vasodilation, may offer some benefit. The Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) enrolled 180 patients with the primary end point of at least a 20% change in the 6MWT at 12 weeks and secondary end points of changes in 6MWT, dyspnea, and quality of life.¹⁰ The trial did not achieve the primary end point; only 10% of patients in the sildenafil arm and 7% of patients in the placebo arm showed an improvement of at least 20% in the 6MWT. There were, however, minor improvements in some secondary end points, such as degree of dyspnea and quality of life. The study authors stated that the trial was too short and enrolled too few patients; however, it may have provided the data needed to justify further research with sildenafil.^{4,10} The 2011 guidelines did not offer a recommendation on the use of sildenafil because data from the trial were not available for review.⁶

Recent Updates to Treatment Guidelines

Guidelines are manuscripts in evolution, and guided by the results of the aforementioned trials, an update to the 2011 guidelines was published in July 2015. Based on the latest clinical evidence, the 2015 updates recommend against the use of anticoagulation therapy (warfarin), imatinib, selective endothelin receptor antagonists (ambrisentan), and the combination of prednisone, azathioprine, and *N*-acetylcysteine.⁸ The guidelines provide conditional recommendation for the use for nintedanib and pirfenidone, which places high value on the potential benefit and patient-centered outcomes, such as disease progression.⁸ Additional changes to the guidelines include a conditional recommendation against the use of dual endothelin receptor antagonists (macitentan, bosentan), which had a strong recommendation against use in the 2011 guidelines, and a conditional recommendation against the use of phosphodiesterase-5 inhibitors, which was not addressed in the previous guidelines.⁸ See the Table^{4,6-10} for a summary of the updates to the 2011 guidelines.^{4,6-10}

Treating Comorbidities

IPF is associated with multiple comorbidities, including coronary artery disease (CAD), congestive heart failure (CHF), pulmonary hypertension (PH), gastroesophageal reflux disease (GERD), pulmonary embolism, obstructive sleep apnea (OSA), and lung cancer which contribute to increased mortality, decreased quality of life, and decreased functional status.²⁷ In addition, many patients experience acute exacerbations of the disease. Recent guidelines recommend identifying comorbidities at diagnosis and throughout monitoring of the disease.¹¹

Acute Exacerbations

One of the most dreaded complications of IPF is an acute exacerbation. Defined as a sudden progression of IPF, acute exacerbations occur in 5% to 15% of patients annually and are a leading cause of morbidity and mortality in this disease, with mortality rates up to 85%.²⁸ Acute IPF is characterized as²⁸:

- Unexplained worsening or development of dyspnea over 30 days
- Worsening gas exchange
- New bilateral ground-glass abnormalities superimposed on an usual interstitial pneumonia pattern on a high-resolution computed tomography (HRCT) scan
- Exclusion of other etiologies (ie, infection, left-sided heart failure, pulmonary embolism, acute lung injury)

The most common histologic correlate of an acute exacerbation is a form of diffuse alveolar damage, but other patterns can be seen (organizing pneumonia), and a pattern of numerous very large fibroblast foci superimposed on underlying fibrosis.²⁹

Although pirfenidone and nintedanib have demonstrated benefits in IPF, neither has been shown to be effective in the treatment of acute exacerbations of IPF. Studies suggest that oxygen therapy, corticosteroids, antibiotics and/or cyclophosphamide may improve prognosis and outcome. However, until these therapies are evaluated in prospective, randomized, controlled clinical trials, their true worth and efficacy in the treatment of acute exacerbations is unknown.²⁸ If patients survive an acute exacerbation, they are at greater risk of developing a recurrence. The 2011 guidelines recommend that the majority of patients experiencing

an acute exacerbation be treated with corticosteroids; however, no guidance was provided regarding the dose, route, or duration of therapy.⁶

Gastroesophageal Reflux Disease

GERD is one of the most significant comorbidities of IPF. GERD may play a role in disease pathogenesis or be a secondary phenomenon.³⁰ It is estimated that distal GERD is present in 67% to 88% of patients with IPF and proximal GERD is present in 30% to 71% of patients, and both are associated with a worsening or exacerbation of IPF.^{31,32} Patients with IPF and GERD do not display typical symptoms, with cough being the most common symptom; therefore, GERD may be silent in this population. It is recommended that asymptomatic GERD be medically treated in most patients.⁶ Lee, et al showed that higher predicted FVC percentage and $D_{L_{CO}}$ (diffusing capacity for carbon monoxide), along with use of GERD medication, was associated with increased survival.³¹ In addition, patients treated with proton pump inhibitors or histamine 2-receptor antagonists had lower fibrosis scores. The use of GERD medications and disease stabilization were associated with longer survival.³¹ A small study of 4 patients with GERD and IPF showed that treatment with antacid therapy for 2 to 6 years resulted in stabilization or improvement of pulmonary function.³³ However, antacid treatment may affect plasma concentrations of antifibrotic agents such as pirfenidone.⁴ Anti-reflux surgery (fundoplication), in which the upper portion of the stomach is wrapped around the lower part of the esophagus, may offer some benefit to patients. A study of 43 patients with various forms of lung disease and GERD, who were undergoing evaluation for lung transplantation and had previously undergone anti-reflux surgery, showed that 85% of these patients had improvements in FVC.³⁴ More studies are needed to demonstrate the benefits of anti-reflux therapy; however, until then, it is recommended that patients be treated with proton-pump therapy and lifestyle modifications, such as elevating the head of the bed and dietary changes.²⁷

Obstructive Sleep Apnea

Sleep fragmentation and sleep-disordered breathing are frequently seen in patients with IPF. OSA has been reported in up to 88% of patients with IPF, but it is often underrecognized by physicians.³⁵ Studies have suggested that continuous pulmonary airway pressure (CPAP) therapy may improve quality of life. Therefore, it is recommended that patients, newly diagnosed with IPF, undergo overnight polysomnography and begin CPAP therapy, if appropriate.²⁷

Pulmonary Hypertension

PH is defined as a mean pulmonary artery pressure of at least 25 mm Hg, and the severity of PH increases as the severity of IPF progresses.³⁶ It is estimated that the prevalence of PH in patients with IPF ranges from 8.1% to 86.4%.^{27,36} It is recommended that clinicians rule out sleep-disordered breathing, venous thromboembolism (VTE), chronic obstructive pulmonary disease, CHF, or any other possible contributing condition to the development of PH. Supplemental oxygen should be used for hypoxemia, and if appropriate, patients should be referred for lung transplantation.²⁷ The 2011 guidelines state that there are limited data on the treatment of PH; however, the committee recommended that vasomodulatory therapy may be appropriate for patients with moderate-to-severe PH with a mean pulmonary artery pressure greater than 35 mm Hg.⁶

Venous Thromboembolism

In patients with IPF, VTE occurs at an incidence 34% higher than that in the general population, necessitating the use of anticoagulants and other medications to prevent thromboembolic events.^{37,38} VTE significantly contributes to mortality, with 3% to 7% of deaths in IPF due to pulmonary embolism.²⁷ The reason for this is unknown; however, one theory is that IPF results in decreased mobility and the resulting stasis increases the risk for VTE.²⁷ Treatment of VTE in this population should follow conventional recommendations for VTE. The ACE-IPF trial was terminated early due to increased mortality in treatment group (ie, warfarin); therefore, treatment with warfarin is not recommended for IPF. This trial did not address the safety of warfarin in patients with IPF and documented VTE.²⁴ Additional studies are needed to determine if other anticoagulants may result in better outcomes for patients with IPF in the absence of associated VTE.²⁷ In the meantime, appropriate VTE treatment and prophylaxis is recommended for hospitalized patients at risk for VTE.²⁷

Coronary Artery Disease

Other cardiovascular comorbidities that may be present in patients with IPF include CAD.³⁹ CAD was found in 28.6% of patients with fibrotic lung disease compared with 9.8% of patients with emphysema, despite the fact that more patients with emphysema were smokers. Therefore, the development of CAD does not appear to be predicated on cigarette smoking.⁴⁰ It is recommended that patients who exhibit ischemic heart disease, moderate-to-severe coronary calcifications, or are being

considered for transplantation, should undergo cardiac evaluation and possible left heart catheterization.²⁷ Declining functional status with relative stability of pulmonary function studies and HRCT should prompt evaluation to exclude CAD in patients with IPF.

Depression and Anxiety

Approximately 20% of patients with IPF experience depression, most likely due to the severity of dyspnea, poor sleep quality, reduced FVC, pain, and decreased functional status. All patients with IPF should be screened for depression and receive cognitive behavioral therapy and treatment with antidepressants.²⁷ The antidepressant fluvoxamine is a strong CYP1A2 inhibitor and should not be given with pirfenidone. Since deconditioning and limited endurance are frequent comorbid conditions in IPF, pulmonary rehabilitation should be recommended, as it improves fatigue, quality of life, and functional capacity (which, in turn, may improve depression).²⁷

Lung Cancer

Patients with IPF face an increased risk of lung cancer, with prevalence estimates of 4.4% to 38%.^{41,42} The most common histological type occurring in patients with IPF is squamous cell carcinoma, with male ex-smokers most often affected.⁴³ The reason for increased prevalence does not appear to be related solely on shared risk factors between IPF and lung cancer, and it is believed to be the result of genetic defects caused by recurrent injury and inflammation.^{27,44} The optimal therapeutic approach is unclear; compared with control patients, surgery carries a higher death rate) primarily because of acute exacerbations after surgery.⁴⁴ It is recommended that patients with IPF undergo surgical resection only after careful consideration and thorough review of the risks and benefits.²⁷

Symptom Management

Some of the symptoms of IPF are the most debilitating aspect of the disease. Healthcare professionals need to be aware of changes in symptoms, and manage them accordingly. Chronic cough may be a primary manifestation of IPF or as a result of GERD, asthma, or upper airway cough syndrome. Although there are limited trials demonstrating effective treatments for chronic cough, antitussives are recommended in some patients, and in severe cases, oral corticosteroids may be considered.³¹ Treatment guidelines state that there are limited data to support the use of corticosteroids or thalidomide for chronic cough and that chronic opioids may be appro-

Report

appropriate for severe dyspnea and cough.⁶ In addition, worsening dyspnea may be treated with supplemental oxygen, pulmonary rehabilitation, sildenafil, or opioids.³¹

Conclusion

IPF is a chronic, debilitating disease associated with multiple comorbidities and poor prognosis. Our understanding of the pathogenesis of this disease has increased tremendously, and great strides are being made in the area of genetics and molecular biology and in biomarkers for IPF. These hold promise for targeted therapy that may lead to improved survival in patients with this disease. Ongoing trials focusing on specific targets or biomarkers for IPF should increase our knowledge, further our understanding of the disease, and potentially offer additional therapeutics for patients with IPF that will go beyond slowing of disease. Stability and reversal of disease are ultimate goals of treatment. Therefore, clinicians should continue to encourage patients with IPF to participate in clinical trials. In addition, therapeutic options and treatment recommendations are evolving, such as with the approval of agents like pirfenidone and nintedanib. Healthcare professionals should keep abreast of therapies, guidelines, and studies that may impact the management of patients with IPF.

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Idiopathic Pulmonary Fibrosis: The Role of the Pharmacy Benefit Manager in Providing Access to Effective, High-Value Care

Thomas J. Morrow, MD

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It primarily affects individuals aged 60 and older, with an annual incidence in a Medicare population between 78.7 and 93.2 per 100,000 person-years. As patients with IPF live longer, the prevalence has increased, from 202.2 cases per 100,000 in 2001 to 494.5 cases per 100,000 in 2011.¹

The condition, although rare, is growing in incidence because of the aging population in the United States. IPF is generally fatal with a median survival of 3 years or less after diagnosis unless patients undergo lung transplantation. Even then, the mortality rate is high.²

Until recently, there were no approved pharmacologic treatments for IPF. Instead, national guidelines from the American Thoracic Society (ATS) and the European Respiratory Society recommended pulmonary rehabilitation, long-term oxygen therapy, lung transplantation, and enrollment in clinical trials.² However, a new update to the guidelines from the ATS released in 2015 recommends conditional use of 2 recently approved drugs: nintedanib and pirfenidone.³

High-Cost Disease

The chronic nature of IPF, coupled with high rates of comorbidities, puts a substantial financial burden on payers, particularly Medicare. A 2015 analysis of a commercial claims database and a Medicare supplemental insurance database found that patients with IPF are twice as likely to be hospitalized and require outpatient medical visits as compared to those without, resulting in direct medical costs twice as high (\$26,378 in 2008 dollars vs \$12,124). That translates into an additional cost of \$1 billion per year. Inpatient mortality for patients with IPF was also 3-fold higher than that of controls (52.5 deaths per 1000 persons/year vs 14.8 per 1000 persons/year [rate ratio = 3.64; 95% CI, 3.12-

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause that primarily affects individuals aged 60 and older. The economic costs of the disease are significant, with patients twice as likely to be hospitalized and twice as likely to require outpatient medical care as compared with those without IPF, resulting in an additional annual cost to the Medicare system of \$1 billion. The first pharmacologic treatments for IPF, nintedanib and pirfenidone, were approved in 2014 for conditional use. Their use is expected to significantly increase the cost of care for this population, given that patients will likely continue to take the medication until their death. The use of these medications requires that payers implement innovative opportunities to manage their utilization and cost, as well as other medical costs related to the disease. Pharmacy benefit managers have an important role to play in managing the cost and appropriate utilization of these new treatments through disease management programs, negotiated discounts and rebates, improved adherence to treatment recommendations, and benefit design to optimize patient care.

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For author information and disclosures, see end of text.

Table 1. Direct Medical Costs of IPF per Person/Year (2008; Dollars)⁴

	IPF	Control
Outpatient medications	\$6565	\$3033
Inpatient services	\$9100	\$5120
Outpatient services	\$10,713	\$6100
Total	\$26,378	\$14,254

IPF indicates idiopathic pulmonary fibrosis.
Adapted from Collard HR, Chen SY, Yeh WS, et al. *Ann Am Thorac Soc.* 2015;12(7):981-987.

4.25)].⁴ **Table 1**⁴ compares medical costs for patients with IPF versus controls.

Another analysis of data from Medicare beneficiaries from 2000 to 2011 revealed that direct medical costs were significantly higher in patients with IPF than in matched controls, even before their diagnosis (\$10,124 vs \$5,888), and nearly 3-fold higher in the year following diagnosis (\$20,887 vs \$8,932). Half of those costs were related to inpatient admissions compared with 43% of costs for inpatient admissions in the control group; inpatient costs doubled after diagnosis, reflecting the rather rapid progression of this disease as well as the historically poor prognosis of the disease.⁵ Costs reflect the seriousness of this disease; patients with IPF also have higher rates of comorbidities than matched controls, including pulmonary hypertension, chronic obstructive pulmonary disease, pulmonary embolism, and pulmonary infection.⁴

The overall cost of this disease is expected to increase substantially with the addition of pirfenidone and nintedanib, the first FDA-approved therapies for IPF, which have an annual cost of \$94,000 and \$98,000, respectively. Unlike patients receiving other high-priced drugs that have received significant attention in the media, such as those for hepatitis C or cancer, patients with IPF will likely remain on these medications until they either receive a lung transplant or die.⁶

Since there were previously no approved therapies for IPF, pirfenidone and nintedanib were approved based on placebo-controlled studies. Although the trials differed in their design and end points, the results were significant enough to allow approval.

Neither drug has been studied against the other, in conjunction with the other, or for other currently used (off-label) pharmacologic and lifestyle therapies. Thus, it remains unclear which patients should receive which treatment. It is also not clear if they should be used simultaneously.⁷ A meta-analysis of trials of the 2 drugs and indirect comparisons between nintedanib

and pirfenidone showed a slower decline in forced vital capacity (FVC) for patients treated with nintedanib compared with patients treated with pirfenidone. There was no difference in mortality rates between the 2 cohorts. Both drugs were better at reducing the rate of decline in FVC than placebo. Analysis of the pooled data suggests a reduction in the rate of acute exacerbations with nintedanib, with a decrease of overall mortality and respiratory-related mortality with pirfenidone.⁸

Other concerns center on the design of the clinical trials, which enrolled patients with mild to moderate IPF and without significant comorbidities. Most trials used FVC as a primary end point. Although FVC is correlated with disease progression, it is not clear that treatment-related changes in FVC correlate with clinically meaningful changes, such as survival.⁹ Instead, it has been suggested that progression-free survival, overall survival, hospitalization, and patient-reported outcomes are better end points.¹⁰⁻¹³ Another concern is that the FDA approved the 2 drugs for use in all patients with IPF, even though the studies were conducted only in those with mild to moderate IPF.^{14,15}

Sales of the drugs are already robust. In the first half of 2015, the manufacturer of pirfenidone reported sales of \$234 million. Nintedanib's manufacturer is privately held and does not publically report sales figures. Overall sales of both drugs are predicted to top \$500 million in 2015.^{16,17}

As with other high-cost specialty drugs, the approvals of pirfenidone and nintedanib will require that payers implement innovative strategies to manage their utilization and cost, as well as other medical costs related to the disease.

Cost Effectiveness of Pirfenidone and Nintedanib

First, we must preface any comparison of cost in other countries with the reality that for a variety of reasons, the cost of these drugs in other countries may not reflect the cost in the United States. However, because there is

scant literature from US-based studies, it is at least worth considering some of the findings from other nations.

A group of British researchers conducted a systematic review of the clinical and cost effectiveness of current treatments for IPF. Fourteen studies—13 randomized, controlled clinical trials (RCTs) and 1 controlled clinical trial from various countries—were selected from 905 references.¹⁸

At an assumed cost of £39,388 a year (US \$61,581 in 2015), the authors' analysis indicated that nintedanib must cost less than £736 a month (US \$1150 in 2015) to be considered cost-effective compared with best supportive care at a willingness-to-pay (WTP) threshold of £30,000 (\$46,904 per quality-adjusted life year). Pirfenidone at an assumed cost of £70,118 (\$109,627) was also not cost-effective at a WTP of £30,000. The authors identified inhaled N-acetylcysteine as the most clinically and cost-effective option at a WTP threshold of £30,000, but noted that its treatment effect was not statistically significant in the 1 reviewed RCT, and that larger studies are required to demonstrate the level of statistical significance required in the clinic.¹⁸ However, there are many additional factors to consider when evaluating cost-effectiveness of therapies.

Managers and Specialty Drugs

Specialty drugs, such as pirfenidone and nintedanib, have accounted for an ever-increasing percentage of overall drug spending. In 2014, specialty drugs accounted for one-third of all pharmaceutical spending in the United States, which is an increase from 23% in 2009. In addition, the \$54 billion the United States spent on specialty drugs over the past 5 years has contributed to 73% of the overall growth in spending on pharmaceuticals.¹⁹ That trend shows no sign of slowing. In 2014, 19 of the 41 new molecular entities the FDA approved (46.3%) fit the definition of a “specialty” drug.²⁰

Pharmacy benefit managers (PBMs) have an important role to play in managing the costs and appropriate utilization of specialty drugs, including those for IPF. Currently, an estimated 95% of insured Americans have prescription drug coverage through a PBM.²¹

Although PBMs initially provided third-party administrative management of pharmacy claims, their role has grown exponentially over the past 20 years. Today, they act as intermediaries between payers and pharmaceutical companies, leveraging volume to elicit rebates and discounts from drug manufacturers and pharmacies. PBMs develop and maintain drug formularies, negotiate directly with drug manufacturers and pharmacies, identify and implement cost-savings programs, provide medication

therapy management, run mail order and specialty pharmacies, and interact with patients to improve adherence and outcomes.^{22,23} Given their role in developing tiered drug formularies, PBMs exert tremendous influence over drug prescribing.

A 2011 report from the Pharmaceutical Care Management Association predicted that PBMs would save plans and consumers about one-third of drug costs (nearly \$2 trillion) between 2012 and 2021 and up to half of the total costs for plans that complied with all PBM recommendations and tools.²⁴ In a 2014 survey of more than 80 large Midwest employers representing 1.5 million employees, 51% of respondents agreed or strongly agreed that their PBM did a “good job” managing specialty drug costs. However, 90% agreed or strongly agreed that new and innovative solutions were required.²⁵

Opportunities to Manage Costs and Utilization

PBMs have many options available to manage high-cost drugs and diseases. These include negotiating rebates and discounts with drug manufacturers, directing patients to generic alternatives, providing disease management programs, increasing medication adherence, encouraging the use of mail order and/or specialty pharmacies, and managing utilization through prior authorization, benefit design, step therapy, and refill limits. Through their specialty pharmacies, they can also help patients find financial assistance to pay for their medication.²⁴

Table 2²⁶ depicts the most commonly used strategies to manage specialty drug utilization based on a 2014 survey of 366 employers covering an estimated 23.5 million enrollees.²⁶

Rebates and Discounts

Rebates are most beneficial when there are several effective treatments available in the same class. However, given the lack of head-to-head clinical trials between pirfenidone and nintedanib and the fact that trials for each demonstrated similar outcomes, PBMs may want to consider negotiating deep discounts in exchange for exclusivity. A good example is hepatitis C, for which 4 new drugs have entered the market in the past 18 months, all with prices nearing \$100,000 for a 12-week treatment. With 4 similarly effective drugs available, PBMs are negotiating deep discounts with manufacturers in exchange for formulary exclusivity.²⁷

Disease Management Programs

PBMs also use disease management programs to improve access and reduce costs for patients to add value to

Table 2. Commonly Used Strategies to Manage Specialty Drug Utilization²⁶

	Pharmacy Benefit				Medical Benefit ^a	
	2011 ^b (n = 122)	2012 ^c (n = 306)	2013 ^d (n = 335)	2014 ^e (n = 300)	2013 (n = 214)	2014 (n = 195)
Prior authorization	82%	84%	90% ^e	86%	68%	72%
Clinical care management programs	81%	74%	82% ^e	76%	55%	61%
Step therapy	60%	68%	74% ^b	68%	43%	51%

Strategies are ranked by their use rate in the pharmacy benefit in 2014. No significant comparisons of 2013 with 2014 in the medical benefit. Tests of comparisons across benefits not performed.

^aBase: Respondents who cover at least one specialty drug under the medical benefit.

^{b,c,d,e}Significantly higher than group indicated by superscripted letter. Groups are identified in the column header.

Strategies are ranked by their use rate in the pharmacy benefit in 2014. No significant comparisons of 2013 with 2014 in the medical benefit. Tests of comparisons across benefits not performed.

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their core PBM functions. These programs identify patients with a specific medical condition, monitor drug use and effects, and encourage adherence and preventive care.²⁸ Disease management programs can also increase the rate of smoking cessation, which is particularly important with a respiratory disease like IPF, improve the delivery of care for related comorbidities, and improve patient quality of life.²⁹

A disease management program is particularly important in a disease like IPF, in which patients experience an overwhelming lack of psychosocial support, educational resources, and information regarding treatment options, supplemental oxygen, pulmonary rehabilitation, and transplantation.³⁰⁻³² In an industry-sponsored survey of 100 patients with IPF and 100 caregivers, 72% of respondents agreed that better disease management could improve their overall well-being.³³

There are 2 published studies on disease management programs for IPF. The IPF Care Patient Support Program (IPF Care), developed and supported by the manufacturer of pirfenidone together with healthcare specialists throughout Europe and the United Kingdom, is designed to support patients taking pirfenidone as they adjust to their diagnosis and treatment, provide patient education, support, and empowerment, including counseling about living with their condition and managing adverse events, and facilitating and enhancing communication between patients and their healthcare teams. The program begins when the patient is prescribed pirfenidone, and it involves phone calls and patient-tailored information booklets. In some countries, the program also involves face-to-face visits with nurses.³⁴

Results from IPF Care in the United Kingdom demonstrated low rates of discontinuation over 18 months. Of

the 465 patients enrolled in the program, 71% remained after 18 months. Sixteen percent discontinued the drug, mostly due to adverse events (8%) and worsening symptoms (3%), and 11% died. A survey sent to 100 patients who completed the program (44 of the 100 patients responded) suggested that IPF care improved patient self-efficacy about their disease, and patients generally agreed that they remained on pirfenidone longer because of the program than they would have otherwise.

The Program to Reduce Idiopathic Pulmonary Fibrosis Symptoms and Improve Management (PRISM), another disease management intervention, was a small pilot study designed to assess the impact of the program on patient and caregiver stress, evaluate how patient health-related quality of life (HRQOL) was affected, help improve symptom control, and encourage end-of-life decision making.³⁴

Researchers randomized 42 patients and their caregivers to either the intervention group or usual care. All patients completed baseline screening to measure anxiety, depression, perceived stress, HRQOL, and dyspnea.³⁵ The intervention consisted of six 2-hour weekly group sessions for patients and their caregivers. Participants received education about the pathophysiology, symptoms, and treatment of IPF; the basic principles of cognitive behavior and distorted cognitive thinking; the interrelationships between illness, depression, and anxiety; living with a terminal condition; and the day-to-day realities of living with IPF. Patients receiving usual care saw their regular clinicians every 3 to 6 months and could call a clinical nurse specialist with questions.³⁵

The researchers found that patients in the intervention group had lower HRQOL scores after the intervention than before, although their caregivers

Report

reported less stress. There were no statistically significant differences in scores measuring dyspnea, perceived stress, or depression for patients.³⁵ However, patients and caregivers participating in PRISM told researchers that they felt less isolated, had a more balanced view of their illness, and received personal satisfaction from participating in research. The researchers suggest that the decline in HRQOL scores and increased anxiety were due to patients confronting many difficult topics in the training, particularly end-of-life issues, and note that the study was underpowered to detect differences between the 2 groups.

Improving Adherence to Treatment Recommendations

A seminal analysis from the World Health Organization revealed that patients with chronic conditions adhere to long-term medication, including specialty medications, only about half the time.³⁶ Adherence to medications in pulmonary diseases is also low, with results from one study in patients with cystic fibrosis finding an average adherence rate of 48%.³⁷

An analysis of 41 studies of adherence to medications for a variety of pulmonary diseases found an average adherence rate of 68.6%.³⁸ Several factors contribute to nonadherence, many of which can be targeted through disease management programs. These include patient understanding of their disease, the importance of the medication, the perception that the medication is ineffective, and lack of professional and/or family support. Other barriers that can be addressed through case management include various social and economic issues and the complexity of the dose regimen.^{39,40} These kinds of barriers may be particularly relevant with a disease such as IPF, which progresses despite treatment.

To reduce nonadherence due to adverse effects, a panel of European experts in pulmonology, gastroenterology, and dermatology developed recommendations for the use of pirfenidone (nintedanib had not yet been approved in Europe at the time of publication).⁴¹ Recommendations include taking each of the 3 capsules throughout a meal, rather than at one time (ie, 1 at the beginning, 1 in the middle, 1 at the end) to help prevent the drug from slowing gastric motility; slowing titration to the full dose from 2 weeks to 4 weeks; reducing the dose to 1 or 2 capsules 2 to 3 times a day and matching the reduced dose to the time of day when the nausea was most severe; and using prokinetic agents such as domperidone, mosapride, and metoclopramide or proton pump inhibitors to manage gastrointestinal-related adverse effects.

To reduce skin-related adverse events, the panel recommended educating patients to avoid UV-A and UV-B light (including sunlamps), intense artificial light sources, and indirect sunlight for several hours after taking a dose; to use a sunscreen effective against both; and to wear clothing that blocks sunlight, a broad-brimmed hat, and gloves when in the sun. Other options include dose reduction, perhaps dose interruption and reintroduction. The panel also recommended that caregivers receive education about the medication from the entire healthcare team.

Most of the recommendations came from a published report on 40 patients with IPF treated with pirfenidone between September 2011 and January 2013. More than half (58%) experienced adverse effects, primarily gastrointestinal, and 15% discontinued the treatment within the first 6 months; however, that number dropped to zero 10 months later, after the clinicians initiated the interventions described in the panel's recommendations.⁴² Specialty pharmacies have numerous patient support functions, many of which are unique to specialty pharmacy. They can also improve patient adherence by proactively and retrospectively monitoring refill rates and reminding patients of refills with phone calls, as well as cards and text messages; the former is common to specialty pharmacies, with the latter being done by both retail and specialty pharmacies.

A regression model found that pharmacy type was the strongest predictor of medication refill adherence, with those using a retail pharmacy having a medication refill adherence rate that was 16% lower than those using a specialty pharmacy when controlling for reimbursement/payment type, copayment/payment amount per prescription, age, sex, and ethnicity.⁴³

Managing Utilization

PBMs have managed utilization of specialty drugs with benefit design, prior authorization, step therapy, and partial fills. Step therapy is highly unlikely with pirfenidone and nintedanib because there are no other approved options. Additional options for utilization management are described below.

Benefit Design

All PBMs use tiered formularies as an integrated part of benefit design, and health plans that have added pirfenidone and nintedanib to their formularies are placing them on the highest tier. This involves significant cost-shifting to patients, with coinsurance often as high as 30%.^{25,44} Manufacturers override those high out-of-pocket

payments, however, with coupons and other discounts, which countermands the intended effect of shifting more costs to patients.⁴⁵ In addition, there are no lower cost alternatives for IPF, so placing the drug on a higher tier and passing more cost to patients will not drive them to lower-cost alternatives. High out-of-pocket payments can also backfire, with numerous studies finding that rates of drug abandonment and nonadherence increase as out-of-pocket payments increase.⁴⁶⁻⁴⁸

Prior Authorization

Prior authorizations are also commonly used for specialty and other high-cost drugs.⁴⁴ Evidence related to their cost savings is mixed, however, with some studies finding little economic benefit given the cost of managing the program, the fact that 80% of requests are approved, and the potential for increased healthcare utilization if patients do not have access to the right medication.⁴⁹⁻⁵² The question, notes the American Society of Consultant Pharmacists, is whether utilization tools, such as prior authorization, provide value. In other words, do savings in drug costs, if any occur, offset other medical costs?⁵³ This question will need to be addressed with regard to the new treatments for IPF.

Partial Fill

Partial fill, in which patients may only receive a half-month supply, is another way to control costs and reduce waste by ensuring patients can tolerate the medication before providing a full supply. A 2015 report on specialty drugs involving a survey of 70 commercial payers found that half reported savings of 1% to 6% from a partial fill, whereas 16% reported greater savings.⁵⁴ Partial fill may be a good option for pirfenidone and nintedanib in the first 3 to 6 months of treatment because of the drugs' adverse effects.

Current Coverage of Pirfenidone and Nintedanib

To date, it appears that most plans have put pirfenidone and nintedanib on tiers 4 and 5, even tier 6 in some instances. Some require prior authorization, limit patients to a 30-day prescription, prohibit their concurrent use, require that patients have a clinically documented diagnosis of IPF and be under the care of a pulmonologist, or obtain the drugs only through a specialty pharmacy.⁵⁵⁻⁶⁰

Not all plans are covering the drugs. Citing a lack of clinical experience and utilization, Kaiser Permanente of the Mid-Atlantic States' Pharmacy and Therapeutics Committee voted in April and May 2015, respectively,

not to add pirfenidone or nintedanib to its commercial formularies or to formularies for its Medicaid managed care programs in Maryland and Virginia.^{55,61} Both are tier-5 drugs on the plan's Part D formularies.

Conclusion

How PBMs manage utilization and costs associated with pirfenidone and nintedanib, which patients will require for the rest of their lives, presents many challenges. The disease is fatal, and even a lung transplant can only delay death due to IPF. There are no other approved therapies indicated for IPF; other drugs are currently used off-label and are poorly studied.

With 2 newly approved therapies, however, PBMs will eventually be able to use data to determine which might be more cost-effective. In addition, nondrug options, including the development of IPF-specific mobile apps and wearable devices, home-monitoring devices, and virtual health assistants might provide PBMs with additional tools and data sources to manage IPF and other diseases.

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Keeping Pace With the Evolving Treatment Landscape in Idiopathic Pulmonary Fibrosis

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Sample of Online Posttest

Choose the best answer for each of the following:

1. Which of the following statements regarding the progression of idiopathic pulmonary fibrosis (IPF) is false?
 - A. Progression is highly variable
 - B. Some patients may stabilize over time
 - C. Most patients continue a path of steady decline over the years
 - D. The majority of patients undergo a period of rapid decline with acute exacerbations
2. What is the estimated median survival among patients with IPF?
 - A. 1-2 years
 - B. 3-5 years
 - C. 7-10 years
 - D. 10-15 years
3. What should clinicians discuss with patients at the time of diagnosis?
 - A. Prognosis, course of illness, and available treatment options
 - B. The safety and efficacy of approved treatments
 - C. Participation in clinical trials
 - D. All of the above
4. Which of the following best describes the clinical presentation of IPF?
 - A. Specific and narrow
 - B. Specific but broad
 - C. Nonspecific and broad
 - D. Nonspecific but narrow
5. Which of the following statements regarding the 2011 treatment guidelines is true?
 - A. They were developed using evidence-based criteria
 - B. They were based on the opinions of a small committee of pulmonologists

- C. They were consensus-based
- D. They contain the most up-to-date treatment information
6. You are treating a 65-year-old woman with moderate IPF. She experiences mild gastroesophageal reflux disease that is managed through lifestyle changes and depression that is managed through cognitive behavioral therapy and fluvoxamine. You want to start her on pirfenidone, which is metabolized via CYP1A2. How would you dose pirfenidone?
- A. Discuss the interaction of fluvoxamine; advise discontinuation or switch to alternative agent before prescribing pirfenidone at the recommended dosage
- B. Continue fluvoxamine and prescribe pirfenidone at the recommended dosage
- C. Continue fluvoxamine and reconsider prescribing pirfenidone
- D. Reduce the dosage of fluvoxamine and prescribe a lower-than-recommended dose of pirfenidone
7. The use of glucocorticoids or immunosuppressive therapy was traditionally the standard approach to treatment of IPF. Which of the following is true regarding the currently recommended approach to treatment of IPF?
- A. Corticosteroids are still the gold standard of treatment
- B. The corticosteroid/azathioprine/acetylcysteine combination should not be used in patients with IPF
- C. Some patients may benefit from a 2-drug or 3-drug regimen, but more data are needed
- D. Only patients with severe IPF should be treated with the corticosteroid/azathioprine/acetylcysteine combination
8. A British cost-effectiveness analysis published in 2014 showed that which of the following treatments for IPF was potentially cost-effective at market price?
- A. Pirfenidone
- B. Nintedanib
- C. N-acetylcysteine
- D. Sildenafil
9. Which of the following strategies is unlikely to be effective in managing the costs of pirfenidone and nintedanib?
- A. Prior authorization
- B. Rebates/discounts
- C. Disease management program
- D. Step therapy
10. Which of the following is recommended to reduce nonadherence due to side effects of nintedanib?
- A. Partial fills
- B. Reducing the dose
- C. Taking the medication all at once
- D. Discontinuing the medication without consulting a healthcare professional

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