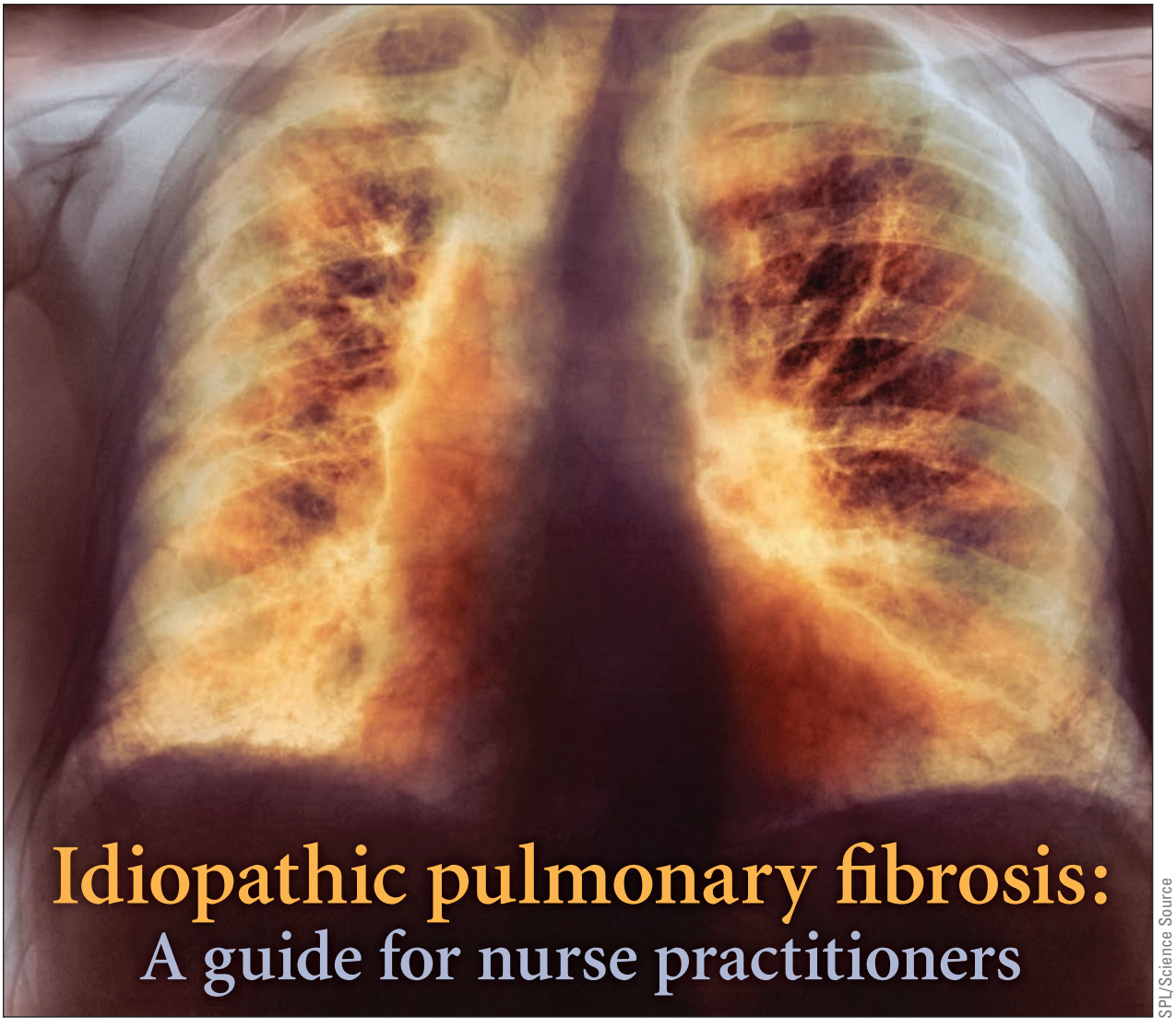

Idiopathic pulmonary fibrosis: A guide for nurse practitioners

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By Michelle Vega-Olivo, CRNP and Gerard J. Criner, MD

Abstract: Idiopathic pulmonary fibrosis (IPF) is a rare disease characterized by decline in lung function, dyspnea, and cough. The clinical course of IPF is variable and unpredictable. Early referral to specialists is key to ensure timely and accurate diagnosis. Two antifibrotic drugs (nintedanib and pirfenidone) have been approved for the treatment of IPF.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial pneumonia of unknown cause.[1] IPF is primarily seen in the sixth or seventh decade of life, is most commonly found in men and in ex-smokers, and is characterized by a pattern on radiology or surgical lung biopsy known as usual interstitial pneumonia (UIP).[1] Although the cause of IPF is unknown, risk factors for the development of IPF include smoking, certain genetic mutations, and possibly gastroesophageal reflux disease (GERD).[2]

IPF is rare; data from a U.S. healthcare insurance claims database from 2004 to 2010 suggested that the

Keywords: cough, dyspnea, idiopathic pulmonary fibrosis, nintedanib, pirfenidone, respiratory function tests

incidence of IPF was 19.3 cases per 100,000 person-years in individuals ages 55 to 64 years.[3]

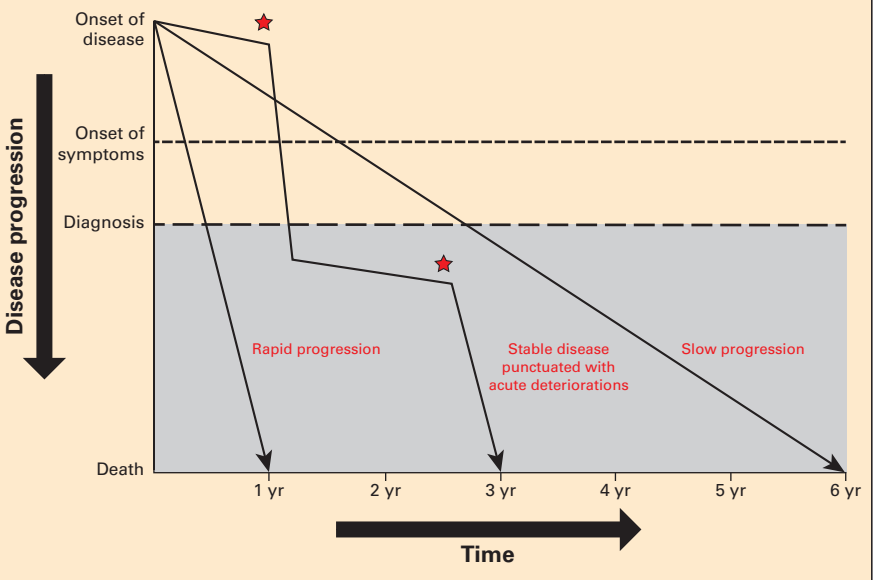
IPF has a poor prognosis, with a median survival time of 2 to 3 years after diagnosis.[4] The course of IPF varies substantially between patients, with survival ranging from a few months to several years.[5] Some patients have periods of relative stability punctuated by acute deteriorations in respiratory function (see *Clinical course of IPF*).[4] These acute exacerbations, which are characterized by radiologic evidence of new, widespread alveolar abnormality, are unpredictable and associated with high morbidity and mortality.[6]

The disabling and relentless symptoms of IPF, its poor prognosis, and uncertainties around the course of the disease can have a devastating impact on the lives of patients and their families.[7] IPF has no cure; however, caregivers can help patients to better understand and manage their disease, evaluate treatment options, and access support to improve their quality of life.

The pathophysiology of IPF is believed to involve excessive activation of fibroblast migration and differentiation when alveolar epithelial cells signal injury.[8] Fibroblasts and myofibroblasts secrete vast amounts of extracellular matrix proteins, such as collagens, resulting in scarring and destruction of the lung architecture, and thus, a decrease in lung volume.[8] Progression of IPF is reflected by a decline in forced vital capacity (FVC). The course of IPF is largely unpredictable, but a decline in FVC of 5% to 10% predicted over 24 weeks has been associated with a greater than twofold increase in mortality over the following year.[9]

A decline in the diffusing capacity of the lungs for carbon monoxide (DLCO) of greater than 15% predicted also appears to be a predictor of mortality.[10] A reduction in a patient's exercise capacity, as evidenced by a decline in the distance that they can walk during a 6-minute walk test (6MWT) has been associated with an increased risk of mortality over the following year.[11]

Clinical course of IPF



Red stars denote acute deterioration in respiratory function.

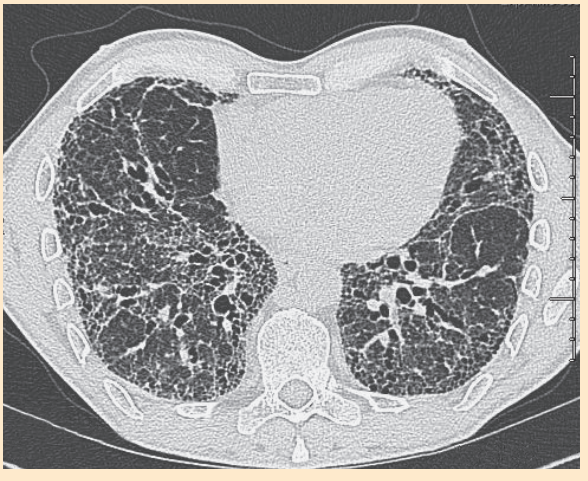
Patient presentation and history

A prospective U.S. study found that the average time between onset of symptoms and referral to an interstitial lung disease (ILD) specialist center in patients with IPF was approximately 2 years. Furthermore, delayed referral was associated with increased mortality.[12] Early referral to specialty IPF care is key to patients receiving an early and accurate diagnosis. Patients with IPF typically present with dyspnea on exertion along with a chronic dry cough.[1] Other symptoms include fatigue, sleeping problems, gastrointestinal (GI) issues, anxiety, and depression.[13]

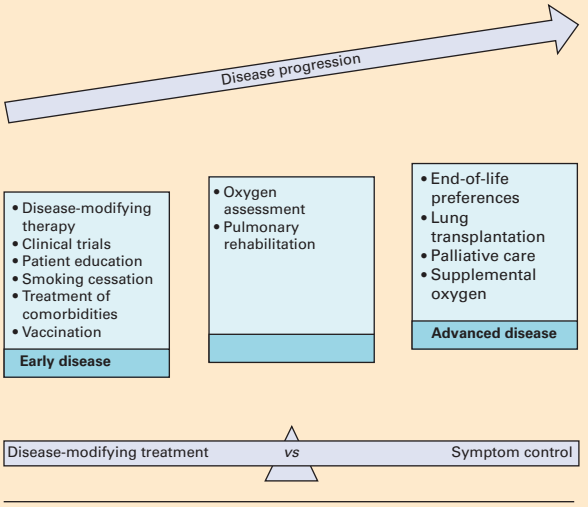
As the symptoms of IPF are nonspecific, they do not prompt clinicians to consider a diagnosis of IPF. Obtaining a careful patient history is important to ascertain predisposing factors, such as smoking history, environmental exposures, and GERD.[1] Any male patient over age 50 with unexplained dyspnea and cough should prompt consideration of IPF. Fine "Velcro" crackles, which sound similar to separating a strip of Velcro, are audible on auscultation and are one of the early signs of IPF. These initially appear in the basal areas of the lung, but in patients with more advanced disease, may be audible throughout the lung fields.[14] Finger clubbing may also be present.[1]

Pulmonary function tests usually demonstrate a restrictive pattern with reduced FVC, DLCO, and forced expiratory volume in 1 second (FEV_1) but normal to increased ratio of FEV_1 to FVC.[15] However, patients with early disease may have normal values on pulmonary function tests.[16] FVC values may also appear normal in patients with concomitant IPF and emphysema due to the combination of restrictive and obstructive ventilatory defects.[16]

HRCT scan showing typical features of UIP



Stepwise approach to managing patients with IPF



Lab workup

There is no lab test specific to IPF; however, blood tests can be valuable in excluding other diseases with a similar clinical presentation to IPF. The presence of autoantibodies is suggestive of ILD associated with connective tissue disease (for example, antitopoisomerase antibodies in patients with systemic sclerosis).[17] Raised levels of serum immunoglobulin G against microbial, avian, or other environmental exposures may be informative in cases of suspected hypersensitivity pneumonitis.[18] Blood test results should not be interpreted in isolation but as part of a comprehensive clinical evaluation.

Diagnosis

IPF is a diagnosis of exclusion, requiring that ILDs of known cause and other idiopathic interstitial pneumonias be ruled out. Evidence-based guidelines endorsed by the American Thoracic Society (ATS) recommend a multidisciplinary approach when considering a diagnosis of IPF.[1] Collaboration between pulmonologists, radiologists, pathologists, and other healthcare workers increases the accuracy of diagnosis.

A high-resolution computed tomography (HRCT) scan of the chest is the cornerstone of the diagnosis of IPF.[1] HRCT scans should be obtained for any patient with an abnormal chest radiograph and clinical findings consistent with ILD. The presence of abnormalities typical of IPF on HRCT permit its diagnosis without the need for a confirmatory surgical lung biopsy.[1] The HRCT scan image shows a definite UIP pattern on HRCT with features including honeycombing, reticular abnormality, and traction bronchiectasis with lower lobe predominance (see *HRCT scan showing typical features of UIP*).

For some patients, a surgical lung biopsy may be required to make a definitive diagnosis if the HRCT pattern is atypical; however, the risks and benefits of a biopsy should be considered when deciding whether it should be performed.[19]

Treatment/management

Optimal management of patients with IPF is multifaceted and evolves over the course of the disease (see *Stepwise approach to managing patients with IPF*). Two antifibrotic drugs, nintedanib and pirfenidone, have been approved for the treatment of IPF in the United States.[20,21] Both of these drugs have been shown to reduce disease progression in patients with IPF by

reducing decline in FVC (see *Effect of disease-modifying therapy on lung function decline*).

Both nintedanib and pirfenidone received conditional recommendations in the latest international clinical practice guidelines for the treatment of IPF, indicating that most patients would want treatment with these therapies; however, patients' individual preferences should be taken into account in making decisions about their care (see *Current recommendations for pharmacologic treatment of IPF*).[22] There are no data to indicate clinical superiority between nintedanib and pirfenidone. At the authors' center, the decision on which agent to use is established on patient preference, lifestyle, medical history, and tolerability.

The efficacy and safety of nintedanib in patients with IPF were demonstrated in the Phase II TOMORROW trial and Phase III INPULSIS trials.[23,24] The INPULSIS trials involved 1,066 patients with a diagnosis of IPF, FVC 50% or greater predicted and DLCO 30% to 79% predicted. Nintedanib reduced the annual rate of decline in FVC by approximately 50%. Investigator-reported acute exacerbations were reported in 4.9% of patients treated with nintedanib versus 7.6% of patients treated with placebo. Diarrhea, the most frequent adverse event associated with nintedanib, was reported in 62.4% of patients treated with nintedanib (versus 18.4% on placebo) but led to permanent discontinuation of treatment in only 4.4% of patients.

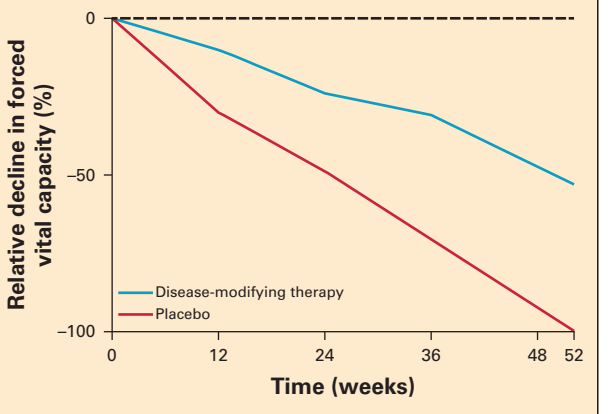
Elevations in liver enzymes have been observed following treatment with nintedanib, and liver function should be monitored prior to and then as clinically indicated during treatment.[20] Based on its mechanism of action, nintedanib may increase the risk of bleeding, and patients at known risk for bleeding should be treated with nintedanib only if the anticipated benefit outweighs the potential risk.[20] Adverse events associated with nintedanib should be managed through dose reductions, treatment interruptions, and measures to control symptoms (for example, the use of loperamide to manage diarrhea).[25] Importantly, the dose adjustments used in the INPULSIS trials have been shown to have no effect on the efficacy of nintedanib.[26]

Pirfenidone was investigated as a treatment for IPF in three international Phase III trials: the two Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY trials) and the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) trial.[27,28] The CAPACITY trials enrolled 779 patients with a diagnosis of IPF, FVC 50% or greater predicted, and DLCO 35% or greater predicted; the ASCEND trial enrolled 555 patients with a diagnosis of IPF, FVC 50% to 90% predicted, and DLCO 30% to 90%.

Treatment with pirfenidone 2,403 mg/day (dosed as 801 mg three times daily) significantly reduced decline in FVC compared with placebo in one of the two CAPACITY trials and in the ASCEND trial. The most frequent adverse events seen in patients treated with pirfenidone were GI events, rash, dizziness, and photosensitivity. Adverse events associated with pirfenidone can be managed through dose reductions and interruptions, avoiding exposure to sunlight and sunlamps, and by wearing sunscreen and protective clothing.[29] Elevations in liver enzymes have been observed following treatment with pirfenidone, and liver function should be monitored prior to and during pirfenidone treatment.[21]

The adverse event profiles of nintedanib and pirfenidone in clinical practice are consistent with those observed in clinical trials. In a study of 186 patients treated at the authors' center, diarrhea and nausea were the most common events in patients treated with nintedanib, whereas nausea, rash, photosensitivity, and dyspepsia were the most common adverse events in patients treated with pirfenidone.[30] For patients who cannot tolerate one antifibrotic agent, it is reasonable to switch to the other agent to maximize the potential for patients to benefit from treatment.

Effect of disease-modifying therapy on lung function decline



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The latest international guidelines included a conditional recommendation for the use of antacid medications in patients with IPF and asymptomatic GERD based on low-quality evidence.[22] It is hypothesized that the progression of IPF may be driven by an abnormal response to repetitive injury to the alveolar epithelium resulting from chronic aspiration of gastric fluid. However, the benefits and risks of antacid medication in patients with IPF remain unclear.[31,32]

The latest international guidelines strongly recommend that patients with IPF not be treated with ambrisentan; anticoagulants; the combination of prednisone, azathioprine, and N-acetylcysteine; or imatinib; and provide conditional recommendations against the use of dual endothelial receptor antagonists, N-acetylcysteine monotherapy, and sildenafil.[22]

In addition to drug therapy, symptom relief and supportive care are important elements of IPF management. Common issues healthcare providers face when treating patients include dyspnea, cough, fatigue, and depression, which are often difficult to manage. Optimal symptom management requires a multidisciplinary approach focusing on patient education and self-management to develop a treatment plan and goals of patient care.[33]

International guidelines strongly recommend the use of oxygen therapy to relieve dyspnea in patients with IPF, clinically significant resting, and exertional hypoxemia.[1] Although there are limited data to support an improvement in survival, supplemental oxygen may improve dyspnea, exercise capacity, and quality of life, especially during the later stages of disease. A 6MWT provides an indication of exercise-induced desaturation and provides a useful indication of the level of prescribed supplemental oxygen needed to avoid hypoxemia.[34] As the disease progresses, resting hypoxemia is an indicator of end-stage disease.

Pulmonary rehabilitation may help improve exercise capacity, dyspnea, and quality of life in the short term and can play an important role in the management of fibrotic lung diseases.[1,35] Patients with IPF should be encouraged to continue maintenance rehabilitation to maximize benefits.

Cough is a common and debilitating symptom of IPF.[13] The mechanisms underlying cough in patients with IPF are unclear, but the mechanical distortion of the lungs that results from fibrosis may lead to an upregulation of sensory fibers.[36] Cough-specific treatments such as over-the-counter cough syrup, opioids, and benzoates have little effect on IPF-related cough. In an open-label study of low-dose thalidomide (an immunomodulator) in patients with IPF, patients reported a significant improvement in cough. A subsequent randomized controlled trial found that patients treated with thalidomide reported an improvement in respiratory quality of life and cough.[37]

Despite these promising results, the cost, adverse events, and access to off-label thalidomide use for cough in patients with IPF make it hard to access for routine clinical care. The use of steroids to treat cough should be evaluated on an individual basis because of their uncertain benefit as well as the complications that may occur with long-term use.[38] Comorbid conditions may also contribute to cough in IPF and may be treatable.

Current recommendations for pharmacologic treatment of IPF

Drug	Strength of recommendation*	Confidence in effect estimates
Recommended for use		
Nintedanib	Conditional	Moderate
Pirfenidone	Conditional	Moderate
Antacid therapy	Conditional	Very low
Recommended against use		
Imatinib	Strong	Moderate
Anticoagulation (warfarin)	Strong	Moderate
Prednisone + azathioprine + N-acetylcysteine	Strong	Low
Ambrisentan	Strong	Low
Macitentan	Conditional	Low
Bosentan	Conditional	Low
Sildenafil	Conditional	Moderate
N-acetylcysteine monotherapy	Conditional	Low

*Strong recommendation: most patients would want the suggested course of action. Conditional recommendation: the majority of patients would want the suggested course of action. Different choices will be appropriate for independent patients depending upon his or her values and preferences. Decision aids may be useful to help patients arrive at a management decision.

Palliative care aims to preserve patient quality of life and may encompass symptom relief, emotional support, and end-of-life care. Palliative care should be available to patients at all stages of their illness and should be personalized to meet the needs of each patient and their caregivers.[1] However, it can be challenging for providers to judge when patients should be referred for palliative care.

Patients with IPF tend to be older adults and frequently have comorbidities that complicate their disease. Often, patients' dyspnea can be exacerbated by cardiovascular disease, emphysema, GERD, sleep apnea, or pulmonary hypertension.[39] Management of these comorbidities can improve patients' quality of life and outcomes, and the prompt identification and treatment of comorbidities is a key part of management.

Lung transplantation should be considered as an option for patients with IPF who meet eligibility criteria. The idiopathic interstitial pneumonias, which include IPF, are the leading cause of lung transplantation in the United States.[40] The ATS, as well as the International Society for Heart and Lung Transplantation, recommend that patients with IPF be evaluated for lung transplant at an early stage, given the progressive and unpredictable nature of the disease.[1,41]

Patient education

Patient education and self-management are critical to help patients with IPF manage their disease and make decisions regarding their care. Patients frequently require support with coming to terms with an IPF diagnosis and coping with the challenges associated with the disease.[42] Educating patients about the disease and its progression allows patients and their caregivers to set realistic goals, feel in control, and prepare for their future. Patients can receive emotional and psychological support via multiple channels, such as from a specialty nurse at an ILD specialty center, during pulmonary rehabilitation, community-based meetings, patient support networks, or one-to-one counseling.

Patients may benefit from receiving information about their disease as it progresses rather than being given all the information at the time of diagnosis.[42] Patients with IPF almost always turn to the Internet to obtain information about their disease, but the information available online is frequently incomplete, inaccurate, and outdated.[43]

Follow-up

The course of IPF is variable and unpredictable. Patients with IPF should be followed up with at regular intervals to assess disease progression, ensure that symptoms and comorbidities are being treated optimally, and to provide emotional support and advice in managing adverse events associated with antifibrotic medications. Regular review of pulmonary function is the practical approach to monitoring disease progression and, while no optimal time interval for repetition of these tests has been defined, FVC and DLCO are usually measured at 3-month to 6-month intervals.[1]

The 6MWT is also frequently used to assess exercise impairment but has poor reproducibility if not conducted in a standardized fashion.[44] While computed tomography scans are not performed frequently to monitor patients, they are important to show disease progression in patients with worsening symptoms. Patients who may be candidates for lung transplantation should be referred to a tertiary center for evaluation as early as possible, as early referral can help identify modifiable contraindications to improve their candidacy for transplantation. Lung transplant centers may also offer patients the opportunity to participate in clinical trials of investigational drugs.

Conclusion

IPF is a devastating disease. Its incidence and prevalence increase markedly with age. The course of IPF is unpredictable, and the mean survival rate is about 3 years from diagnosis. Early referral of patients to a lung transplant center is advisable even if they do not appear to be a suitable candidate. Care for patients with IPF should focus on maximizing length and quality of life.

The development of antifibrotic therapies was a major step forward in treating IPF.[45] Starting either nintedanib or pirfenidone as soon as a diagnosis of IPF is made should be considered for all patients, since these drugs slow the rate of loss of lung function. Treatment of comorbidities, symptom management, and integrating ongoing education into patient care are all crucial in improving a patient's quality of life.

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The authors have disclosed the following financial relationships related to this article:

Michelle Vega-Olivo: charitable grants for a patient advocacy seminar for IPF from Genentech and Boehringer Ingelheim.

Gerard J. Criner: fees and honoraria from AstraZeneca, Boehringer Ingelheim, Nuaira, Mereo, Third Pole, PneumRX, Pulmonx, Pearl, Amirall, CSA Medical, Broncus, AVISA, Lungpacer and GlaxoSmithKline, and contracted clinical trials from AstraZeneca, Avisa, Mereo, Boehringer Ingelheim, Broncus, GlaxoSmith-Kline, Lungpacer, Novartis, Pulmonx, PneumRx/BTG, and Yungjin.

Acknowledgments: The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors received no direct compensation related to the development of the manuscript. Writing support was provided by Julie Fleming and Wendy Morris of FleishmanHillard Fishburn, London, UK, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

DOI-10.1097/01.NPR.0000531121.07294.36