Progress in the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis

Randall S Schwartz, MD1 and Marilyn Glassberg, MD, FACP, FCCP2,3

1. Pulmonary and Critical Care Fellow, Jackson Memorial Hospital, University of Miami, Miami, Florida, US; 2. Director, Interstitial Lung Disease Program, Jackson Memorial Hospital, University of Miami, Miami, Florida, US; 3. Director, Pulmonary Diseases at Interdisciplinary Stem Cell Institute, Jackson Memorial Hospital, University of Miami, Miami, Florida, US

Abstract
Current management of patients with idiopathic pulmonary fibrosis (IPF) requires attention to the exclusion of other causes of interstitial lung disease and either a definitive pattern on high-resolution computed tomography (HRCT) or a suggestive HRCT plus surgical lung biopsy. The main differential considerations include chronic hypersensitivity pneumonitis and connective tissue disease-associated interstitial lung disease (CT-ILD). Treatment includes smoking cessation, anti-reflux therapy, and the therapeutic option of one of two recently approved drugs, pirfenidone or nintedanib. IPF remains a deadly disease despite these drugs; thus the greatest emphasis should be on exclusion of alternative, potentially favorable diagnoses, continued option for enrollment in ongoing clinical trials, and, for eligible patients, early lung transplant evaluation.

Keywords
Fibrosis, idiopathic, interstitial, IPF, nintedanib, pirfenidone

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Diagnosis
Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias1 and accounts for about 20 % of all interstitial lung diseases (ILD).2 IPF should be considered in all adult patients with unexplained chronic exertional dyspnea,3 though it is rare in patients less than 50 years of age.4,5 The latest guidelines for diagnosis require exclusion of other known causes of ILD and presence of either a characteristic pattern on high-resolution computed tomography (HRCT) or specific combinations of HRCT and surgical lung biopsy with the pattern of usual interstitial pneumonia (UIP).3 Other disease processes that may cause UIP include collagen vascular disease (CT-ILD), drug toxicity, chronic hypersensitivity pneumonitis (CHP), asbestosis, and Hermansky–Pudlak syndrome.4 Diagnosis of an underlying cause, if known, is of great significance in terms of treatment and survival. For instance, in one study, patients with UIP secondary to CT-ILD lived 63 % longer than those with idiopathic UIP.5

Classic HRCT patterns seen in IPF include a basilar and subpleural predominant distribution of reticulation and honeycombing, commonly with, though not requiring, traction bronchiectasis.6 Presence of ground glass does not exclude UIP so long as there is a greater degree of reticulation.8 Emphysematous changes may complicate HRCT interpretation and has been shown to result in mistaking UIP for chronic pulmonary emphysema with fibrosis (CPEF) as well as nonspecific interstitial pneumonia (NSIP).6 Appearance of the UIP distribution may be asymmetrical in up to 25 % of cases.8

The most common differential diagnoses for IPF are CHP, CT-ILD, and pneumoconiosis with particular emphasis on asbestosis.2 Concomitant features such as centrilobular nodules, air trapping, and relative sparing of the bases may be suggestive of hypersensitivity pneumonitis; pleural plaques suggest asbestosis; and septal or bronchovascular nodules may be present in sarcoidosis.10 CT-ILD should be considered in the presence of pleural effusion and/or pleural thickening, as well as esophageal dilation.10

Differentiating CHP from UIP/IPF may be difficult, as many times the offending antigen may not be discoverable.12 While bronchoalveolar lavage (BAL) showing >40 % lymphocytes suggests a diagnosis of CHP and gene expression signatures have been shown to distinguish UIP from CHP,13 retrospective data suggest only 8 % of patients with a UIP pattern on HRCT have BALs suggestive of alternative diagnoses,14 and hence current guidelines recommend against routine BAL when evaluating for IPF.13
IPF may present with a low-titer positive antinuclear antibody (ANA) and/or rheumatoid factor (RF) at a rate similar to that of healthy controls. In such patients, further evaluation for connective tissue disease (CTD) should be pursued, including both clinical and serologic workup. In the absence of additional evidence for CTD, a diagnosis of IPF may be appropriate, though periodic repeat evaluations for CTD should be done. Distinguishing idiopathic pneumonia with autoimmune features (IPAF) from CT-ILD is critical, but difficult, due in part to the lack of reliable biomarkers.

Failed Therapies
Potentially harmful medications in the treatment of IPF include warfarin and the combination of prednisone, azathioprine, and N-acetylcysteine. Sildenafil has failed to show improvement in forced vital capacity (FVC), dyspnea score, and mortality. A signal of harm was displayed with the use of selective endothelin receptor antagonist (ERA), ambrisentan, even in the presence of pulmonary hypertension (PH). In general, nonselective ERAs (bosentan, macitentan) should not be used in IPF, though it remains unclear if there may be a beneficial role in patients with PH secondary to IPF.

Current Principles of Management
Gastroesophageal reflux (GER) is seen in up to 90% of patients with IPF, but often clinically silent. Antacid treatments may decrease the risk of microaspiration-associated lung injury and have been shown to decrease the rate of FVC decline. Most studies have included proton pump inhibitors (PPIs) more than histamine-2 receptor antagonists (H2RAs), without a recommendation for one class over the other. More recently, PPIs have been suggested to have more pleiotropic effects, including suppression of profibrotic proteins.

Pirfenidone
Pirfenidone is an antifibrotic agent first approved for use in IPF in Japan in 2008 following a trial that showed a 43% reduction in the rate of decline in FVC and improved progression-free survival. This was followed by two CAPACITY (Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes) trials. The first trial, 004, showed a decline in FVC of 8.0% after 72 weeks with 2,403 mg/day versus a 12.4% loss in the placebo group. More impressively, 63 patients receiving pirfenidone experienced a decline in FVC≥10% compared with those in the placebo group. The 006 trial, however, did not maintain this effect through 72 weeks.

Comparison of the available data shows similar reductions in FVC decline of 45.1% with pirfenidone, and 52.2% with nintedanib. With time, nintedanib may show an improvement in mortality comparable to that of pirfenidone. The practical interpretation and application of the differences in data between the two drugs is unclear in that the groups of patients studied were not the same. The selection of one medication over the other should be done on a case by case basis, following a discussion with the patient regarding dose scheduling (nintedanib is twice daily, pirfenidone three times daily), adverse effects, and cost/availability. Although there are plans to study the two drugs together, no data are currently available to support combination therapy or to prefer one drug over the other.

Current guidelines do not address appropriate timing for referral for patients with IPF for lung transplantation. Consider referring patients with IPF for lung transplant evaluation if they have dyspnea with routine exercise that is greater than their usual baseline activity level or if they are unable to perform their usual activities due to symptoms of IPF. Prolonged use of oxygen supplementation may also be beneficial in patients with IPF who experience symptoms of hypoxemia during exertion.
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daily activities and are requiring oxygen therapy with an anticipated survival of <5 years. Regarding single- versus double-lung transplant, a recent meta-analysis of available observational studies from 1990 to 2013 did not show any difference in mortality after adjustment for patient characteristics. Ongoing cell-based therapy trials may promote new directions in the management of this fatal disease.

Conclusion

Despite the recent addition of two medications for IPF that slow lung function decline, IPF remains a deadly disease. Avoidance of smoking should be strongly advised, and poignant management of comorbidities such as GER should be undertaken. We have entered a new era in the management of IPF, but curing the disease remains a current goal.