

Idiopathic pulmonary fibrosis: past, present, future – a review from Talmadge King’s ATS 2016 presentation

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Interstitial lung disease (ILD) represents a large and heterogeneous group of parenchymal lung diseases. ILD is characterized by diffuse “infiltrates” on radiographic imaging, architectural distortion of the gas exchange units by histology and evidence of restriction of lung volumes [FVC] and impairment of gas exchange [DLCO] on pulmonary function testing. A precise and timely diagnosis of the cause of the ILD is critical for effective management. The present review covers the presentation entitled “idiopathic pulmonary fibrosis (IPF): Past, Present, Future,” that was provided by Dr. Talmadge King at the 2016 American Thoracic Society International Conference

IPF a chronic, progressive fibrosing interstitial pneumonia occurs worldwide. It has a predilection for men and most commonly affects people over the age of 50 years. Potential risk factors include smoking, environmental pollutants, gastro-esophageal reflux, infections and genetic predisposition. Obtaining an accurate diagnosis requires an integrated approach by clinicians, radiologists and pathologists (1). Non-productive cough and dyspnea on exertion are the main respiratory complaints. Examination often reveals inspiratory rales and digital clubbing; however, these symptoms are not specific for IPF. Radiological changes in IPF are estimated to be apparent approximately 1,000 days before the onset of dyspnea (2).

High resolution computed tomography (HRCT) can help differentiate IPF from other ILDs. Imaging for IPF typically reveals reticular opacities in the peripheral and basal distribution, traction bronchiectasis, thickened interlobular septae and subpleural honeycombing. Ground glass opacities are absent to minimal. Discerning IPF from other ILDs based on imaging can be difficult. Interobserver

agreement among radiologists for the criteria for an IPF pattern on HRCT is only moderate at best (3). Additionally, the presence of the IPF specific radiographic findings may only obviate the need for surgical lung biopsy about 60% of the time (4). For patients with an inconsistent IPF pattern on HRCT, establishing the diagnosis requires a surgical lung biopsy (5).

Video-assisted thoracic surgery (VATS) remains the gold standard for diagnosis, but it is not without risk. Hutchinson *et al.* recently published a review of 9,700 surgical lung biopsies from 2001 to 2011 and found that 66% of surgical biopsies were performed electively and 32% non-electively (6). The overall in-hospital mortality after a surgical lung biopsy was 6.4%, with 1.7% occurring in elective procedures and 16% occurring in non-elective procedures. This finding underscores the need for early biopsy to clarify the diagnosis and avoid risks associated with biopsies performed on patients with more advanced disease. In some specialized centers, transbronchial cryobiopsy is emerging as an alternative to VATS. It allows for a much larger tissue specimen as compared to standard transbronchial biopsies and less invasive than VATS. The diagnostic yield is approximately 60%, with a risk of bleeding at 24% and a pneumothorax rate of 17% (7-9). Additional studies and technical expertise have yet to determine its role in diagnosing ILD.

Despite a thorough clinical, radiographic and histological examination, up to 10% of patients can have “unclassifiable ILD”. Compared to IPF, “unclassifiable ILD” has a longer survival than IPF and portends a similar prognosis to other ILDs (10).

The natural progression in the decline in lung function is

variable. Some patients experience preserved lung function for years while others experience more rapid declines (11). Overall, the median survival for IPF is 3.8 years (12). There is no curative therapy for IPF. The goals of therapy are to alleviate symptoms, improve exercise tolerance and slow the lung function decline. These goals can be achieved through a comprehensive management plan by early recognition and therapy for GERD, smoking cessation, pulmonary rehabilitation, vaccinations, supplemental oxygen and cough suppressants. The conventional use of corticosteroids and azathioprine is no longer recommended therapy. The PANTHER-IPF trial, demonstrated that the three-drug therapy combination of prednisone, azathioprine, and N-acetylcysteine (NAC), compared to placebo, was associated with increased adverse events, hospitalizations and all-cause mortality (13). Another trial NAC yielded no reduction in the FVC decline as compared to placebo (14).

Nintedanib and pirfenidone have emerged as proven IPF-specific treatment options. Both appear to be equivalent at slowing the rate of decline in FVC. Treatment with either nintedanib or pirfenidone have been shown to reduce the relative risk of FVC decline $\geq 10\%$ by 50% at 1 year (15,16). Adding NAC to pirfenidone, however, may lead to a greater decline in FVC compared to pirfenidone monotherapy (17).

Until recently, there were no available data to guide the decision making for patients who do not re-

spond to therapy at 6 months. Two observations were noted recently by Nathan *et al.* (18). First, FVC is highly variable and cannot be predicted based on prior trends. Second, continued use of pirfenidone may reduce the risk of subsequent FVC decline $\geq 10\%$ or death at 1 year, in a subset of patients who had disease progression at 6 months. If at 12 months, there is ongoing decline in FVC, given the considerable cost and potential for side effects of these medications, it is best to stop therapy. Common adverse side effects related to nintedanib include nausea, vomiting, diarrhea, and liver function test abnormalities. It can also increase the risk of bleeding if the patient is on anticoagulation. Adverse side effects related to pirfenidone include nausea and vomiting, elevated transaminases and photosensitivity.

It is important to remember that neither pirfenidone nor nintedanib stops disease progression or restores lung function. Lung transplantation is a therapeutic option for patients with severe lung disease that is refractory to medical therapy. Once a FVC $< 60\%$ or DLCO $< 50\%$ has been established, the patient should be referred for

consideration of lung transplantation (19). Early referral allows for careful evaluation and optimization of the medical status to decrease the surgical risks and medical complications thereby improving outcomes.

At the conclusion of the presentation, three issues that remain to be resolved were discussed. First, there needs to be consensus on the timeliness and accuracy of establishing the diagnosis. Second, it is yet to be determined whether or not to start treatment in the early stages of IPF. Third, better management strategies are needed to care for patients effectively as they continue to live longer with IPF.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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