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Perspectives on the Diagnosis and Management of Idiopathic Pulmonary Fibrosis

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ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease (ILD) that occurs primarily in the elderly. Patients with IPF typically present with chronic dyspnea and dry cough. Determining an IPF diagnosis requires the presence of a usual interstitial pneumonia pattern on high-resolution computed tomography or surgical lung biopsy and the exclusion of known causes of ILD such as rheumatologic diseases and exposure to certain environmental irritants, antigens, or drugs. The course of IPF is variable and unpredictable and is often characterized by acute exacerbations—episodes of acute respiratory worsening associated with very high morbidity and mortality. Optimal management of IPF includes the use of antifibrotic drugs, pulmonary rehabilitation, supportive care, and evaluation for lung transplantation. In this review, we discuss the barriers to patients obtaining an accurate and timely diagnosis of IPF and current international experience with antifibrotic therapies.

KEYWORDS: Idiopathic pulmonary fibrosis, diagnosis, interstitial lung disease, therapeutics

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease (ILD) characterized by dyspnea and loss of lung function.[1] The underlying cause of IPF is unclear, but the disease is believed to be the result of aberrant wound healing in response to repeated alveolar epithelial cell microinjury in genetically susceptible individuals.[2] IPF has a variable natural history but is ultimately fatal.[3] The morbidity associated with IPF has a broad and

profound impact on patients' health-related quality of life[4,5] and is associated with high health care resource utilization and costs.[6]

EPIDEMIOLOGY OF IPF

IPF is more common in men than in women and is primarily a disease of the elderly, with most patients presenting in their sixth or seventh decades.[1,7] Estimates of the incidence and prevalence of IPF vary widely depending on the methodology used for case ascertainment.[8] A systematic review of population-based studies conducted since 2000 provided a conservative estimate for the incidence of IPF in Europe and North America of between 3 and 9 cases per 100,000 person-years, with lower incidences in East Asia and South America (1-2 cases and 0.5 cases per 100,000 person-years, respectively).[9] Based on claims-based algorithms, the incidence of IPF in the United States has been estimated at 6 per 100,000 person-years[7] or 15 per 100,000 person-years[10] depending on methodology. Data are conflicting on whether the incidence of IPF is increasing or decreasing, but the prevalence of IPF seems to be increasing as patients survive longer after diagnosis.[11] Data collected in the United States prior to the availability of antifibrotic therapies suggest that patients with IPF have a median survival following diagnosis of 3 to 5 years.[12-14]

Diagnosis and Assessment

IPF is a diagnosis of exclusion, requiring that ILDs of known cause and other forms of idiopathic interstitial pneumonia be ruled out. The characteristic radiologic/pathologic presentation of IPF is usual interstitial pneumonia (UIP). Diagnosis of IPF requires the presence of features of UIP on high-resolution computed tomography (HRCT) or specific combinations of features of UIP on HRCT and lung biopsy.[1,15]

Clinical History and Risk Factors

Patients with IPF typically present with chronic exertional dyspnea and dry cough.[1] On physical examination, Velcro-like bibasilar inspiratory crackles are usually audible.[16] Finger clubbing and oxygen desaturation, which can be measured in the office by ambulatory pulse oximetry, are also suggestive of IPF.[1] In order to exclude ILDs of known cause, it is essential that clinicians screen for the presence of potential causative factors and associations. This includes screening for signs of connective tissue diseases (eg, rheumatoid arthritis, scleroderma) and conducting a comprehensive clinical history to ascertain environmental exposures (eg, asbestos), antigens (eg, feathers, mold), or drugs (eg, chemotherapeutic agents, immunosuppressants) that may be causes of ILD.[17,18] While IPF is, by definition, a disease of unknown etiology, potential risk factors have been described, including family history; cigarette smoking; exposure to metal, wood, and silica dusts; and farming.[1] Gastroesophageal acid reflux has also been postulated as a contributor to lung injury in IPF via microaspiration,[19] but whether gastroesophageal reflux plays a significant role in the pathogenesis of IPF remains unclear.[20] Genome-wide linkage and

plays a significant role in the pathogenesis of IPF remains unclear.[20] Genome-wide linkage and association studies have identified loci that appear to confer risk for IPF. These include polymorphisms in the *MUC5B* promoter affecting airway host defense and in genes related to telomere biology and epithelial barrier function.[21]

HRCT and Surgical Pathology

An HRCT scan should be obtained in all patients in whom there is a clinical suspicion of IPF.[1,15] The latest American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society (ATS/ERS/JRS/ALAT) guideline for the diagnosis of IPF defines 4 HRCT scanning patterns: UIP, probable UIP, indeterminate for UIP, and alternative diagnosis.[1] These are similar to the HRCT patterns defined in a white paper on the diagnosis of IPF issued by the expert members of the Fleischner Society.[15] A UIP pattern on HRCT in the appropriate clinical setting is sufficient to diagnose IPF without the need for a surgical lung biopsy or bronchoalveolar lavage (BAL).[1,15] However, it is important that clinicians are aware that the absence of honeycombing on HRCT does not preclude a diagnosis of IPF.

In patients who have an HRCT pattern of probable UIP or indeterminate for UIP, or a pattern suggesting an alternative diagnosis, the latest ATS/ERS/JRS/ALAT guideline recommends that cellular analysis of the BAL fluid be conducted,[1] but it is unclear to what extent this recommendation will be implemented in clinical practice. In considering whether to conduct a surgical lung biopsy in patients with probable UIP, clinicians need to consider the probability that the patient will have UIP on biopsy given the clinical context (eg, the patient's age, gender, symptoms), and weigh the benefits of securing a more confident diagnosis vs the risks of conducting a surgical lung biopsy in that patient.[1,15] In a recent review of approximately 8000 elective surgical lung biopsies conducted in the United States in patients with ILD, in-hospital mortality was 1.7%, with mortality being higher in men and in patients who were older, had comorbidities, or had nonelective biopsies.[22] Transbronchial lung cryobiopsy is a less-invasive method for obtaining biopsy samples, but the value of transbronchial cryobiopsies compared with surgical lung biopsy has not been prospectively evaluated.[23,24] The guidelines issued by the Fleischner Society suggest that if lung tissue is not available, a working diagnosis of IPF could be made in patients with a clinical suspicion of IPF after a careful multidisciplinary assessment; this should then be reviewed at regular intervals, since the diagnosis might change.[15] Effective communication between radiologists and pulmonologists is essential to ensure that the most accurate diagnosis is made.[25]

Pulmonary Function Testing/6-Minute Walk

Pulmonary function testing in IPF usually shows a restrictive pattern with reduced forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity for carbon monoxide (Dlco). However, patients with early disease may have an FVC and TLC that are within the range of normal predicted values.[26] A diffusion capacity that is reduced disproportionately to FVC could

normal predicted values.[26] A diffusion capacity that is reduced disproportionately to FVC could indicate concomitant pulmonary hypertension and/or chronic obstructive pulmonary disease (COPD). Decline in FVC is a well-established predictor of mortality in patients with IPF,[27] and pulmonary function testing at regular intervals is important for monitoring disease progression.

The 6-minute walk test (6MWT) assesses functional exercise capacity, approximating to the exercise level of everyday activities. Decline in 6MWT distance is a strong predictor of mortality in patients with IPF,[28] but it is important that consistent protocols are used for all the tests in a given patient, since factors such as the use of supplemental oxygen can have a considerable impact on the results.[29] Desaturation (oxygen saturation ≤88%) during 6MWT has also been shown to be a significant predictor of mortality in patients with IPF.[30]

Prognosis: From Slow Decliners to Unpredictable Acute Exacerbations

The clinical course of IPF is variable, with some patients experiencing rapid decline and an early death, others progressing much more slowly, and some experiencing periods of relative stability interrupted by episodes of acute respiratory worsening.[3] Predictors of mortality in patients with IPF include low FVC,[27] Dlco,[27] or 6MWT distance.[31] Decline in FVC or 6MWT distance are even stronger predictors of mortality.[27,31] A greater extent of fibrosis on HRCT, and increases in the extent of fibrosis on HRCT, have also been demonstrated to be predictors of mortality in patients with IPF.[32] Composite scores such as the composite physiologic index (CPI)[33] and the GAP (gender, age, physiology) index and staging system[34] that predict mortality based on demographics and pulmonary function tests can be used in clinical practice. Blood molecular and cellular biomarkers, mainly surfactant proteins, chemokines, and proteases, have also been assessed as predictors of disease progression[35] but remain investigational.

It is important to remember that, while at a population level, predictors of disease progression in patients with IPF have been identified, the course of disease for an individual patient remains unpredictable. Recent decline in FVC is not a good predictor of future decline in lung function, nor is preservation of FVC to date an indicator that FVC will continue to be preserved.[36,37] Indeed, data from the INPULSIS trials showed that placebo-treated patients with an FVC greater than 90% predicted at baseline showed the same rate of FVC decline over the following year as patients with more severely impaired lung function.[38]

Acute respiratory deteriorations in patients with IPF are known as acute exacerbations. As more data have become available, several definitions of an acute exacerbation have been proposed. In 2016, an international working group proposed that an acute exacerbation of IPF be defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new, widespread alveolar abnormality.[39] The requirement for the event to be idiopathic included in the definition proposed by the previous working group[40] was removed based on a lack of clinical or biologic rationale for distinguishing idiopathic from events with a known trigger (eg, an infection). Acute exacerbations of IPF are associated with considerable morbidity and mortality:

median survival following an acute exacerbation is 3 to 4 months.[39] While acute exacerbations are more common in patients with lower FVC percent predicted, they can also occur in patients with less advanced disease,[39,41] even in patients with almost normal FVC percent predicted.[38]

TREATMENT

Antifibrotic Therapies

Two antifibrotic therapies have been approved for the treatment of IPF: nintedanib[42] and pirfenidone.[43] The latest international clinical practice guideline for the treatment of IPF, issued by ATS/ERS/JRS/ALAT in July 2015, gave conditional recommendations for the use of nintedanib and pirfenidone, indicating that either would be an appropriate treatment choice for most patients while acknowledging that patients' preferences should be taken into account in making decisions about their care.[44] Data from clinical trials conducted in patients with IPF and mild or moderate impairment in lung function have shown that these drugs reduced the rate of FVC decline over 1 year by approximately 50%.[45,46] Both nintedanib[38,47] and pirfenidone[48,49] reduced FVC decline consistently across subgroups defined based on a variety of baseline characteristics, including age, gender, race, and FVC percent predicted. The effect of nintedanib on slowing FVC decline was found to be the same in patients with possible UIP plus traction bronchiectasis on HRCT as in patients with honeycombing on HRCT and/or confirmation of UIP by surgical lung biopsy,[50] suggesting that the presence of definite UIP does not increase the benefit that a patient with IPF gains from antifibrotic therapy.

Gastrointestinal tract adverse events, particularly diarrhea, are the most frequent adverse events associated with nintedanib treatment.[45,51] In the 12-month INPULSIS trials, diarrhea was reported in 62.4% of nintedanib-treated patients compared with 18.4% of placebo-treated patients, but only 4.4% of patients discontinued nintedanib due to diarrhea.[45] Adverse events associated with nintedanib can be managed through dose reduction (to 100 mg twice daily) and treatment interruption, and through measures to manage symptoms (eg, use of loperamide). Importantly, the dose adjustments needed to manage adverse events had no significant impact on the efficacy of nintedanib in reducing FVC decline.[52]

Due to the mechanism of action of nintedanib, patients treated with it are at an increased risk of bleeding, and nintedanib should be used in patients with known bleeding risk only if the anticipated benefit outweighs the potential risk.[42] In the INPULSIS trials, bleeding adverse events were reported in 10.3% of patients treated with nintedanib and 7.8% of patients treated with placebo.[52] Epistaxis and contusion were the most frequently reported bleeding events. The US label recommends that caution be used when treating patients at higher cardiovascular risk including known coronary artery disease.[42] In the INPULSIS trials, similar proportions of patients treated with nintedanib and placebo had cardiac disorder adverse events (10.0% vs 10.6%, respectively); however, a higher proportion of patients in the nintedanib group than in

the placebo group had a myocardial infarction (MI) (2.7% vs 1.2%), while a lower proportion had other ischemic heart disease (1.7% vs 3.1%).[52] The event rates of MI in the nintedanib and placebo groups in the INPULSIS trials were 1.68 and 0.48 per 100 patient-years, respectively. In the open-label extension of the INPULSIS trials (INPULSIS-ON), the event rate of MI was 1.3 per 100 patient-years in patients who continued nintedanib in INPULSIS-ON (having taken nintedanib in an INPULSIS trial) and 0.7 per 100 patient-years in patients who initiated nintedanib in INPULSIS-ON (having taken placebo in INPULSIS).[51] Similar low rates of MI have been observed in other studies in real-world settings.[53-55]

The most frequent adverse events associated with pirfenidone use are nausea and rash.[46,56,57] Adverse events can be managed through dose reduction or treatment interruption and by avoiding sun exposure. The safety and tolerability profile of pirfenidone observed in clinical trials is supported by safety data collected in the real world and in postmarketing studies. The PASSPORT European safety registry collected data on adverse drug reactions judged to have a possible causal relationship to pirfenidone from more than 1000 patients followed for a median exposure of 442 days. In this registry, photosensitivity/skin rashes were reported in 29.0% of patients, nausea in 20.6% of patients, and fatigue in 18.5% of patients.[58]

Elevations in liver enzymes and bilirubin have been observed in patients receiving antifibrotic therapy. Hepatic enzymes should be monitored prior to initiation of treatment and at regular intervals during treatment. Most hepatic adverse events are reversible with dose modification or treatment interruption.[42,43]

The safety and efficacy of nintedanib with add-on pirfenidone vs nintedanib alone were investigated in the 12-week, open-label, randomized INJOURNEY trial.[59] The adverse event profile of the combination was in line with the profiles of the individual drugs. In an exploratory analysis, there was a smaller numerical decline in FVC in patients treated with combination therapy than with nintedanib alone; however, these findings should be interpreted with caution given the small number of patients analyzed (N=92) and the short treatment duration.[59] Data from a single-arm, open-label, 24-week study of pirfenidone with add-on nintedanib suggested that the adverse event profile of this combination was consistent with the profiles of the individual drugs.[60]

Lung Transplantation

Lung transplant offers a survival benefit to selected patients with IPF.[61] The introduction of the Lung Allocation Score (LAS) in 2005 increased the number of patients with IPF undergoing a lung transplant and reduced their waitlist time and mortality.[62] However, restrictive lung diseases still account for the second largest proportion of patients on the waitlist for a lung transplant in the United States.[63] Given the progressive and unpredictable nature of IPF, guidelines recommend that patients with IPF be evaluated for lung transplant at an early

guidelines recommend that patients with IPF be evaluated for lung transplant at an early stage.[1,64] Few data are available on the safety of using antifibrotic therapies prior to lung transplant, but the small studies published to date have shown no increase in postoperative complications in patients previously treated with antifibrotic drugs.[65-69]

Symptom Management and Supportive Care

Symptom management and supportive care are important facets of the overall care of patients with IPF.[4] Patients with IPF need education and emotional support in either group or individual settings to help them live with the consequences of having IPF and come to terms with their prognosis.[70-72] Although sometimes regarded as end-of-life care, clinicians should consider whether palliative care would be of benefit to patients throughout the course of the disease.[73] The dyspnea and cough associated with IPF are difficult to treat, but pulmonary rehabilitation can provide benefits including improvements in exercise capacity, dyspnea, and quality of life[74] and is valued by patients.[75] International guidelines strongly recommend the use of supplemental oxygen for patients with IPF and significant resting hypoxemia.[1]

Comorbidities such as gastroesophageal reflux disease (GERD), emphysema, cardiovascular disease, pulmonary hypertension, and sleep apnea are common in patients with IPF, and management of comorbidities is an important part of the overall care of the patient.[76] The latest international clinical practice guideline for the treatment of IPF gave a conditional recommendation for the use of antacid medications in patients with IPF and asymptomatic GERD based on very low-quality evidence,[43] but the risk–benefit ratio of antacid medications in patients with IPF remains controversial.[77] Recent data from the randomized WRAP-IPF study in patients with IPF and abnormal acid reflux showed that laparoscopic anti-reflux surgery was not associated with a significant reduction in FVC decline over the following 48 weeks compared with patients who did not undergo surgery.[78]

Investigational Therapies

Several compounds with various mechanisms of action are under investigation as potential treatments for IPF.[79] Phase 2 trial results, focusing on safety and tolerability, have been published for 5 investigational compounds: TD139 (a galectin-3 inhibitor),[80] PBI-4050 (a synthetic medium-chain fatty acid analogue that displays agonist/antagonist ligand affinity toward GPR40/GPR84, respectively),[81] pamrevlumab (FG-3019) (an inhibitor of connective tissue growth factor),[82,83] recombinant human pentraxin 2 (which inhibits the differentiation of monocytes into proinflammatory macrophages and profibrotic fibrocytes),[84] and GLPG1690 (an inhibitor of autotaxin, the primary enzyme responsible for production of lysophosphatidic acid).[85] Phase 3 trials of these new compounds are needed to continue this work. Trials often allow background therapy with existing antifibrotic agents, allowing future opportunity to explore the utility of combination therapy. Investigation into the safety and efficacy of infusion of bone marrow–derived mesenchymal stem cells in patients with IPF is at a very preliminary stage.[86] At

marrow–derived mesenchymal stem cells in patients with IPF is at a very preliminary stage.[86] At present, stem cell–based therapies should not be used outside of carefully designed clinical trials given the paucity of data to support their use and the serious potential risks.

Barriers to Diagnosis and Treatment

Over the past decade, transformative clinical and scientific advancements have led to an improved understanding of the pathogenesis of IPF and to the approval of 2 antifibrotic drugs. Despite such progress, patients still experience delays in diagnosis and treatment. Some challenges are due to practical and logistical hurdles, while others represent knowledge gaps and misconceptions among the patient and clinical community. Patients may delay presenting to a health care professional if they attribute their symptoms to aging. Among primary care clinicians or community pulmonologists, insidious onset of dyspnea is frequently attributed to the more common diagnosis of COPD, particularly in former smokers. Velcro-like crackles may be mistaken for congestive heart failure. Subtle reticular markings are overlooked on plain chest radiographs. Interstitial lung abnormalities are frequently detected in lung cancer screening programs,[87] but clear pathways for further assessment are often lacking. A delay in time from the onset of dyspnea to access to tertiary care has been associated with higher mortality in patients with IPF.[88]

The expert multidisciplinary team needed to make a differential diagnosis in patients with ILD is often lacking in the community. Not all clinicians have access to chest radiologists who are familiar with diagnostic guidelines for ILD. Thoracic surgeons in the community who are unfamiliar with ILD may take only small biopsies from the most fibrotic areas of the lung instead of the larger pieces from multiple lobes needed to characterize the underlying pathology. Pulmonologists may not be familiar with guidelines recommending serologic testing or how to interpret positive serologies that are uncovered during diagnostic workup. The diagnostic guidelines themselves also present challenges. Most elderly patients with possible UIP on HRCT have UIP on biopsy[89,90] but do not wish to undergo a surgical lung biopsy given the risks that it entails; to conduct a surgical lung biopsy in such vulnerable patients is not recommended in current guidelines.[1,15]

While there has been a concerted effort on the part of the scientific community, industry, and patient foundations to educate the clinical and patient community, many still consider IPF to be a terminal condition with no treatment options. This may lead to a nihilistic rather than proactive approach to therapy. Clinicians and patients may choose to forego antifibrotic therapy (which is known to have adverse effects) or referral for evaluation for lung transplant if a patient is regarded as “stable” or “too sick.” Clinicians should explain to patients the progressive nature of IPF and the variability in its natural history to ensure they are aware that prior stability does not preclude deterioration, or a potentially fatal acute exacerbation, in the near future. Clinicians have a key role to play in explaining the benefits of treatment to patients with IPF while

managing expectations that antifibrotic therapy will not halt disease progression or relieve their symptoms and educating them about potential adverse effects.

Conclusions

The diagnosis of IPF presents several challenges: its symptoms are nonspecific and insidious; its characteristic features on HRCT are not present in all patients and require specialist expertise for their identification; and clinicians must exclude other potential causes of ILD before making a diagnosis of IPF. Patients in the community may not have access to the expert multidisciplinary team needed to make an accurate differential diagnosis. However, timely diagnosis of IPF is critical to enable treatment options, including administration of antifibrotic therapies, evaluation for lung transplantation, and the institution of supportive care such as supplemental oxygen, pulmonary rehabilitation, palliative care, and, when needed, hospice care to be discussed with the patient. Clinicians have a key role to play in explaining to patients the unpredictable natural history of IPF, the benefits and risks of therapy, and how the progression of their disease will be monitored.

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