Management of Idiopathic Pulmonary Fibrosis

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing lung disorder characterized by progressive dyspnea, exercise intolerance and, ultimately, respiratory failure and death. The incidence of IPF seems to be increasing, whereas its etiology remains unelucidated. Agents capable of modulating inflammation, kinase pathways, vascular tone, coagulation and fibrosis have been tested in clinical studies although not always in large, randomized, placebo-controlled prospective trials. Despite this effort, a therapy capable of improving survival remains elusive. Consequently, the management of IPF focuses on the early identification of subjects for lung transplantation and on the treatment of comorbidities such as hypoxemia, cough and deconditioning. Until effective therapies are identified, patients and referring physicians are urged to consider participation in well-designed clinical trials.

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Idiopathic pulmonary fibrosis (IPF) is a progressive disorder characterized by relentless deterioration of respiratory function due to lung fibrosis. More than 160,000 Americans are affected by IPF, which is the most common of the idiopathic interstitial pneumonias.[1] A typical patient with IPF is older than 50 years and shows bibasilar crackles on physical examination. Imaging studies reveal bilateral infiltrates with peripheral and basilar predominance, traction bronchiectasis and honeycombing. Physiological abnormalities with a restrictive pattern are common and often associated with hypoxemia at rest or during exertion. Lung histology reveals heterogenous distribution of lung fibrosis, honeycombing, fibroblastic foci and a paucity of inflammation; this pattern is known as a pattern of usual interstitial pneumonitis (UIP).[2]

A diagnosis of IPF is a diagnosis of exclusion as other conditions can mimic the above clinical presentation including other idiopathic interstitial pneumonias such as nonspecific interstitial pneumonitis. Other conditions that resemble IPF are interstitial lung diseases related to connective tissue disorders such as rheumatoid arthritis, systemic lupus erythematosus and progressive systemic sclerosis and conditions triggered by environmental exposures such as chronic hypersensitivity pneumonitis.[3,4] An accurate diagnosis of IPF is important considering the differences in prognosis with IPF showing only a 50% 3-year survival rate. More importantly, no therapies have been proven to reverse, halt or delay the progression of disease in IPF in large, well-conducted, double-blinded, placebo-controlled, prospective clinical trials.

Before the 1990s, many patients with pulmonary fibrosis of unknown etiology were diagnosed with IPF and were often treated with high doses of steroids. However, although some patients showed improvement, others showed continuing deterioration despite similar clinical presentation and treatment. This led many to conclude that patients initially diagnosed with IPF actually suffered from a variety of conditions; some steroid responsive, others less responsive. This new understanding prompted the careful analysis of the histology of subjects diagnosed with IPF, which ultimately led to the classification of the idiopathic interstitial pneumonias, of which IPF is a member.[5] In contrast to other idiopathic interstitial pneumonias, IPF shows a characteristic histological pattern termed UIP. Later, clinical studies that considered histological diagnosis showed that patients diagnosed with IPF in association with histology of UIP represented the most common subgroup of patients with idiopathic interstitial pneumonias and, importantly, the one with the worse prognosis. Specifically, although no well-controlled prospective studies were conducted, a general consensus grew about the lack of responsiveness of IPF to steroids. Despite the above, and considering the lack of effective therapies, many patients with IPF are currently treated with steroids and/or other immunosuppressants pending the identification of new therapies. It is for this reason that a stronger emphasis is being placed on the conduct of clinical trials designed to prospectively evaluate the safety and effectiveness of new therapies.[6] To date, these efforts have failed to unveil a "magic bullet" but much has been learned through these trials, which have helped shape the standard of care for this condition.

THE SEARCH FOR EFFECTIVE THERAPIES IN IPF

There are a variety of new studies testing treatment options for IPF. Clinicaltrials.gov, a registry of federally and privately supported clinical trials, lists 90 currently recruiting (active) or recently completed studies of IPF (http://clinicaltrials.gov). The trials listed show how changing ideas about the pathogenesis of this condition have shaped our approach to therapy. For example, it was originally thought that IPF was caused by relentless inflammation, and this explains why early clinical trials often involved anti-inflammatory agents such as corticosteroids. These early studies were often flawed by misclassification of patients with or without IPF, as well as the lack of placebo control groups, but recent publications suggest that there is no apparent benefit of corticosteroid use for treatment of IPF.[7] Subsequent studies testing other anti-inflammatory agents (eg, etanercept, interferon-γ and interferon-β), among others, have also failed to show much benefit.[6,8,9] (Tables 1–3).

Knowledge has accumulated suggesting that tissue fibrosis can occur without inflammation or dissociated from it. In fact, in cases where IPF is suspected, significant tissue inflammation should lead clinicians to search for an alternative diagnosis. Despite the above, a statement published by the American Thoracic Society/European Respiratory Society in 2000 suggested the use of low-dose prednisone (a corticosteroid) with azathioprine (an immunosuppressant) for treatment. This combination became a standard therapy largely due to the lack of available treatment options. However, in 2008, the Idiopathic Pulmonary Fibrosis International Group Exploring N-acetylcysteine I Annual Study tested the addition of an

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TABLE 1. Drugs found to be ineffective in the treatment of IPF

Medications	Results	Study comments
IFN-γ vs. placebo	No increase in survival	New study testing IFN-γ by an inhaled route is planned
Bosentan	No change in 6MWT seen	New study is testing to see whether Bosentan delays time until death/ decreases lung deterioration
Imatinib	Negative study	
Prednisolone + IFN-γ vs. prednisolone + colchicine	Inconclusive results	

IFN, interferon; MWT, minute walk test.

antioxidant, *N*-acetylcysteine, to the standard regimen.[10] Although this study showed delays in the progression of IPF, it was heavily criticized for its small size and for the lack of a control group. Nevertheless, despite the lack of proven effectiveness, it appears this new, largely untested, treatment regimen including *N*-acetylcysteine has evolved as the new standard of care. If this regimen is to be used, however, it is recommended that close follow-up be given to disease progression and that, in the absence of improvement, the regimen should be stopped within a few months.

As other concepts about IPF pathogenesis emerged, phase I, phase II and phase III clinical trials have been conducted to test their accuracy. In general, the agents tested show benefits when examined in animal models of lung fibrosis. These include inhibitors of fibrotic growth factors (eg, connective tissue growth factor, transforming growth factor β and platelet-derived growth factor), endothelin receptor antagonists (eg, bosentan), inhibitors of kinases (eg, imatinib), anticoagulants (warfarin) and pirfenidone.[6,11–14] Unfortunately, benefits have not always been observed in these studies, improved survival has not been demonstrated and much controversy still remains. However, the data generated suggest that some of these approaches should be further considered. More importantly, these studies have prompted the generation of new and testable hypotheses about IPF pathogenesis.

There are several important factors to consider when designing a new study. Of particular importance is the use of a placebo-only control group. Also, a standard or at least a minimum criteria for primary endpoints should be established. Although enhanced survival is the most robust endpoint for a trial, other factors such as a change in forced vital capacity or performance on 6-minute walk test and possibly the use of biomarkers (once suitable markers are identified) should be considered for use as primary and secondary endpoints.

Clinical studies are often limited by a small sample size, especially in the case of a disease such as IPF. In part, the limited number of patients available for participation in trials is addressed by involving multicenter clinical trials. Collaboration between different centers can and should be encouraged. Recruitment criteria are established and include confirmation of a diagnosis of IPF in all the participating patients. Until effective treatments are found, attention should be given to the treatment of comorbid conditions. A recent clinical trial tested the ability of Sildenafil, a phosphodiesterase-5 inhibitor, to improve patients with advanced IPF. The primary outcome was not achieved; however, small but significant differences in arterial oxygenation, carbon monoxide diffusion capacity, degree of dyspnea and measures of quality of life were seen.[15]

OTHER IMPORTANT CONSIDERATIONS REGARDING IPF MANAGEMENT

The lack of Federal Drug Administration-approved medications for the treatment of IPF does not mean that physicians have nothing to offer in this setting. This is far from the case considering that lung transplantation and oxygen supplementation have been shown to extend survival in these patients.[16] In addition, these and other interventions can improve quality of life. Thus, it is important that patients suspected and/or diagnosed with IPF be referred to centers with expertise in this field, so that patients are evaluated thoroughly and appropriate treatment strategies are considered. The general management of IPF is summarized in Figure 1 and specific interventions are described later.

Oxygen Therapy

As the disease progresses, IPF causes dyspnea on exertion mainly due to increases in the work of breathing and alterations in gas exchange capacity and hypoxemia. In this setting, supplemental oxygen therapy is useful as it may diminish dyspnea and improve exercise tolerance. However, the need for supplemental oxygen may be missed if patients have only resting arterial blood gas or oxygen saturation measurements.

TABLE 2. Drugs requiring further investigation

Medications	Results	Study comments
Etanercept	Improved FVC and DL_{CO}	Original study did not reach primary end point
Prednisone + azathioprine vs. prednisone + placebo	Trend to improved resting arterial O_2, small increase in survival	Small test group, only a trend toward improvement, changes not significant
Prednisolone + anticoagulant vs. prednisolone	Significant increase in survival	Not a double-blinded study. Diagnostic criteria used were not standard
Pirfenidone	Improvement of lung function variables	Primary end points for study were atypical and were not met, and 22% of the patients stopped participating in the study
N-acetylcysteine vs. Bromhexine	No improvement in pulmonary function tests or quality of life	May delay disease progression in *N*-acetylcysteine group

DL_{CO}, diffusing capacity for carbon monoxide.