Advances in the management of idiopathic pulmonary fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a common form of interstitial lung disease and usually results in progressive respiratory insufficiency and death. Steady progress has been made in understanding the pathogenesis of IPF and multiple clinical trials are ongoing, but effective therapy remains elusive.

Introduction and context

Idiopathic pulmonary fibrosis (IPF) is the most common form of interstitial lung disease and occurs predominantly in middle-aged and older adults. It is defined by the histopathologic pattern of usual interstitial pneumonia occurring in the absence of an identifiable cause of lung injury such as drug toxicity, inhalational agents, connective tissue disease, and so on [1-3]. Median survival time following diagnosis of IPF is 2-3 years [2-5]. Although consensus has been achieved in the definition of this disorder and advances have occurred in our understanding of the mechanisms of lung fibrosis, effective therapy has remained elusive.

The cause of IPF remains unknown. Developing knowledge of the pathogenesis of IPF has shifted focus towards the role of epithelial injury, dysregulated wound healing, and fibrosis and away from inflammation as the predominant pathologic process [6,7]. Thus, the search for effective therapeutic agents for the treatment of IPF has also shifted to agents with antifibrotic properties and away from anti-inflammatory treatments [8]. In addition, there is growing interest in vasomodulators to treat pulmonary hypertension, which commonly occurs in patients with IPF, as well as pulmonary rehabilitation to improve the quality of life of these patients [9,10].

Recent advances

Pharmacologic agents

Traditional therapy for IPF has used glucocorticoids in conjunction with azathioprine or cyclophosphamide

with the aim of reducing inflammation in the lung parenchyma as dictated by the previous paradigm [5]. This approach is associated with drug-related adverse effects and efficacy has never been validated.

Gamma-interferon

Gamma-interferon caused excitement as a treatment for IPF when Ziesche and colleagues [11] reported dramatic improvement in an open, randomized trial of 18 IPF patients. This initial enthusiasm was tempered when a randomized, double-blind, placebo-controlled clinical trial of 330 IPF patients showed no difference between placebo and gamma-interferon groups in progression-free survival, pulmonary function, or quality of life outcome measures [12]. A third study evaluated the role of gamma-interferon therapy in selected IPF patients with mild-to-moderate physiological impairment ('early disease') and also failed to show improved survival [13]. Gamma-interferon therapy is not recommended in the treatment of IPF.

N-Acetylcysteine

N-Acetylcysteine (NAC) is an antioxidant available in an oral form with or without a prescription. In a study of IPF patients treated with prednisone and azathioprine the addition of NAC compared to placebo was associated with a slower deterioration in forced vital capacity and single breath carbon monoxide diffusing capacity at 12 months [14]. However, the measured functional benefit was rather modest. In addition, the absence of placebo control in this study makes interpretation of these results uncertain.

Etanercept

A tumor necrosis factor- α antagonist, etanercept (a recombinant soluble human tumor necrosis factor receptor), was investigated in a clinical trial exploring its possible role in the treatment of IPF. Etanercept therapy was well tolerated but no differences were noted in the primary endpoints, including changes from baseline in forced vital capacity (percent predicted), diffusing capacity for carbon monoxide (percent predicted), and alveolar-arterial oxygen gradient at 48 weeks [15].

Pirfenidone

Pirfenidone is a pyridone compound with broad antifibrotic properties. In a double-blind, randomized, placebo-controlled trial involving 107 subjects, no significant difference was seen in the primary endpoint of the change in the lowest oxygen saturation by pulse oximetry during a 6-minute exercise test between baseline and 9 months [16]. However, pirfenidone therapy was associated with a smaller decline in vital capacity and reduced incidence of acute exacerbations. In a subsequent trial (275 subjects) that employed change in vital capacity as the primary endpoint, pirfenidone therapy was associated with a decreased rate of decline in vital capacity and increased progression-free survival time (a secondary endpoint). A manuscript describing the results of this study has been published online [17]. Pirfenidone is currently under review by the US Food and Drug Administration for use in the treatment of IPF.

Imatinib

Imatinib is a tyrosine kinase inhibitor that has been shown to inhibit lung fibrosis in bleomycin models of pulmonary fibrosis. A randomized clinical trial of 119 patients with mild-to-moderate IPF failed to show a favorable effect on survival or lung function [18]. There was a significant dropout rate in this study, which may have been underpowered. It remains unclear whether other tyrosine kinase inhibitors may have a role in the treatment of IPF.

Anticoagulant therapy

In 2005, Kubo and colleagues reported prednisolone plus anticoagulant therapy was associated with a marked reduction in mortality in patients with acute exacerbation of IPF compared to those on prednisolone alone. However, this was an unblinded study that included a relatively modest number of patients (56 subjects) and had a 26% dropout rate in the anticoagulant arm of the study. It is possible that anticoagulant therapy may have a role in the treatment of IPF since parenchymal injury in IPF may be associated with pulmonary vascular microthrombi and IPF patients are at risk for venous thromboembolism. Therefore, a multicenter clinical trial

investigating the use of anticoagulant therapy has been initiated within the National Institutes of Health (NIH)-sponsored IPF Clinical Research Network. At the present time, we do not recommend the use of anticoagulant therapy in the treatment of IPF.

Vasomodulatory agents

Pulmonary hypertension is a relatively common complication of IPF and adversely affects prognosis [9,20-23]. Increasing numbers of vasomodulatory agents have become available in recent years and some of these agents have been studied in IPF patients with pulmonary hypertension [24]. In a double-blind, randomized clinical trial, bosentan therapy failed to show superiority over placebo on 6-minute walk distance but did demonstrate a trend toward delayed time of death or disease progression, and improvement in quality of life measures. Results of another bosentan study, BUILD-3 (Bosentan Use in Interstitial Lung Disease 3), are pending. In an open-label study of 14 IPF patients, sildenafil therapy improved 6-minute walk distance and was well-tolerated [25]. A multicenter clinical trial on the effects of sildenafil therapy was recently completed in the NIH-sponsored IPF Clinical Research Network and the results are pending. Based on the data available to date, bosentan and sildenafil are not recommended in the treatment of IPF patients with pulmonary hypertension.

Other management modalities

Although there are no high-quality data demonstrating the benefit of supplemental oxygen therapy for patients with IPF, it is prudent to provide supplemental oxygen therapy for those with resting hypoxemia or significant oxygen desaturation with exercise on room air. In such patients supplemental oxygen therapy likely provides benefit in symptoms and quality of life. Other supportive measures to be addressed include optimization of the nutritional status and updating of immunizations.

Deconditioning is a common problem for IPF patients, particularly those with advanced disease, and can exacerbate functional and psychosocial impairments. Pulmonary rehabilitation can improve symptoms, walk distance, and quality of life [10].

The role of gastroesophageal reflux and acid aspiration in the pathogenesis of IPF remains unsettled [26]. It is reasonable to treat IPF patients who have symptomatic gastroesophageal reflux with acid-suppressive medications and anti-reflux measures. Fundoplication may be indicated in IPF patients with persistent gastroesophageal reflux symptoms or esophagitis who fail medical therapy or in those likely to undergo lung transplantation.

Lung transplantation in IPF is associated with a 5-year survival rate of 40-50% [27,28]. Appropriate patients with IPF should be offered an opportunity for lung transplant evaluation without undue delay since those with IPF have excess mortality compared to patients with other lung diseases awaiting lung transplantation.

Implications for clinical practice

In the absence of strong evidence favoring the use of any pharmacologic agent in the treatment of IPF, clinicians and patients need to reach an informed decision regarding possible management options. None of the currently available pharmacologic agents is supported by enough evidence to warrant their routine clinical use. In those patients who wish to undergo a trial of pharmacologic therapy, options include NAC monotherapy and NAC combined with prednisone and azathioprine. Pirfenidone may also prove to be a reasonable option, if it becomes available. Whenever possible, patients with IPF should be offered participation in ongoing clinical trials in order to identify effective treatments for IPF. Those patients who are appropriate candidates for lung transplantation should be referred promptly for an evaluation since the clinical course of IPF can be unpredictable, (e.g., acute exacerbation).

Abbreviations

IPF, idiopathic pulmonary fibrosis; NAC, N-acetylcysteine; NIH, National Institutes of Health.

Competing interests

The authors declare that they have no competing interests.

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