Idiopathic Pulmonary Fibrosis: Impact of prednisone, colchicine or no therpay on survival: Proposal for a randomized controlled trial

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A. Study Purpose and Rationale

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis or usual interstitial pneumonia, is a chronic interstitial lung disease characterized by progressive fibrosis on a background of mild inflammation. It is a disease of unknown etiology, believed to be the result of sequential lung injury followed by an exuberant fibroblastic response; this leads to fixed fibrosis and architectural changes that disturb pulmonary function, manifested by progressive dyspnea and hypoxemia. The clinical course is often rapidly progressive, with studies demonstrating a median survival of ~2-4 years from the time of diagnosis. Given the inflammatory and fibrotic nature of IPF, many anti-inflammatory, cytotoxic and anti-fibrotic agents have been used in the treatment of this disease. The current standard of care is a 3-6 month trial of prednisone plus a cytotoxic agent (cyclophosphamide or azathioprine). However, no good clinical data exists to suggest any therapy attenuates the course of IPF; the vast majority of studies are retrospective or extremely small prospective trials (n<15/group) that lack significance or power. In addition, evaluation of data collected prior to the late 1990's is complicated by the evolving definition of IPF, a term that historically included what are now recognized as a number of pathologically distinct entities, some of which have now been shown to be particularly steroid responsive. Recognizing these difficulties, the ATS released a statement in 2000 that called for the initiation of large, multi-center, randomized, placebo-controlled trials of potential therapies for IPF. The purpose of this study, therefore, is to test the efficacy of two potentially therapeutic agents for the treatment of IPF in a randomized, placebo-controlled study: (1) prednisone, a well-known anti-inflammatory agent used for immunomodulation in multiple disease states and (2) colchicine, which has been shown in vitro to interfere with intracellular collagen processing, increase the expression of enzymes that degrade collagen and inhibit the release of fibroblast growth factors from macrophages.

B. Study Design and Statistical Analysis

The proposed study is a randomized double-blinded multi-center trial with three arms: (1) placebo, (2) prednisone and (3) colchicine. Patients will be assigned consecutively to group 1, 2 or 3 based on order of enrollment. There will be no cross-over period. Assuming a 3.5 year survival of 50% , 171 patients in each arm will be required to detect a 20% improvement in survival to allow for a type I error rate of 0.05 with a power of 0.8 (accrual time one year, follow-up time, 3.5 years). Two hundred patients will be enrolled in each group to protect against disqualification based on autopsy/post-transplant finding of misdiagnosis. Given the current estimate of an incidence of ~10 cases of IPF per 100,000 per year, this would require a population base of 6 million with enrollment of every incident case. Patients will be followed for three years, with the primary end-point of death or lung transplant. Surrogate endpoints of functional deterioration will be evaluated by comparing the FEV1, FVC and DLCO at presentation and at 3, 6, 12, 18, 24 and 36 months after enrollment; these measurements, in particular the DLCO, have been shown to be strongly correlated with survival of patients with IPF (Panagiota et al, 2003).

All patients will be included in the analysis on an intention-to-treat basis, with the exception of those who on post-mortem exam are found to have pathology inconsistent with IPF. Data will be presented as mean +/- SD for continuous variables and as percentages for discrete variables. Baseline characteristics of age, sex, smoking status (never, past, current), time since onset of dyspnea, PFT's and

DLCO at presentation, and history of steroid use will be compared across treatment groups using one-way analysis of variance for continuous variables and the chi-square test for discrete variables. Survival and changes in pulmonary function studies will be compared between study groups using Student's t-test. Survival will be assessed using the Kaplan-Meier method. The Cox proportional hazards regression model will be used to identify variables associated with survival.

C. Study Procedure

Diagnosis of IPF will be made on the basis of (1) clinical history, (2) high-resolution CT scan of the chest, (3) serologic markers to rule out granulomatous and collagen-vascular diseases, (4) pulmonary function tests, lung volumes and DLCO, and (5) open-lung or video-assisted thoracoscopic lung biopsy in patients able to tolerate this procedure (DLCO>35%). This work-up is standard-of-care for the diagnosis of interstitial lung disease. Patients unable to tolerate lung biopsy due to poor pulmonary reserve will agree to post-transplant or post-mortem examination of lung tissue to verify the diagnosis of IPF. Post-mortem examination is done solely for research purposes.

During the course of this trial, patients will be required to return to the primary research center for serial pulmonary function testing at 3, 6, 12, 18, 24 and 36 months. This is more frequent testing than is generally required for the monitoring of the course of this disease. These tests are non-invasive and cause minimal discomfort to the patient. They involve (1) blowing into a tube to measure the force of expiratory flow and the volume of air the patient is able to expire and (2) single breath inspiration and expiration of a mix of CO and helium.

The expected duration of this trial is approximately five years (one year for accruement, four years follow-up). Patient participation will be 3.5 years.

D. Study Drugs

Two drugs will be tested in this study, prednisone and colchicine. Both are approved drugs that are routinely used in the treatment of IPF and other diseases and have well recognized safety profiles.

a. Prednisone

Routinely used in the treatment of inflammatory conditions, prednisone has been traditionally used to treat IPF. No prospective RCT has studied the efficacy of prednisone in the treatment of IPF, and the available data suggest that response to this drug is poor, perhaps because the inflammatory component of this disease is minimal. Prednisone has many well-described adverse side-effects, including increased risk of infection, osteoporosis, HTN, GI distress/PUD, glucose intolerance, weight gain, impaired skin healing, depression, psychosis, weakness, cataracts and adrenocortical insufficiency. Prednisone will be orally administered at standard treatment doses for IPF: 1 mg/kd/d x 4wk, 0.75 mg/kg/d x 2wk, 0.5 mg/kg/d x 6 wk, then tapered to 0.5 mg/kg every other day, to be continued as long as tolerated by the patient.

b. Colchicine

In vitro studies have shown that colchicine interferes with intracellular collagen processing, increased the expression of enzymes that degrade collagen and inhibits the release of fibroblast growth factors from macrophages. Given this mechanistic basis, it has therefore been considered in the treatment of IPF. Again, the data are of poor quality, but demonstrate perhaps a trend towards increased survival. Colchicine has long been used in the treatment of gout. The most common side-effects are abdominal distress, pain, diarrhea, nausea and vomiting. Uncommon adverse reactions are myelosuppression and myoneuropathy. Colchicine will be orally administered at a dose of 1.2 mg/d (in one past study 1 mg/d was associated with mild diarrhea in ~10% of patients) to patients with CrCl>50, and at a dose of 0.6 mg/d to patients with CrCl 10-50.

E. Medical Devices

No medical devices will be used in this study.

F. Study Questionnaires

No questionnaires will be used in this study.

G. Study Subjects

Subjects will have clinical, radiologic and functional evidence of IPF that will be confirmed by lung biopsy in all subjects, excluding those unable to tolerate lung biopsy due to poor pulmonary reserve (DLCO<35%); these patients, however, must agree to post-transplant or post-mortem examination of lung tissue to verify the diagnosis of IPF. Patients will have only recently received the diagnosis of IPF (within 2 months), and will be naïve to any form of treatment for this disease.

Clinical criteria: progressive dyspnea for a period of at least 3 mo; typical end-inspiratory "velcro" rales on lung exam; no evidence of another cause of interstitial pneumonia including evidence of connective tissue disease (rash, fevers, joint swelling), history of significant asbestos exposure, use of drugs known to induce fibrosis at the time of symptom onset, previous radiation therapy to chest, history of acute lung injury at time of symptom onset.

Radiologic criteria: symmetric bilateral interstitial process that are preferentially localized to subpleural regions of both lung bases. These infiltrates must be predominantly irregular linear or reticular opacities with evidence of architectural distortion such as traction bronchiectesis. Some honeycomb changes must be present, as well as minimal ground-glass opacity; however, ground-glass cannot be the predominant pattern. The presence of a centrilobular micronodular process suggests an alternative diagnosis and excludes the patient.

Pathologic criteria: patchy interstitial process with variable distribution characterized by fibrosis and inflammation, at different stages of development, preferentially localized to the peripheral and subpleural regions of the lung. The presence of granulomas suggests an alternative diagnosis and excludes the patient.

Exclusion criteria for this study are as follows: history of allergy, intolerance, or unwillingness to take either of the drugs proposed for this study; women who are pregnant or who may become pregnant but are not taking adequate birth control; patients with concurrent pulmonary diseases i.e. chronic asthma, active TB within past year, lung cancer, collagen-vascular disease; patients with a history of exposures listed above under "clinical criteria"; patients with a CrCl<10; history of steroid or colchicine use within the past year. Subjects requiring open-label steroids for unrelated medical issues during the course of this study will be limited to xmg prednisone equivalent. Patients exceeding this pre-determined limit will be considered treatment failures.

H. Recruitment of Subjects

Subjects will be recruited by referral to the study by their pulmonologists or primary care physicians; the referring doctor will agree that the patient is suitable and willing to participate in the study.

I. Confidentiality of Study Data

Each patient will be assigned a unique 6-digit number randomly generated and secured from parties not involved in the study.

J. Potential Conflict of Interest

None of the investigators involved in the trial has proprietary interest in either of the drugs under study.

K. Location of the Study

With the exception of the lung biopsy, which will be performed in the operating room with appropriate post-operative management, the studies proposed involve no risk to the subjects, and will be performed in an outpatient setting.

L. Potential Risks

Current ATS guidelines for the treatment of IPF suggest initial therapy with steroids and a cytotoxic agent for a trial period of 3-6 months. However, the official ATS statement on IPF recognizes that no agent has yet been proven to be clinically effective in the treatment of IPF, and recommends the establishment of multi-center, placebo-controlled trials to determine the efficacy of drugs routinely used to treat this disease, as well as for newer experimental therapies. There remains a possibility that subjects receiving placebo in this trial will be deprived of a [default] therapy that would have attenuated the course of their disease, or even have been life-saving. However, the inclusion of a placebo arm in this trial is justified given (1) the current lack of evidence documenting the effectiveness of prednisone or any other agent in the treatment of IPF, (2) the long list of known complications of prolonged steroid use, (3) evidence that high-dose steroid use may in fact contribute to deterioration in some patients with IPF, and (4) the ATS endorsement of placebo controlled trials in the study of this disease.

M. Potential Benefits

Potential benefits of this study include (1) the possibility of randomization to a study drug that has some efficacy in treating this uniformly fatal disease; (2) the possibility of avoiding therapy with a drug that has many known toxicities, yet no proven benefit in the treatment of IPF; (3) the societal benefit of helping to clarify the role of two commonly used, yet controversial, drugs in the treatment of IPF. However, the subject may not benefit from participation in this study.

N. Alternative Therapies

No medication has been proven effective in the treatment of IPF. However, a number of other experimental drugs are currently under consideration for treatment of this disease. These include pirfenidone, an anti-fibrotic agent with a benign side-effect profile that has been shown to have some efficacy in slowing the progression towards respiratory failure in a subset of patients with another fibrosing alveolitis, Hermansky-Pudlock Syndrome; also IFN-gamma, relaxin, gleevec, N-acetyl-cysteine, embrel, bosentan, endothelin-1 and leukotrienes.

O. Compensation to Subjects

Subjects will not be compensated for their participation in this trial. However, the costs of all testing will be covered by the study.

P. Costs to Subjects

There will be no cost incurred by participants in this study.

Q. Minors as Research Subjects

IPF does not occur in children, therefore there is no need to include minors in this study.

R. Radiation and Radioactive Substances

Patients will have a CT scan as part of their initial workup. There will otherwise be no subject exposure to radiation or radioactive substances.