June 2014 Tucson Pulmonary Journal Club: Pirfenidone in Idiopathic Pulmonary Fibrosis

King TE, Bradford WZ, Castro-Bernardini S, et al. ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New Engl J Med. 2014;370(22), 2083-92. [CrossRef] [PubMed]

Idiopathic pulmonary fibrosis is a chronic, progressive, and fatal lung disease that is characterized by irreversible loss of lung function. The 5-year survival rate that is similar to the rates for several cancers (1).

In the 2011, the official ATS/ERS/JRS/ALAT statement regarding idiopathic pulmonary fibrosis underlined that the preponderance of evidence to date suggests that pharmacologic therapy for IPF is without definitive, proven benefit (2). The committee made recommendations of varying strength against most therapies.

Pirfenidone is a pyridone compound with anti-inflammatory, antifibrotic, and antioxidant properties, with antagonism of Transforming Growth Factor (TGF)-B1 effects. Pirfenidone inhibits fibroblast proliferation and collagen synthesis and reduce cellular and histological markers of fibrosis in animal models of lung fibrosis.

Three previous phase 3 randomized, double-blind, placebo-controlled, that examined pirfenidone for idiopathic pulmonary fibrosis had varying results (3,4). That led to the approval of pirfenidone for idiopathic pulmonary fibrosis by many governing bodies worldwide but not by the US Food and Drug Administration. This prompted US regulatory authorities to request an additional trial to support the approval of pirfenidone.

The Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) is the fourth in a series of randomized, double blind, placebo-controlled trials. Pirfenidone was compared with placebo in patients with idiopathic pulmonary fibrosis. The study was conducted at 127 sites in 9 countries. Eligible patients were between the ages of 40 and 80 years and had received a centrally confirmed diagnosis of idiopathic pulmonary fibrosis. Patients were recruited July 2011 through January 2013. A total of 555 patients were enrolled; 278 were assigned to receive pirfenidone, and 277 were assigned to receive placebo. Physical examination and clinical laboratory assessments were performed at baseline and at weeks 2, 4, 8, 13, 26, 39, and 52. Pulmonary function, exercise tolerance, and dyspnea were assessed at baseline and at weeks 13, 26, 39, and 52.

The major inclusion criteria were having clinical symptoms consistent with IPF of 12 months duration; diagnosis of IPF, defined as the first instance in which a patient was informed of having IPF, at least 6 months and no more than 48

months before randomization; age 40 through 80 years, inclusive, at randomization; diagnosis of UIP or IPF by High resolution CT or surgical lung biopsy.

Major exclusion criteria included end stage renal disease, obstructive lung disease, congestive heart failure, end stage liver disease, arrhythmias and recent IPF exacerbations.

The primary outcomes of the study were to confirm the treatment effect of pirfenidone 2403 mg/d compared with placebo on change in percent predicted forced vital capacity (%FVC) in patients with idiopathic pulmonary fibrosis (IPF) and confirm the safety of treatment with Pirfenidone 2403 mg/d compared with placebo in patients with IPF.

In this randomized, controlled trial, the use of pirfenidone in patients with idiopathic pulmonary fibrosis led to a slower rate of loss in forced vital capacity than the use of placebo. Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths.

The major strengths of the include the randomized double-blinded control study design, straightforward hypothesis, minimal drop out rates, similarity to previous studies, however with a larger sample size and more central confirmation of diagnosis.

The study offers “New Hope for Idiopathic Pulmonary Fibrosis” (5). Major concerns would be extrapolating findings to treat patient populations that were not assessed in this study. That includes patients with more severe disease; other interstitial lung disease, and patients with comorbidities that were excluded in this study. The study also doesn't assess if the effects are durable beyond 1 year.

Mohammed Alzoubaidi MBBS and Kenneth S. Knox MD
University of Arizona
Tucson, Arizona

References

1. Nicholson AG, Colby TV, Dubois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med. 2000;162(6):2213-7. [CrossRef] [PubMed]

2. Raghu G, Collard HR, Egan JJ, et al. ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788-824. [CrossRef] [PubMed]
3. Noble PW, Albera C, Bradford WZ, et al. CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760-9. [CrossRef] [PubMed]
4. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone Clinical Study Group in Japan. (2010). Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35(4):821-9. [CrossRef] [PubMed]
5. Hunninghake GM. A new hope for idiopathic pulmonary fibrosis. New Engl J Med. 2014:,370(22), 214-3. [CrossRef] [PubMed]