# Pirfenidone for idiopathic pulmonary fibrosis: could it be a panacea?

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Idiopathic pulmonary fibrosis (IPF) is an inevitably progressive and invariably fatal condition with a median survival from diagnosis of 2.8-4.2 years[1]. The pathogenesis of IPF is poorly understood, but it is thought to arise as the consequence of an aberrant wound healing response following recurrent alveolar injury occurring in susceptible individuals. It is characterized by alterations in multiple pathways involved in fibrogenesis, wound healing, coagulation, apoptosis, oxidative stress and inflammation[2]. In the past decade significant progress has been made in the clinical investigation of IPF. Basic insights into mechanisms of fibroproliferation have been translated into novel investigational agents. Networks have been developed of clinical centres capable of enrolling hundreds of patients in research studies, and multiple high-quality treatment trials have been successfully completed and published[2].

Pirfenidone (5-methyl-1-phenylpyridin-2[1*H*]-one; Shionogi, Osaka, Japan; trade name *Esbriet®*, InterMune, California, US) is an orally available pyridone derivative that exhibits anti-inflammatory, antioxidant and anti-fibrotic properties[3]. The observation, first made in 1997, that pirfenidone attenuates pulmonary fibrosis in a variety of animal models, paved the way for its clinical development and subsequent evaluation as a treatment for IPF. Pirfenidone has been shown to inhibit fibroblast proliferation and collagen synthesis *in vitro,* and also to inhibit the expression of TGF-β induced heat shock protein HSP47, a molecular chaperone of collagen, the synthesis of which is known to correlate with fibroblast extracellular matter (ECM) deposition. *In vivo* pirfenidone attenuates bleomycin-induced lung fibrosis in both prophylactic and therapeutic doses, and this attenuation is associated with a reduction in the levels of lung platelet derived growth factor (PDGF) and TGF-β[3]. Its anti-inflammatory properties are manifested by attenuation in TNF-α and IFN-γ levels in experimental models of inflammation[4]. The precise molecular mechanism of action of pirfenidone, however, remains unclear.

In a Cochrane review to assess the efficacy of nonsteroid agents in adult patients with IPF[5] 4 trials assessing the efficacy of pirfenidone were identified. Three of these studies, conducted in a total of 1,046 patients, were eligible for inclusion in the metanalysis of progression-free survival; based on these studies, pirfenidone appears to significantly reduce the risk of disease progression. Only the results on pulmonary function from two studies could be combined in a metanalysis involving 324 Japanese

patients; a positive effect of pirfenidone in slowing the reduction of pulmonary function was observed[5].

In May 2011, in *The Lancet,* Paul Noble and colleagues reported the results of the Clinical Studies Assessing Pirfenidone in Iidiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY) programme, accompanied by an editorial by Professor Bouros[6,7]. Two concurrent phase 3 clinical trials (studies 004 and 006) investigated the role of pirfenidone in patients with mild to moderate idiopathic pulmonary fibrosis (i.e., forced vital capacity [FVC] ≥50% predicted, and diffusing capacity of the lung for carbon monoxide ≥35% predicted). Patients were randomly assigned to blinded treatment with oral pirfenidone or placebo for a minimum of 72 weeks. In study 004, 174 patients were assigned a high drug dose (pirfenidone 2403 mg/day), 87 patients a low drug dose (pirfenidone 1197 mg/day), and 174 placebo; in study 006, 171 patients were assigned the same high dose and 173 patients placebo. The primary endpoint was change in percentage predicted FVC at week 72. Secondary endpoints included progression-free survival and 6-minute walk-test (6MWT) distance. In study 004, high-dose pirfenidone significantly reduced the decline in percentage predicted FVC with an effect size of 4.4% at week 72. In study 006, there no difference was observed between the groups in the primary endpoint, but a consistent pirfenidone treatment effect was found up to week 48 (p=0.005) and in the repeated measures analysis of all study time points (p=0.007). In study 004, high-dose pirfenidone improved progression-free survival (hazard ratio 0.64, 95% CI 0.44–0.95, p=0.023). In study 006, a significant reduction in the decline from baseline to week 72 in 6MWT distance was observed in patients assigned pirfenidone (absolute difference 31.8 m, 95% CI 3.2-60.4). Both trials showed a relatively safe profile, especially for gastrointestinal adverse events, abnormalities in laboratory indicators of liver function, photosensitivity, and rash.

A marketing authorization application for pirfenidone was considered by the European Medicines Agency (EMA) and in February 2011 the drug was approved. Based on the recommendation of the Committee for Medicinal Products for Human Use of the European Medicines Agency in December 2010, the European Commission has granted marketing authorization for pirfenidone in the European Union for the treatment of mild to moderate IPF. Pirfenidone is expected to be available to European patients in autumn 2011, beginning with Germany in September 2011. In contrast, despite the vote of an advisory committee in favour of approval, in May 2010 the FDA refused to approve pirfenidone for the U.S. market. In Greece a name patient programme is ongoing in three centres (Alexandroupolis, Athens and Heraklion, Crete), providing the drug to patients with IPF.

Overall, the findings with respect to pirfenidone are promising, although they must be regarded with caution as the decision for its use was based on the mixed results from the CAPACITY programme, with only one of the two trials meeting its primary endpoint defined as absolute change in percent predicted FVC from baseline to Week 72. With these challenges in mind, the ideal trial endpoint in IPF studies is mortality[8]. It is now widely accepted, however, that lung function, particularly the change in FVC, represents an adequate surrogate for mortality. More recent data support the notion that across a population of patients change in FVC is likely to be a continuous variable when used as a predictor of subsequent outcome, with even small changes portending a poorer survival[9]. The FDA has asked for another clinical trial to provide additional and stronger evidence of efficacy of pirfenidone in the treatment of IPF. In any case, convincing additional data on survival and quality of life are needed.

Pirfenidone is a novel compound with antifibrotic, anti-inflammatory and antioxidant actions, which has been shown to slow disease progression in patients with IPF. Given the lack of available effective forms of treatment for patients with this devastating and inexorably progressive condition, pirfenidone represents an important development in the treatment of IPF. Further experience in the long term administration of pirfenidone is required to reassure physicians and their patients of the long-term safety of the drug. It also remains to be seen whether the combination of pirfenidone with other drugs, such as immunosuppressants or the antioxidant *N*-acetylcysteine, will further improve outcomes for patients with IPF. These are all major accomplishments that unarguably move the field forward, but for the patients and providers faced with this devastating diagnosis, there remain distressingly few management options, and no definitive therapy has yet been identified[11-16].

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