Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Review

Pirfenidone: Clinical trials and clinical practice in patients with idiopathic pulmonary fibrosis

*Masashi Bando**

Division of Pulmonary Medicine, Department of Medicine, Jichi Medical University, Tochigi, Japan

ARTICLE INFO

Article history:
Received 17 November 2015
Received in revised form
18 March 2016
Accepted 22 March 2016
Available online 26 April 2016

Keywords:
Idiopathic pulmonary fibrosis
Pirfenidone
Clinical trial
Clinical practice

ABSTRACT

Pirfenidone is an oral drug that exerts not only anti-fibrotic activity but also pleiotropic effects, such as anti-inflammatory and anti-oxidative effects. Because it suppresses reduction in vital capacity and improves progression-free survival, it was approved in October 2008 in Japan for the first time in the world as an anti-fibrotic agent for treatment of idiopathic pulmonary fibrosis (IPF). In October 2014, the agent was approved in the U.S., based on the results of the ASCEND study. Today, it is commercially available in 38 countries worldwide.

In clinical practice, it is important to pay attention to the balance between the effectiveness and adverse events (such as gastrointestinal symptoms and photosensitivity reactions, among others) of treatment with pirfenidone. It is important to investigate pirfenidone's most cost-effective usage, and the ideal time of treatment initiation, the condition in which treatment should be initiated, and duration of treatment.

Contents

*Tel.: +81 285 56 7850; fax: +81 285 44 3586.
E-mail address: bando034@jichi.ac.jp

http://dx.doi.org/10.1016/j.resinv.2016.03.007
2212-5345/

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause in adults [1]. The natural history of IPF is variable and unpredictable at the time of diagnosis [2]. In consideration of treatment strategies for IPF, it is most important to evaluate aspects of the clinical course and multiple factors for poor prognosis, and elucidate the necessity of treatment intervention and treatment goals.

The preferred therapeutic approach for IPF began to change after the emergence of the physiopathological hypothesis of the disease, in which the development of the condition was proposed as an epithelial-mesenchymal reparative abnormality that could commence without previous inflammation [3]. Based on this new concept, different research avenues were opened with the aim of inhibiting the fibrogenic process triggered in the disease; this was the beginning of the "anti-fibrotic" era. Pirfenidone is an oral anti-fibrotic drug; it was approved for IPF in Japan in October 2008 for the first time in the world. Seven years have passed since it became commercially available, and it has become a key drug for treatment of IPF in Japan. Experiences of using the agent in clinical practice have been collected. Meanwhile, the results of the ASCEND study were reported in 2014, and the Food and Drug Administration (FDA) in the U.S. approved the agent as a treatment for IPF that year. Currently, it is on the market in 38 countries worldwide.

2. Mechanism of pirfenidone

Pirfenidone is a low-molecular-weight compound with a pyridone ring and was first synthesized by Margolin in the U.S. in 1974 [4]. It shows pleiotropic effects, such as suppression of the production of reactive oxygen species; inflammatory cytokines such as TNF-α, IL-1β, and IL-6 derived from monocytes (anti-inflammatory and anti-oxidative activities); expression of growth factors such as TGF-β, b-FGF, and PDGF; and proliferation and collagen synthesis of fibroblasts (anti-fibrotic activity). It also improves the balance of Th1/Th2 by inhibiting the decrease in IFN-γ [5–7], although its exact mechanism is unknown. Recently, new mechanisms of action have been reported, such as the inhibition of the conversion of the phenotype of fibroblasts into myofibroblasts by inhibiting the intracellular signal pathway of TGF-β and the inhibition of fibrotic activity via suppression of the formation of nod-like receptor (NLR) P3 inflammasomes in cardiac muscle [8,9]. It is anticipated that a new mechanism of action will be elucidated by basic and clinical research.

3. Pirfenidone in clinical trials

The first clinical trial to investigate the use of pirfenidone in IPF was a phase II open-label trial for severe IPF that started in the U.S. in 1995 [10], in which stabilization of respiratory function was observed for two years. Later, a phase II clinical trial [11] and a phase III trial [12] were carried out for the first time in Japan. Two phase III trials (CAPACITY and ASCEND studies) [13,14] were carried out in North America, Europe, and Australia.

3.1. *Japan*

The study period was determined as 1 year in the phase II trial [11], but interim analysis 6 months after the start of the study showed significant acute exacerbation in the placebo group, and the key was opened at 9 months. When all subjects were analyzed, there was no significant difference in the primary endpoint. However, there was a significant difference when the subjects were limited to the cases that completed a walking test with SpO_2 maintained at $\geq 80\%$. In addition, vital capacity (VC) reduction, a secondary endpoint, was significantly suppressed.

In the phase III trial [12], the annual rate of decline in VC, a primary endpoint, was significantly suppressed in the high-dose (1800 mg/day) and low-dose pirfenidone groups (1200 mg/day) compared with those of the placebo group. Progression-free survival (PFS), a major secondary endpoint, was significantly prolonged in these groups compared with that of the placebo group. Azuma et al. [15] examined the association between pirfenidone efficacy and the baseline lung functions including %VC, arterial oxygen partial pressure, and the lowest SpO_2 in the 6-min steady-state exercise test (6MET). The results of these explanatory analyses identified IPF patients having baseline %VC $\geq 70\%$ and $SpO_2 < 90\%$ during 6MET as the subpopulation that benefited most from pirfenidone treatment.

3.2. *Foreign countries*

The CAPACITY trial [13] was carried out in a twin-trial manner (CAPACITY 1 and 2), and a reduction in FVC from the baseline, a primary endpoint, and PFS, secondary endpoint, showed a significant difference in the CAPACITY 2 trial but not in the CAPACITY 1 trial. When the results of the two trials were integrated, there was a significant difference found in not only the primary endpoint but also in PFS, six-minute walking distance, change in % FVC in each category, and IPF-associated death, compared with those of the placebo group. On the basis of these results, the U.S. FDA decided against approving pirfenidone for IPF in May 2010. An additional trial (ASCEND trial) was then planned in North America and Australia. In Europe, meanwhile, the European Medicines