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Pirfenidone treatment in a patient with IPF and possible initial hypersensitivity pulmonitis

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Abstract. The diagnosis of idiopathic pulmonary fibrosis (IPF) requires exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, systemic connective tissue disease, and drug toxicity), the presence of a 'usual interstitial pneumonia' (UIP) pattern on high resolution computed tomography (HRCT), and specific combinations of HRCT and histopathologic patterns in patients subjected to surgical lung biopsy (SLB). A clear diagnosis and early treatment with currently the only approved anti-fibrotic drug, pirfenidone, represents the standard of care for the treatment of mild-to-moderate IPF. This case report describes a patient with possible initial hypersensitivity pneumonitis and subsequent diagnosis of IPF with late development of pulmonary hypertension, and who was a candidate for lung transplantation. The patient showed slow progression of IPF during pirfenidone treatment in the CAPACITY and RECAP studies. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30 Suppl 1: 40-43)*

Key words: idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, therapy, lung transplantation, pirfenidone

Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown aetiology associated with progressive parenchymal fibrosis (1). Patients with IPF face substantial morbidity and mortality and report substantially impaired quality of life (2). Potential risk factors for the development of IPF include cigarette smoking, wood, mineral and metal dust environmental exposure, and past viral infection (3). Patients with IPF may have sub-clinical or overt comorbid conditions including pulmonary hypertension (PH), gastro-oesophageal reflux, obstructive sleep apnoea, obesity, and emphysema, but the impact of these conditions on the outcome of patients with IPF is unclear (1).

Until recently, lung transplant has represented the only therapeutic strategy that potentially improves survival in IPF (4). Pirfenidone, an anti-fibrotic agent with beneficial anti-inflammatory properties, may also have lung allograft protective properties (5). Pirfenidone has been investigated as a treatment option in IPF patients with no prior treatment with either *N*-acetylcysteine or steroids in the CAPACITY clinical trials (6). In addition, a Cochrane meta-analysis has been performed including results from the CAPACITY and Japanese phase III pirfenidone trials (7, 8). The RECAP Extension (open label) phase of the CAPACITY studies also provided safety and tolerability data from patients treated with a median duration of 2.9 years (9).

In the CAPACITY studies, approximately one-quarter of patients had baseline percent-predicted

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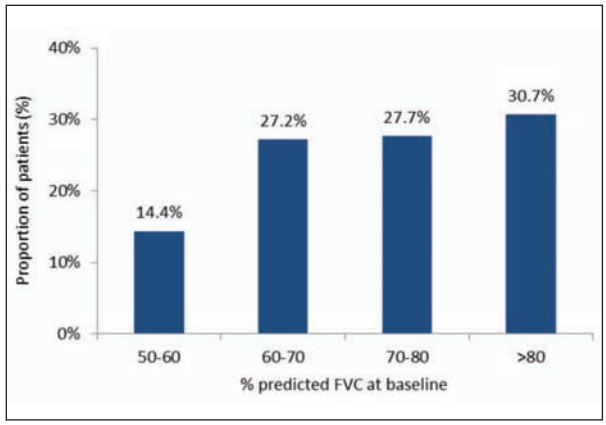

Fig. 1. The majority of patients enrolled in the CAPACITY Studies had a baseline percent predicted FVC above 70%

FVC values between 60 and 70%, with the majority above 70% (data provided by InterMune) (Figure 1).

Pirfenidone was approved in 2011 by the European Medicines Agency for the treatment of patients with mild-to-moderate IPF. This case report describes a patient who was a candidate for lung transplantation and who was treated with pirfenidone during the CAPACITY and RECAP studies.

Case Report

Clinical history

This female patient was a non-smoking farm worker. During 2001–2002, she was treated with steroids for suspected hypersensitivity pneumonitis (HP), without any noticeable benefit in the progression of lung disease.

Presentation

After a period of 2-3 years the patient was referred to our unit in 2005 complaining of breathlessness. High resolution computed tomography (HRCT) findings were relatively non-specific. A surgical lung biopsy (SLB) obtained in July 2006 was suggestive of a pattern of 'usual interstitial pneumonia' (UIP). Pulmonary function tests (PFT) were consistent with the diagnosis of IPF.

Treatment

After the histologic diagnosis of UIP, the possibility of an enrollment into a clinical investigational drug trial for IPF was considered. In early 2007, the patient entered the multinational, double-blind, placebo-controlled, 72-week CAPACITY 004 clinical trial of pirfenidone (6). During the trial, a consistent lowering of PFT indices was observed (Table 1A; Figure 2). At study completion, in November 2008, unblinding data revealed that the patient had been randomised to the active arm of the study, receiving the full dosage of 2403 mg/day pirfenidone.

In 2009, the patient continued to receive pirfenidone in the open-label extension RECAP study (9), during which further stability of PFTs was demonstrated (Table 1B), with a particularly notable improvement in the 6-minute walk test (6MWT) (Figure 3). Right-heart catheterisation (RHC) performed during transplantation checklist tests showed absence of pulmonary hypertension (PH). The patient was also placed on the transplantation waiting list at this time. After 1–1.5 years, in the Easter of 2010, the patient received the propos-

Table 1. Pulmonary function tests during the course of treatment with pirfenidone

	A. 2007: CAPACITY	B. 2009: RECAP	C. 2012
FVC (%)	67	43	42
FEV_1 (%)	69	47	46
FEV_1/FVC	109	103	102
DL_{CO}	83	35	54
6MWT (m)	320	310	135
PAP (echo) (mmHg)	–	48	65
RHC	–	No PH	–
PO_2	–	–	66
O_2 during exercise (L/min)	–	–	2.5

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; CPT: total lung capacity; DL_{CO}: diffusing capacity for carbon monoxide; 6MWT: 6-minute walk test; PAP: pulmonary artery systolic pressure; RHC: right-heart catheterisation

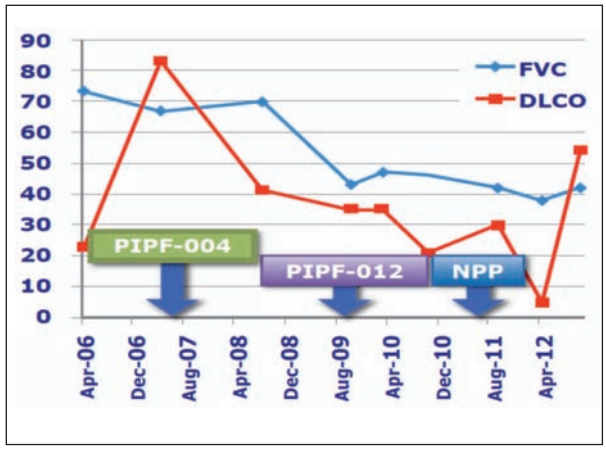

Fig. 2. Decline in FVC and DL_{CO} during pirfenidone treatment

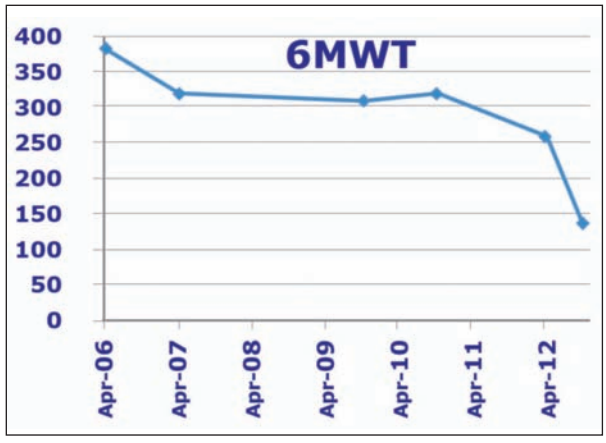

Fig. 3. Decline in 6MWT during pirfenidone treatment

al phone call for the lung transplantation. However, living alone, the patient was unable to decide, and therefore lost the opportunity for the transplantation procedure.

Follow-up

During the following two years (2011–2012), pirfenidone treatment was continued with a moderate stabilisation of disease progression, as demonstrated by further lowering of PFT results (Table 1C). Radiological assessment confirmed a relatively slow disease progression. In late 2012, however, the patient demonstrated a significant progression of disease and home oxygen treatment was initiated. Echocardiographic-estimated pulmonary arterial pressure suggested possible severe PH. Thus, a further RHC was performed in early 2013 and confirmed moderate PH. The patient has been recently re-admitted onto the transplantation waiting list.

Discussion

This case suggests that pirfenidone may slow disease progression in a non-smoking patient with possible exposure to environmental risk factors. Despite an original reasonable suspicion of HP, which could have been masked by steroid treatment, subsequent clinical progression and analyses were suggestive for IPF and histological diagnosis was consistent with UIP. After a significant decline in PFT results in the first year of treatment, pirfenidone had apparently induced a slowing of disease progression, as demonstrated by slight lung function decline at consecutive PFTs performed during the follow-up. On the basis of these data, it might be speculated that the UIP pattern at time of diagnosis may not have been the predominant clinical disease signature, only afterwards becoming the main character of the clinical progression.

The classification and staging of IPF patients may allow a better follow-up of this disease and is also critical for adequate lung transplantation indications (10). Indeed, although this patient was managed according to the guidelines available at initial presentation, the management may have been different with the availability of the most recent guidelines and recommendations on pharmacologic and non-pharmacologic approaches in IPF (11). Nevertheless, our case report exemplifies the efficacy of pirfenidone in the treatment of patients with mild-to-moderate IPF. Clinical use of the agent has been tested in a number of non-transplant recipients and has a favourable safety profile based on available clinical data. Building on these observations and findings, and considering the role of fibrosis in chronic allograft rejection, pirfenidone has also been studied as adjunct therapy in a rat heterotopic tracheal transplantation model and may well be worth considering for further investigation in clinical transplantation management (12).

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