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Treatment switching in idiopathic pulmonary fibrosis: from triple therapy to enrollment into a clinical investigational drug trial

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Abstract. A number of pharmacological agents have been the focus of clinical trials over the past years. Although no single pharmacological agent is recommended by current guidelines, preliminary negative findings regarding the safety of a triple therapy regimen consisting of prednisone, azathioprine and N-acetylcysteine have raised the question of whether it is no longer a treatment option. More recent data have resulted in the approval of pirfenidone in Europe. Pirfenidone shows a favourable risk–benefit profile and a beneficial effect in reducing the decline in lung function in patients with IPF. This case study describes the diagnosis and initial treatment of a patient with IPF with triple therapy of prednisone, azathioprine and N-acetylcysteine (NAC) followed by inclusion into a double-blind, randomised, placebo-controlled study and subsequent open-label extension trial of pirfenidone in IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30 Suppl 1: 44-47)*

Key words: diagnosis, idiopathic pulmonary fibrosis, pirfenidone, switching, triple therapy

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic disease limited to the lung, which is associated with the histological and/or radiological usual interstitial pneumonia (UIP) pattern. This is the most common and most lethal of all idiopathic interstitial pneumonias, with a median survival after diagnosis of approximately three years (1, 2). The clinical course is variable, usually with a progressive loss of lung function, although some patients have a rapid deterioration and between 5-10% of patients present with episodes of acute exacerbations of IPF (3).

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Although there are some variables that influence prognosis, predicting survival in patients with IPF is difficult. In this sense the longitudinal change in lung function is an important predictor of mortality. A decrease in forced vital capacity (FVC) greater than or equal to 10% at six or 12 months has been closely associated with decreased survival. Recent data suggest that even smaller decreases of between 5-10% could predict mortality (4). The recent publication of the results of three Phase III studies evaluating the efficacy and safety of pirfenidone are very promising. The results show that pirfenidone is able to reduce the decline in lung function in patients with IPF (5, 6). This case study describes the diagnosis and initial treatment of a patient with IPF with 'triple therapy' of prednisone, azathioprine and **N**-acetylcysteine (NAC) followed by inclusion into a double-blind, randomised, placebo-controlled study and subsequent open-label extension trial of pirfenidone in IPF.

Case Report

Presentation

A male patient of 45 years of age was referred to our diffuse interstitial lung disease (ILD) unit in early 2005 with a persistent dry cough of two months of evolution after a common cold. The patient had been a smoker of two packs a day until the age of 35 years, with an index of 25 pack-years, but without clinical criteria of chronic bronchitis. He had no symptoms of systemic connective tissue diseases (i.e. arthralgia, myalgia, Raynaud's phenomenon, or dry eyes or mouth), but did have a personal history of hypercholesterolaemia, hypertension, and an episode of left renal colic, and rheumatic fever in childhood. The patient worked in an office as a sales analyst and did not report any pulmonary toxic exposure or any pharmacological history.

Clinical evaluation

Physical examination revealed bibasilar 'velcro' crackles and an O_2 saturation of 97% on breathing room air. Hypercholesterolaemia (240 mg/dL) was the only notable laboratory test finding. Immunological analyses included a low positive anti-nuclear antibodies (ANA) titre (1:160), but negativity for extractable nuclear antigens (ENA), and perinuclear or cytoplasmic anti-neutrophil cytoplasmic antibodies (ANCA).

High resolution computed tomography (HRCT) showed lung parenchymal septal thickening in peripheral regions of both lungs with subpleural basal predominance. Some incipient honeycombing areas with traction bronchiectasis were visible with some ground-glass opacities. Bronchoscopy revealed no specific endobronchial abnormalities. Transbronchial biopsy bronchoalveolar lavage (BAL) cell counts showed no signs of specificity and CD1 markers were negative. Whilst the HRCT results were considered suggestive of a 'possible' pattern of UIP, a surgical lung biopsy (SLB) was performed by video-assisted thoracoscopy. The histology results showed a UIP pattern. After a multidisciplinary debate between radiologists, pulmonologists, and pathologists, the diagnosis of IPF was confirmed.

Pulmonary function tests (PFTs) at diagnosis (March 2005) showed both a restrictive pattern and a reduced diffusion capacity for carbon monoxide (DL_{CO}) (Table 1). Data for arterial blood gases included a pH of 7.43, arterial carbon dioxide tension ($PaCO_2$) of 37.4 mmHg, arterial oxygen tension (PaO_2) of 76.0 mmHg, a bicarbonate (HCO_3) level of 25.0 mmol/L, O_2 saturation of 96.1%, and an alveolar-arterial gradient of 18.2 mmHg.

Table 1. Summary of pulmonary lung function test results

Parameter	Absolute value	% predicted
FVC	3570 cc	73.1
FEV_1	2860 cc	71.9
FEV_1/FVC	80%	80.0
TLC	5260 cc	72.0
DL_{CO}	6.65 mmol/min/kPa	60.1
K_{CO}	1.51 mmol/min/kPa/L	99.7

FVC: forced vital capacity; FEV1: forced expiratory volume in one second; CPT: total lung capacity; DL_{CO}: diffusing capacity for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient

Treatment and clinical course

In April 2005, the patient began treatment with 'triple therapy' of prednisone (45 mg/day), azathioprine (50 mg/day) and NAC (1800 mg/day). The corticosteroid dose was reduced gradually to 10 mg/day and azathioprine increased to 100 mg/day. Despite treatment, however, the patient experienced clinical and functional worsening. The patient was therefore invited to enter the CAPACITY 006 multinational, randomised, double-blind, placebo-controlled clinical trial of pirfenidone (6). Triple therapy was terminated and after a washout period the patient was enrolled into the study in February 2007 (Figure 1). After stopping triple therapy, during the trial the patient showed a progressive improvement in pulmonary function with the per cent-predicted FVC increasing to 70% in July 2007 and reaching, in January 2008, the value at the time of initial diagnosis, 74%.

The CAPACITY 006 study concluded in October 2008, at which point, unblinding revealed that the patient had been included in the placebo arm of the trial. The patient was therefore immediately included in the open-label RECAP extension study (October 2008) and started treatment with pirfenidone, with escalating weekly doses from 267 mg/day (one tablet every 8 hours) up to the usual dose of 2403 mg/day (3 tablets every 8 hours). At this point, the patient had only mild dyspnoea and

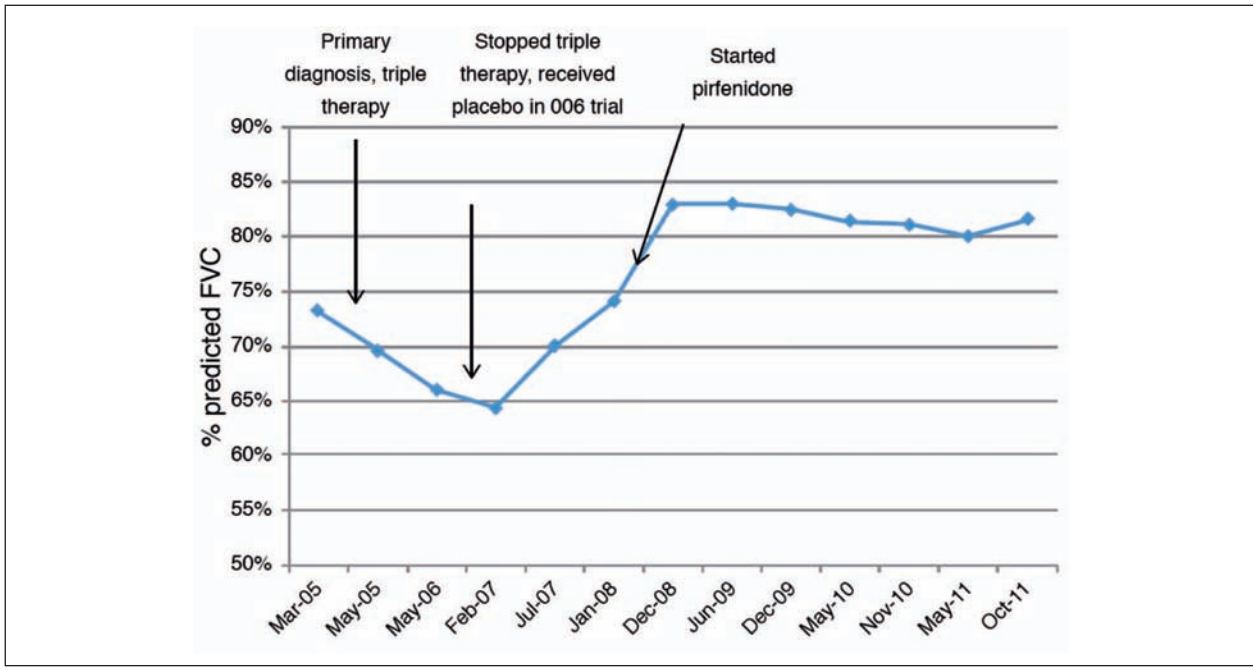

Fig. 1. Overview of clinical course of patient

no cough. During follow-up, he has not experienced any episodes of acute exacerbations, and no adverse effects or complications related to treatment have been evident to date.

Discussion

In the present case, the patient showed a worsening of his lung function, manifested predominantly by a progressive deterioration of FVC. Despite receiving treatment with triple therapy, per cent-predicted FVC decreased from 73% at initial diagnosis (March 2005) to 64% in February 2007. Triple therapy was therefore withdrawn and, after washout, the patient was enrolled into the double-blind, placebo-controlled CAPACITY 006 trial of pirfenidone in February 2007 during which a progressive improvement was observed.

At the end of the study, in October 2008, unblinding revealed that the patient was included in the placebo group. This leads to the question of the apparent improvement of lung function experienced by this patient. It seems interesting to note that this improvement coincided with the suspension of conventional triple therapy. These findings may be concurrent with data from an interim analysis of the PANTHER study, still in progress, which initially analysed three groups of treatments for IPF, prednisone-azathioprine and NAC versus NAC alone versus placebo. An interim analysis comparing the triple therapy and placebo groups showed a high risk of mortality and more frequent hospitalisations with the combination therapy, but no significant difference was found in the primary FVC endpoint (7). This may have been due to the premature interruption of triple therapy. Thus, without any other obvious cause, it appears that triple therapy may have been responsible for the functional worsening apparent in this patient and supports existing evidence against its use in patients with IPF.

On completion of the CAPACITY 006 trial, the patient was included in the open-label RECAP study of pirfenidone in October 2008. Almost three months after initiation of pirfenidone, the patient showed improvement in FVC of 10% predicted percentage relative to baseline levels in 2005 and has remained stable over the past three years without any significant adverse events. This case study demonstrates the importance of an accurate diagnosis based on multidisciplinary discussion in each patient. It also gives an example of the beneficial effect of pir-

fenidone treatment in preserving lung function in patients with IPF. Its favourable risk–benefit profile makes pirfenidone a valid therapeutic option for patients with mild-to-moderate IPF and highlights the importance of including IPF patients in a clinical trial as a treatment option.

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Disclosures:
Claudia Valenzuela has participated in clinical trials sponsored by Actelion, Boehringer, InterMune and has been a paid speaker for InterMune. Julio Ancochea reports receiving funds for speaking at conferences in educational events and to give scientific advice and/or research at Boehringer Ingelheim, Actelion, Zambon and InterMune.