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Pirfenidone experience in mild-to-moderate idiopathic pulmonary fibrosis in a general hospital

Title in Spanish: *Experiencia con pirfenidona en fibrosis pulmonar idiopática leve-moderada en un hospital general*

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ABSTRACT: This article present the experience and outcomes of patients treated with pirfenidone. FVC and DLCO parameters during 12 months were collected in patients treated with pirfenidone. Eight of the ten patients continued treatment until month 12. 7 patients presented at 12 months an adequate response treatment, 1 patient did not achieve therapeutic targets established (improvement or stability). At week 52, our patients had a mean of change in FVC(%) of -2.38±6.93%; patients of clinical trials showed -5.2% and -8.3% treated with pirfenidone and placebo respectively. Higher incidence of adverse effects was observed than clinical trials. Our results show that pirfenidone is a well-tolerated drug, whose toxicity can be controlled by dose adjustment, and it is effective in mild-moderate IPF. Due to no proven effectiveness and safety in medium / long term and the high economic impact, it is necessary to identify those patients who may get more clinical benefits.

RESUMEN: Este artículo presenta la experiencia y los resultados de pacientes tratados con pirfenidona. Se obtuvieron parámetros de FVC y DLCO durante 12 meses en pacientes tratados con pirfenidona. Ocho de los diez pacientes continuaron el tratamiento hasta el mes 12. 7 pacientes presentaron a los 12 meses un tratamiento de respuesta adecuada, 1 paciente no logró objetivos terapéuticos establecidos (mejoría o estabilidad). En la semana 52, nuestros pacientes tenían una media de cambio en FVC(%) de - 2.38±6.93%; los pacientes de los ensayos clínicos demostraron-5.2% y-8.3% tratados con pirfenidona y placebo respectivamente. Se observó mayor incidencia de efectos adversos de los ensayos clínicos. Nuestros resultados muestran que pirfenidona es un fármaco bien tolerado, cuya toxicidad puede ser controlada mediante el ajuste de la dosis, y es eficaz en IPF de leve a moderada. Debido a la no probada eficacia y seguridad a medio/largo plazo y alto impacto económico, es necesario identificar a aquellos pacientes que pueden obtener mayores beneficios clínicos.

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1. BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is an interstitial chronic pulmonary disease, which affect patients older than 50 years old. Disease aetiology is unknown, but has been associated with risk factors such as tobacco consumption, viral infections, environmental pollution, drug and genetic predisposition (1-2). Estimated incidence varies between 7 and 16 cases/100000 inhabitants/year, with a prevalence ranging between 14 and 43 cases/100000 inhabitants (3).

IPF is characterized by an abnormal histopathological mesenchymal cell proliferation, fibrosis, overproduction and disorganized collagen deposition, extracellular matrix changes with distortion of pulmonary architecture and appearance of subpleural cysts (honeycomb cysts), with accumulation of myofibroblast and fibroblast (3-5). In early stages, clinical pattern is similar to other lung diseases; signs and symptoms is unproductive cough, fatigue, eosinophilia, clubbing and increased acute phase reactants.

There is no clear consensus about patients' classification. The mild, moderate and severe terms are used depending on symptoms and function tests, although only mild-to-moderate IPF has been characterized (Forced Vital Capacity (FVC) ≥50%, Diffusion of Carbon Dioxide (DLCO) ≥35% (6)). Despite the mild diagnosis, medium-term prognosis is poor, with a median survival between two and four years after diagnosis. Respiratory failure is the most common cause of death (40%). Other causes of death in patients with IPF include heart failure, ischemic heart disease, infection, and pulmonary embolism. Age under 50 years, female gender, preserved lung function and increased proportion of lymphocytes (20-25%) in bronchoalveolar fluid have been associated with more survival (7). Age over 70 years, Comorbidities (pulmonary hypertension), emphysema and lung cancer), DLCO under 40%, FVC decrease≥10% and DLCO decrease≥15%

(percentage of predicted) at 6-12 months, desaturation during (Six Minute Walk Test) 6MWT≤88% and extension of the fibrosis in HRCT (High Resolution Computed Tomography) were associated with worst prognosis (6).

The therapeutic approach aims to preserve lung function and reduce the inflammatory component of the disease. Pirfenidone is an antifibrotic agent that inhibits the transforming growth factor beta (TGB-b), increasing the synthesis of collagen, decreasing extracellular matrix and blocking the proliferation of fibroblasts. It is indicated for the treatment of mild-moderate IPF (FVC> 50%, DLCO> 35%). The clinical efficacy of pirfenidone has been studied in three studies in Phase 3, multicenter, randomized, double-blind, placebo-controlled patients with IPF, which has shown a 30% improvement versus placebo in the FVC (8,9).

2. OBJECTIVE

To describe the main clinical outcome in patients mild-moderate IPF treated with pirfenidona after a year of monitoring follow-up the therapeutic protocol stablished in the hospital.

3. METHOD

When pirfenidone was available for clinical practice in our hospital, Pneumolgy and Pharmacy departments reached an agreement about the use of pirfenidone, demarcating clinical conditions that must be met to start the treatment. The pirfenidone-use criteria for a new patient was: diagnosis of mild-moderate IPF (forced Vital Capacity (FVC) >50% and diffusion of Carbon Dioxide (DLCO) >35%, age<80 years, charlson index<3 (excluding age), absence of severe renal impairment (ClCr<30 ml/min), absence of acute liver failure, advanced fibrosis, cirrhosis or hepatocellular carcinoma, no hypersensitivity to pirfenidone and no significant drug interactions (no administered with fluvoxamine, grapefruit juice or other inhibitors of cytP4501A2 and rifampicin, snuff or other inducers cytP4501A2). Patients starting treatment between January and March 2014 were chosen. A monitoring program was established during the first year of treatment which included lung function and biochemical study at months 1, 4, 8 and 12 from the beginning. The main clinical outcome was evaluated by the response; at month 12 was considered as positive when FVC and DLCO were increased from baseline, and was considered stable when FVC and/or DLCO do not decrease more than 10% and 15% from the baseline respectively. Withdrawal criteria were established when FVC and/or DLCO were reduced more than 10% and 15% respectively (All reductions were considered absolute from the baseline value). All patients were treated with an oral pirfenidone increasing-dose schedule: induction dose of 267 mg (1 pill) each 8 hours during the first week, 534 mg (2 pill) each 8 hours during second week, and maintenance dose of 801 mg (3 pills) each 8 hours from the third week if adequate tolerance.

From electronic clinical records, were obtained: demographic data, FVC, DLCO, date of start of treatment, dosage and adverse effects experienced. From pharmacy record were obtained dispensed pills. Adherence was computed as percentage of dispensed pills with respect to theoretical total pills must be taken during follow up period. Cost of pirfenidone was calculated as acquisition hospital costs at December 31, 2014.

4. RESULTS

Ten patients (9 males) with mild IPF met the criteria for starting treatment. The mean age was 69.5±5.0 years and the average time from diagnosis to starting treatment with pirfenidone was 2.7±1.8 years (range 1-7 years). Seven patients received N-acetylcysteine as a pretreatment. Until the time of marketing, all treatments initiated were authorized by the Agencia Española del Medicamento (AGEMED) and processed as “foreign drugs”. Eight of the ten patients continued on treatment until month 12. One patient died a month after starting treatment for not related lung pathology reasons. One patient discontinued pirfenidona in the eleventh month due to adverse effect (severe tremor). According with established criteria, 7 patients presented at month twelve a positive response, and only one patient did not achieve therapeutic targets established (improvement or stability) and treatment was changed to nintedanib at 12th month from the beginning. Mean baseline of FVC and DLCO were 85.3±15.4% and 55.6±16.7% respectively. Figure 1 compares our population with the results published in the clinical trials (8-9); at week 52 (12 months), our patients had a mean change in FVC (%) of -2.4±6.9% versus -5.2% reported on clinical trials in the pirfenidone group (-8.3% with placebo). Table 1 shows FVC and DLCO results at 12th month and response for each patient.

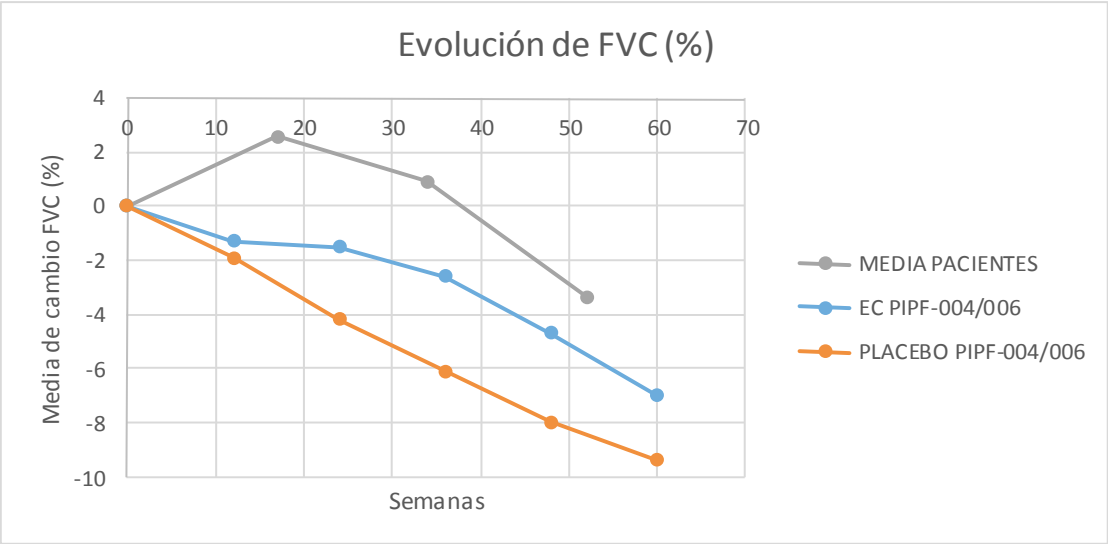

Figure 1. Comparison of mean change in FVC (%) of our sample of patients with clinical trials.

Table 1. FVC and DLCO change from baseline at the end of follow up period (month 12 from start) and response.

Patient number	change FVC(%)	Change DLCO(%)	Response at the end of follow up period (12 months)
1	-7	1	WITHDRAWAL AT 11TH MONTH (ADVERSE EFFECTS: TREMOR)
2	-13	-11	WITHDRAWAL AT 12TH MONTH. CRITERIA NON COMPLISHED.
3	-7	-8	POSITIVE RESPONSE
4	-2	3	POSITIVE RESPONSE
5	-8	-10	POSITIVE RESPONSE
6	Not lung-related death		
7	1	-2	POSITIVE RESPONSE
8	7	-5	POSITIVE RESPONSE
9	-3	-6	POSITIVE RESPONSE
10	6	-11	POSITIVE RESPONSE

The most common adverse reactions in our patients were nausea 18%, asthenia 22%, dyspepsia 19%, dizziness 18%, photosensitivity 12% and joint pain 10%; in clinical trials were nausea 40%, asthenia 20%, dyspepsia 30%, dizziness 40%, photosensitivity 40% and joint pain 10%. All patients showed any adverse effect. In all cases were mild or moderate severities. Higher incidence of adverse effects was observed than clinical trials reported. However, none of the patients experienced a significant increase of liver enzymes. In four patients pirfenidone dose was reduced due to adverse effects (All cases with reduction to 534 mg/8hours as maintenance dose); 3 patients showed gastrointestinal intolerance and 1 patient showed photo-toxicity.

Treatment adherence was 100% according to pharmacy records and considering dose reductions. At full dose, cost per patient and year was 30563€. Total cost per response was 37233€.

5. DISCUSSION

Our study population data compared to clinical trials show that pirfenidone had an effectiveness about 50% higher with a higher incidence of adverse effects than in clinical trials which in all cases were mild or moderate severities. With our small population study can not be compared with the clinical trials, but suggest a good handling of the drug by the multidisciplinary clinical team. Therefore, pirfenidone showed effectiveness and was well tolerated in clinical practice for patients with mild-moderate IPF within a twelve months follow up period where adverse effects can be controlled by dose adjustment. However, either in clinical trials or in our experience, results cannot be extrapolated to longer periods of time according with the course of the illness, where final outcome variables as survival, quality of life or functional status are more relevant than changes in FVC or DLCO. It is also necessary to observe results of

effectiveness and toxicity in the longer term. Taking into account high cost of pirfenidone, will be necessary perform economic evaluations in order to identify those patients that reach a greater clinical benefit with the lower cost possible. This type of analysis is necessary if we consider the availability of alternative therapy (nintedanib) for the same clinical objective.

6. CONFLICT OF INTEREST

None.

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