ANTIFIBROTIC THERAPY FOR IDIOPATHIC PULMONARY FIBROSIS: OUR REAL-LIFE EXPERIENCE

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Abstract

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial pneumonias, It is a fibrosing, chronic and progressive pneumonia, limited to the lung,cause unknown, with malicious prognosis, without curative treatment in this moment. Is characterized for a radiological and histological pattern of Usual Interstitial Pneumonia (UIP).

Especially affectsover 50 years old. Its evolution is unpredictable at the time of diagnosis conditioning a progressive decrease in lung function.

Currently, there are antifibrotic treatments that have proven effective in Progression of the disease and, therefore, improving the prognosis[1]. Regarding the use of these treatments in real life, outside the clinical trials.

Objetive: We present the results of the follow-up of 27 patients diagnosed withidiopathic pulmonary fibrosis, according to ATS / ERS 2011 criteria[2], 8 of them being treated with pirfenidone and 19 on treatment with nintedanib. Both treatments have been well tolerated, its adverse events have been digestive symptons and photosensibility.

Key words: Idiopathic pulmonary fibrosis, pirfenidona, nintedanib, antifibrotics

TRATAMIENTO ANTIFIBRÓTICO EN LA FIBROSIS PULMONAR IDIOPÁTICA. NUESTRA EXPERIENCIA EN LA VIDA REAL

Resumen

La fibrosis pulmonar idiopática (FPI) es la forma más común de las neumonías intersticiales idiopáticas. Es una neumonía fibrosante, crónica y progresiva, limitada al pulmón, de causa desconocida, con mal pronóstico y, hasta el momento, sin tratamiento curativo. Se caracteriza por un patrón radiológico e histológico de Neumonía Intersticial Usual (NIU).Afecta sobre todo a adultos mayores de 50 años. Su evolución es impredecible en el momento del diagnóstico, condicionando una disminución progresiva de la función pulmonar.

Actualmente, existen tratamientos antifibróticos que han demostrado eficacia en frenar la progresión de la enfermedad y, por tanto, mejorando el pronóstico[1]. Existe poca información con respecto al uso de estos tratamientos en la vida real, fuera del ámbito de los ensayos clínicos.

Presentamos los resultados del seguimiento de 27 pacientes diagnosticados de fibrosis pulmonar idiopática, según los criterios de la ATS/ERS 2011[2], 8 de ellos en tratamiento con pirfenidona y 19 en tratamiento con nintedanib. Ambos tratamientos han sido bien tolerados, siendo sus efectos adversos más comunes los síntomas digestivos y la fotosensibilidad, de carácter leve.

Palabras clave: Fibrosis pulmonar idiopática, pirfenidona, nintedanib, antifibróticos.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia. It is a chronic and progressive pneumonia which leads to fibrosis. Limited to the lungs with an unknown origin and poor prognosis, until now there has been no curative treatment. The average survival rate is estimated to be between 3 and 5 years from the onset of symptoms[3].

There are currently antifibrotic therapies available which can slow down the progression of the disease. Both pirfenidome and nintedanib have proven to be effective in decreasing the rate of deterioration in lung function, measured in terms of forced vital capacity (FVC); they manage to slow the progression of the disease and, in the case of pirfenidome, data shows an increased survival rate[4]. In general, the treatments are well tolerated according to data from clinical trials and they produce few side effects, those that do appear being easy to manage. As of now, there is little information about the response to these treatments outside of clinical studies.

Both treatments are approved for mild-moderate IPF when FVC is greater than 50%[5].

OBJECTIVES

The objective of the present study is to provide a descriptive and retrospective analysis of the clinical and functional characteristics, as well as the response to antifibrotic therapy and the tolerance in real life through a cohort of patients diagnosed with idiopathic pulmonary fibrosis who have been prescribed treatment with antifibrotic drugs.

METHODS

A descriptive, observational study has been carried out on a retrospective cohort comprised of 27 patients diagnosed with IPF, according to ATS/ERS 2011 criteria[2], included from October 2014 to November 2015. Pirfenidome (Esbriet®) treatment was administered to 8 of the 27 patients in said cohort in the form of 267 mg tablets. Treatment began with 3 tablets per day (1 tablet every 8 hours), and the dosage was increased weekly according to tolerance, until reaching a normal dosage of 9 tablets per day (3 tablets every 8 hours, corresponding to a total dosage of 2,403 mg). The remaining 19 patients received a 150 mg dosage of nintedanib (Ofev®) every 12 hours.

Data was collected regarding: age, gender, anthropometric data (weight, size, body mass index); lung function tests at the start and end of the monitoring period (FVC, diffusion, distance covered during the 6-minute walk test); tobacco use (pack-year); method of diagnosis (high resolution computerized tomography [HRCT], lung biopsy, multidisciplinary session); type of antifibrotic treatment prescribed; length of treatment; side effects and clinical progress.

The chi-square test was used for the statistical analysis of the qualitative variables and the student's t-test was used for quantitative variables using 0.05 as the value for statistical significance. Data was analyzed with the SPSS 13 software package.

RESULTS

Data for 27 patients was analyzed (Table 1), of which 19 received treatment with nintedanib at an average dosage of 300 mg for an average of 6.3 ± 3.9 months (1-12 month range) and 8 received treatment with pirfenidome at an average dosage of 2,403 mg for an average of 10 ± 3.9 months (3-14 month range).

Average patient age was 70 ±10 (53-81 years old) for pirfenidome and 68 ± 2.1 (54-79) for nintedanib. There were more men than women in both groups, with a proportion of 3:1.

With regard to functional tests, moderate limitation was shown, with a FVC of 68 ± 4% for the pirfenidome group and 71 ± 3.9% for those receiving nintedanib. The group undergoing treatment with pirfenidome had significantly higher DLCO values at the beginning of treatment, 43 ± 14 with a range of 43-61% versus 32 ± 8 with a range of 23-52% in the nintedanib group ($p < 0.01$). This difference continued until the end of the evaluation period. There were no differences in meters walked during the walk test between groups.

Lung function remained stable, with drops in both FVC and DLCO of less than 5% during the monitoring period.

All patients underwent HRCT for diagnosis and, in the cases where HRCT did not show a definitive NIU pattern, a biopsy was done via video-assisted thoracoscopic surgery: in 3 cases within the pirfenidome group and 5 in the nintedanib group. A higher incidence of emphysema was seen in the nintedanib group: 36.8% versus 11% in the pirfenidome group ($p < 0.01$). For all cases not requiring a biopsy, a diagnosis was made through a multidisciplinary

evaluation by the pulmonologist, radiologist and pathologist.

Both drugs were well tolerated, with both groups showing primarily digestive side effects in addition to mild photosensitivity in the case of pirfenidome treatment. However, these side effects caused very few patients to stop treatment (Table 2).

During the monitoring period, 2 patients in the pirfenidome group and 3 in the nintedanib group passed away, all of which were due to disease progression. One of the 19 patients from the nintedanib group received a successful transplant.

Table 1. Demographic and functional data

	PIRFENIDOME (n= 8)	*ASCEND*	*NINTEDANIB (n= 19)*	*INPULSIS-1*
AGE (years)	70 ± 10 (53-81)	68.4 ± 6.7	68 ± 2.1 (54-79)	66.9 ± 8,4
MALE/FEMALE (%)	75/25	79/21	89/11	81/19
TOBACCO (pack-year)	37 ± 12			
Initial FVC (%)	68 ± 4 (47-76)	67.8 ± 11.2	71 ± 3.9 (49-104)	79.5 ± 17
Final FVC (%)	60 ± 3 (45-10)		68 ± 4 (46-100)	
Initial DLCO (%)	43 ± 14 (43-61)	43.7 ± 10.5	32 ± 8 (23-52)	47.8 ± 12.3
Final DLCO (%)	41 ± 1.5 (40-57)		30 ± 3 (20-52)	
6-minute walk test (meters)	422 ± 54	415 ± 98.5	458 ± 23	
Initial/final saturation	95 ± 1/84 ± 3		93 ± 0.65/82 ± 1.28	
HRCT emphysema	1 (11%)	32%	7 (37%)	39%
BIOPSY	2 (22%)	30.9%	5 (26%)	19.4%

Table 2. Side effects

	PIRFENIDOME (n= 8)	*ASCEND (n 278)*	*NINTEDANIB (n 19)*	*INPULSIS (n 329)*
None	5 (55%)		9 (47%)	
Epigastralgia	2 (22%)	17.6%	2 (22%)	3.3%
Photosensitivity	1 (11%)	28.1%	--	--
↑Transaminases	1 (11%) ≠	3%	1 (5%)	4.9%
Diarrhea	--	22.3%	5 (26%)	63.2%
Weight loss	--	12.6%	2 (22%)	--
Exitus	2 (22%)	3.5%	3 (18%)	5.5%
Withdrawal	1 (11%)	19.8%	2 (22%)	23.7%

≠. *In one case a single patient experienced more than one side effect.*

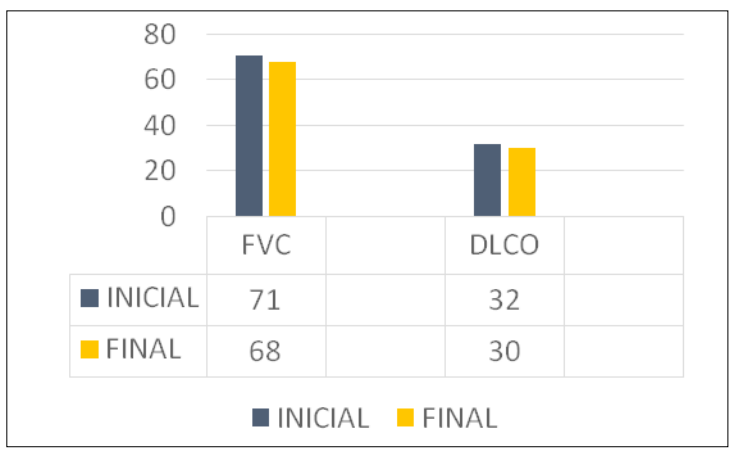

Figure 1: nintedanib functional progression in % throughout the monitoring period.

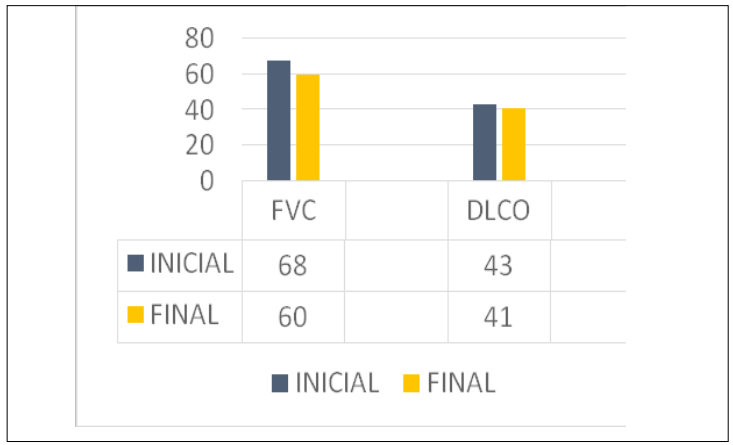

Figure 2: pirfenidome functional progression in % throughout the monitoring period.

DISCUSSION

The data presented shows that the new antifibrotic therapies are well tolerated, have few side effects which can easily be managed in most cases and do not usually require patients to withdraw from treatment.

IPF is a chronic and progressive disease with a poor short-term prognosis for which there had been no effective treatment until now[3]. In 2014, 3 studies were published which analyzed the efficacy of different IPF treatments. The PANTHER study[6] showed that N-acetyl cysteine was not more effective than the placebo in terms of drop in FVC. The ASCEND study[7] reflected that pirfenidome was effective in slowing the drop in FVC, with differences from the placebo group in disease progression and, jointly analyzed with patients from the CAPACITY program[8], IPF treatment was shown to increase survival for the first time. The INPULSIS study with nintedanib[5] showed an improvement in the drop in FVC with respect to the placebo group and this drug was then proven to decrease the number of exacerbations[9].

There is little information about the effects and tolerance for new drugs in real life, outside the area of clinical trials, especially for drugs recently being marketed. Our patients' characteristics were very similar to those included in the clinical trials and, in general, the drugs have been well tolerated. Although it must be pointed out that the data presented was taken over a short period, the side effects were those anticipated, especially digestive problems in both cases, and the incidence has been even better than that reflected in the clinical trials. Drug treatment only needed to be stopped in 3 out of 27 cases due to intolerance. There was a slight increase in transaminases in only one case, which was resolved without requiring any further treatment and did not require the drug dosage to be reduced.

Both treatments require periodical checks for liver function. In the case that liver enzymes increase 2-fold, the dosage needs to be reduced over 15 days and, if the patient stabilizes, the initial dosage can be resumed. Treatment must only definitively be suspended in cases of a more than 5-fold increase in enzymes[10]. This has not been necessary within our cohort. The incidence of diarrhea, the most frequent side effect of nintedanib, was 26%, lower than the 63% reported in the clinical trials and which has not required stopping drug treatment. To manage the side effect, dietary measures should be taken and it may require oral administration of loperamide 2 mg. In the case of pirfenidome treatment, photosensitivity has been very mild, occurring in a single case and it did not require stopping drug treatment. Avoiding sun exposure and the use of sunscreen year-round is recommended, which considerably reduces the incidence of this problem[11].

There have been some differences in the functional tests between treatment groups. In the nintedanib group, the DLCO was significantly lower, which can explain the higher number of patients with emphysema in this group (37%). The presence of emphysema in the upper lobes is frequent among IPF patients, especially those who have smoked and this may lead to a greater decline in DLCO[12] and a higher incidence of pulmonary hypertension[13]. The rate of emphysema in the clinical trials was 39% in the INPULSIS study and 32% in the ASCEND study. The rate of patients with emphysema within our cohort is very similar, 37%. This fact is not believed to have had any influence on drug tolerance. There were no differences between groups at either the start or end of evaluation for FVC and meters covered during the walk test.

This study has some limitations. A retrospective descriptive analysis of the tolerance for antifibrotic therapies in real life has been done. There are a greater number of patients being treated with nintedanib than with pirfenidome. As our objective was not to evaluate the efficacy of these drugs, which has already been contrasted in randomized clinical trials, we do not have information about the clinical and functional progression (FVC, dyspnea, 6-minute

walk test) before and after the start of treatment. It is a small cohort, 27 patients studied over a short period, and this may be why there have not been withdrawals due to lack of efficacy, but we believe this reflects the true activity of our consults. Although work is beginning to appear regarding real-life effects[14], there is little information available in the area of antifibrotic therapy for IPF.

In summary, both pirfenidome and nintedanib are recommended medicines for the treatment of IPF[15]. They have shown to be effective in slowing the progression of IPF, are well tolerated and have mild short-term side effects which can easily be managed.

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