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## Conflict of interests

I have no conflict of interests related directly or indirectly to the contents of this study.

# Patients with idiopathic pulmonary fibrosis can improve with antifibrotic drugs? results from a retrospective study

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# Idiopathic pulmonary fibrosis (IPF)

- IPF is a chronic respiratory disease, characterized by progressive lung scarring and loss of lung function.
- IPF has an estimated annual incidence in Europe of between 0.22 and 7.4 per 100,000 of the population, whereas prevalence ranges from 1.25 to 23.4 per 100,000 persons. In Lombardy, the most populous region of Italy (10 million inhabitants), annual incidence rate of IPF varies between 2.3 and 5.3 per 100,000 person-years, and prevalence is between 12.6 and 35.5 per 100,000 person-years.
- The prognosis is poor, with a median survival of 3–5 years.
- The progression of disease is variable, with some patients showing stable lung function over time, whereas others progress rapidly or experience episodes of acute deterioration.
- Change in forced vital capacity (FVC) is an accepted marker of disease progression in patients with IPF. An absolute or relative decline in % predicted FVC ≥10% is associated with increased mortality.

# IPF treatment: antifibrotic drugs

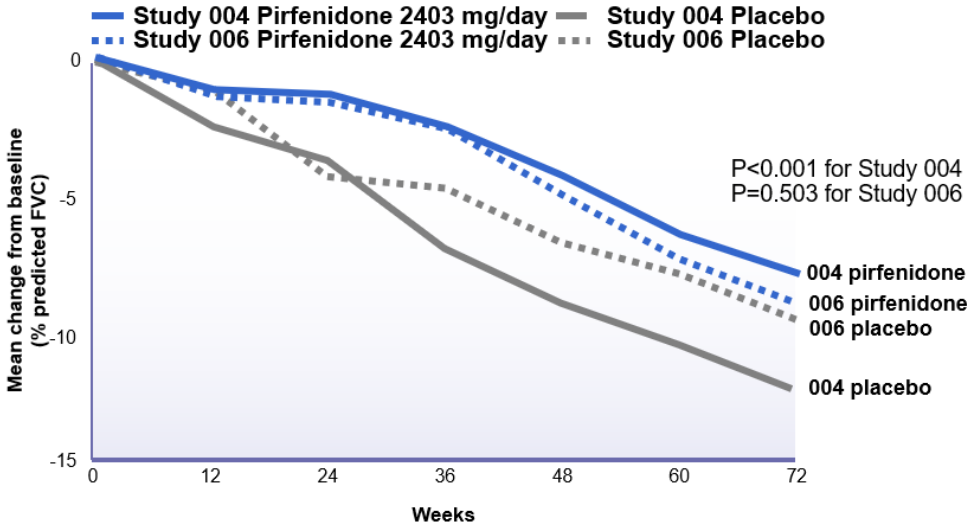
***Pirfenidone***

In multicentre randomised placebo-controlled trials *(CAPACITY 004 and 006, ASCEND),* pirfenidone slowed the rate of decline in predicted FVC, thereby slowing down disease progression. CAPACITY 006: 8% decline in FVC in the treated group *vs* 12.4% in placebo, p=0.001.

ASCEND: in the treated group there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline ≥ 10% in %FVC in comparison to placebo group).

Pirfenidone can reduce the risk of death by 48% (week 52; pooled analysis CAPACITY-ASCEND).

CAPACITY




ASCEND

* P-value <0.0001

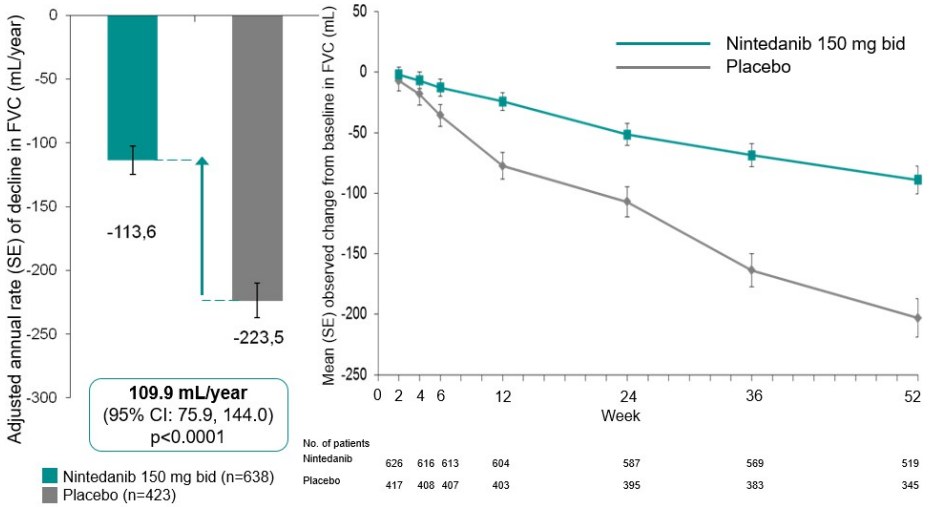
Relative Difference
47.9%*

at week 52

***Nintedanib***

Data from *INPULSIS 1 and 2 trials* showed that nintedanib 150 mg twice daily compared with placebo significantly reduced the rate of decline in FVC over the 52-week treatment period (pooled analysis: between-group difference in the annual rate of FVC change, 109.9 ml [95% CI, 75.9 to 144.0]). In addition, the data revealed a reduction in the incidence of acute exacerbation and an increase in time to first exacerbation with nintedanib (*INPULSIS 2*).

INPULSIS 1 and 2



# IPF treatment

- However little data are available in literature about IPF treated patients showing functional improvement....

## Clinical Experience of the Long-term Use of Pirfenidone for Idiopathic Pulmonary Fibrosis

Masashi Bando[1], Hiroyoshi Yamauchi[1], Takashi Ogura[2], Hiroyuki Taniguchi[3], Kentaro Watanabe[4], Arata Azuma[5], Sakae Homma[6] and Yukihiko Sugiyama[1]; The Japan Pirfenidone Clinical Study Group

**Abstract**

**Objective** Long-term effects of pirfenidone have been poorly understood to date. This study investigated the clinical efficacy and safety of long-term pirfenidone use for idiopathic pulmonary fibrosis (IPF) in clinical practice.

**Methods** This survey study was a retrospective observational study. A survey was used to collect clinical information on IPF cases that were treated with pirfenidone. This survey sheet came from physicians belonging to the Diffuse Lung Diseases Research Group.

**Results** 502 patients at 22 institutes received pirfeidone treatment. Of the 502 cases, pirfenidone treatment was terminated in under one year in 186 cases (37.1%); adverse effect was the most frequent reason for termination. The pirfenidone treatment lasted for two years or longer in 111 cases (22.1%). The mean change in the forced vital capacity (FVC) was -30±224 (SD) mL in the first year of treatment, -158±258 mL in the second year, and -201±367 mL in the third year. FVC improved by 10% or more in the first year in 10 (14.7%) of 68 cases, and showed a change of ±10% in 47 (69.1%) cases. It showed a change of ±10% in the second and third years in 61.7% and 62.5% of the patients, respectively.

**Conclusion** The FVC improved in only a small percentage of patients who received pirfenidone treatment for a long period of time. However, a decrease in the FVC was prevented for three years in over half of the cases.

(Intern Med 55: 443-448, 2016)

# Aim of the study

- to evaluate prognosis and clinical course of IPF patients with significant improvement of FVC (absolute increase ≥ 10%) after one year of treatment with antifibrotic drugs.

# Methods

**Study population**:

we conducted a monocentric, retrospective and observational study of patients with IPF treated with antifibrotic drugs.

*Inclusion criteria:*

- Diagnosis of IPF confirmed by HRTC UIP pattern and/or surgical lung biopsy (according to 2018 IPF guidelines)
- Mild, moderate and severe stage of disease
- Follow up of at least 3 years after starting antifibrotic drugs.

# Methods

**Study design:**

- The observation period lasted from April 2015 to December 2021.
- We collected
  - Clinical and radiological data at baseline
  - Functional data (FVC, DLCO, 6MWT, pO2) at baseline ad after one year of antifibrotic treatment.
- We selected among our population *functionally improved* patients, defined as the ones with absolute increase in FVC ≥ 10% at one year of antifibrotic treatment. For this group of patients FVC was evaluated also after 3 years.

# Methods

**Difference between absolute and relative change**

- Calculation:
  - Absolute change is calculated as follows: baseline FVC ± final FVC
  - Relative change: (baseline FVC ± final FVC)/baseline FVC
- Both measurements are similar when the patient's FVC is preserved but differ increasingly as FVC declines. The more severe baseline FVC, the greater the risk of identifying random or non-clinically significant fluctuations using the relative method.

# Methods

## Data analysis

- Data were summerized by descriptive statistics including mean ± SD.
- Survival of the group of improved was matched with the group of non-improved patients with Kaplan-Meier method. Differences in the survival curves were assessed using the log rank test.

# Results

- FVC improved by absolute 10% or more in 17 of 92 patients (18.5%) in the first year of treatment, whereas the other patients (81.5%) showed stable/worsened FVC after 1 year.
- All patients continued treatment during study period; dose reductions and/or brief treatment interruptions were permitted to manage adverse effects.

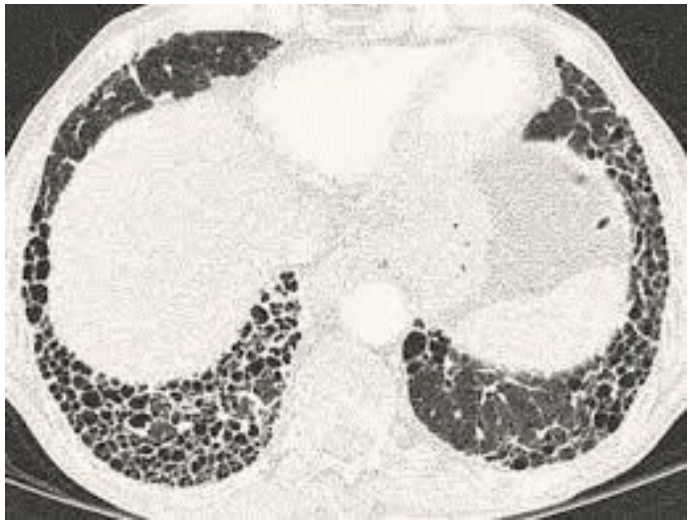
Tabel 1. Patients characteristics at baseline and antifibrotic drug chosen for treatment

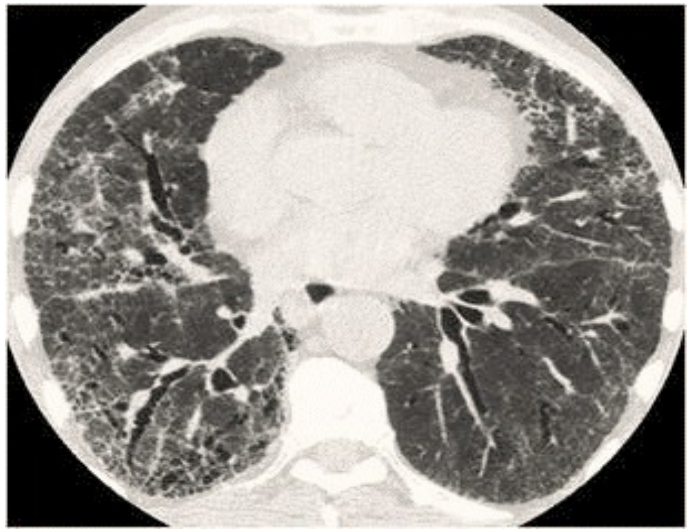
| Variables | Functionally improved (N=17) | | Non improved (N=75) | |
|---|---|---|---|---|
| Age (yr) mean ± SD | 72.6 ± 7 (min 61, max 84) | | 71.6 ± 6,5 (min 56, max 86) | |
| Male sex --no. (%) | 12 (70.6%) | | 57 (76%) | |
| Smoking status -- no. (%) | Never smokers | 5 (29.4%) | Never smokers | 23 (30.7%) |
| | Former smokers | 11 (64.7%) | Former smokers | 44 (58.6%) |
| | Current smokers | 1 (5.9%) | Current smokers | 8 (10.7%) |
| FVC % at baseline: mean±SD | 82.6 ±16.5% (min 54, max 117) | | 84.3 ± 21.5% (min 42, max 140) | |
| Antifibrotic drug –no. (%) | Pirfenidone | 6 (35.3%) | Pirfenidone | 32 (42.6%) |
| | Nintedanib | 11 (64.7%) | Nintedanib | 40 (53.4%) |
| | Shift | 0 | Shift | 3 (4%) |

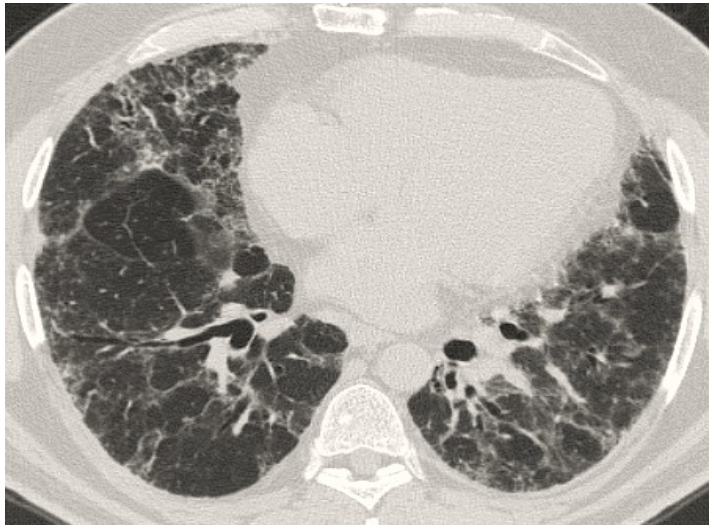
# Results

Radiologic evaluation with HRTC of functionally improved patients (N=17) at baseline

- 14 patients showed a typical UIP pattern
- 2 probable UIP pattern (cryobiopsy confirmed the diagnosis)
- 1 indeterminate pattern (cryobiopsy confirmed the diagnosis)







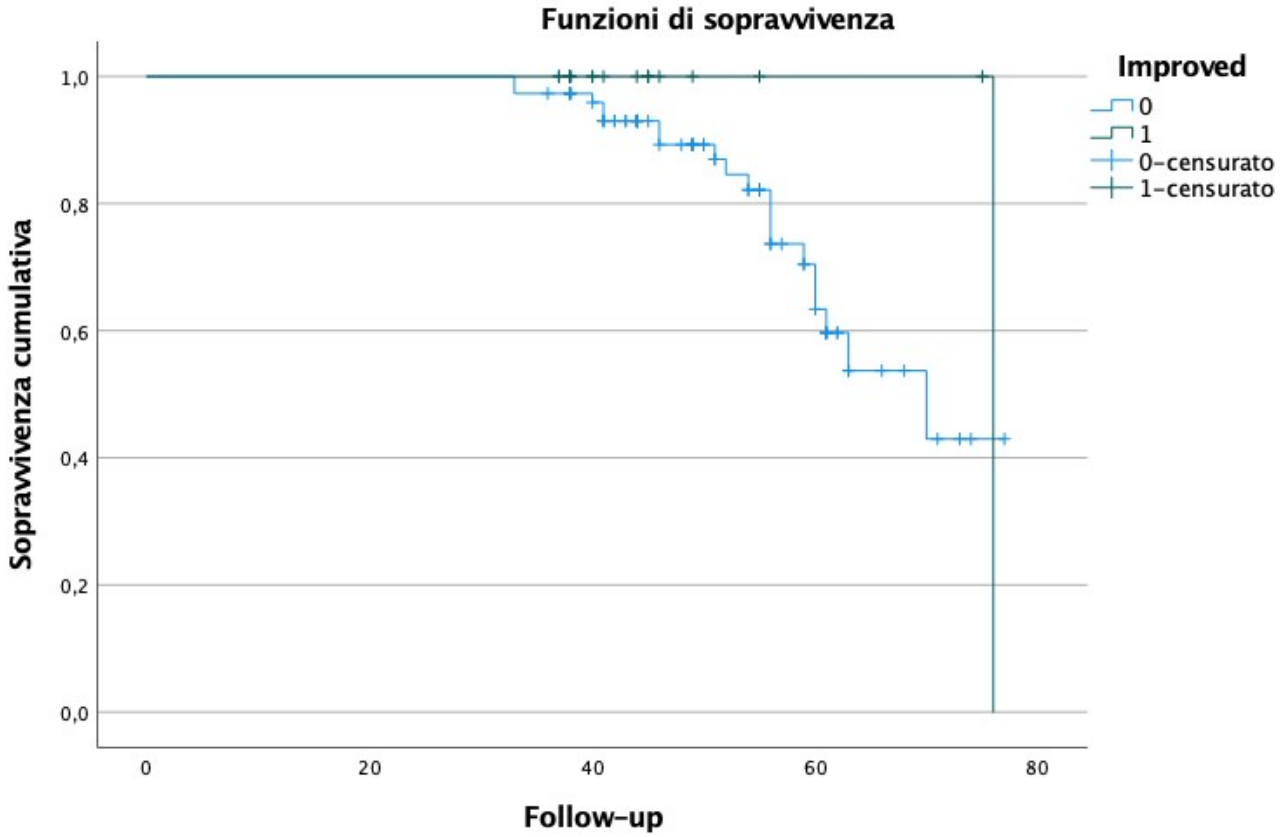
# Results

- Functional evaluation

| Variable | Functionally improved (N =17) |
|---|---|
| FVC % at baseline: mean±SD | 82.6 ±16.5% (min 54, max 117) |
| FVC % 1-yr after: mean±SD | 99 ±14.6% (min 68, max 128) |
| FVC % 3-yr after: mean±SD | 93.5 ± 17.2% (min 63, max 120) |
| DLCO at baseline | 52 ± 13% (min 31, max 69) |
| DLCO 1-yr after | 51 ± 14.5% (min 30, max 77) |

# Results

- We observed only 1 death at 3 years in the improved group vs 14 (18.6%) in the non improved group (p 0.097).



# Discussion

- Our study shows that in a small percentage of IPF patients FVC can significantly improve after treatment and this improvement is sustained over time.
- No clinical and radiological baseline characteristics predicted the improvement in FVC, however all patients had a functional mild-moderate disease and antifibrotic treatment was started early.
- The percentage of improved group [18.5% (17 of 92 patients)] is similar to that of the retrospective observational study of Bando et al. [14.7% (10 of 68 patients)], however functional evaluation at 3 years in this latter study was available for only 16 of 68 patients (23.5%). In addition we considered both antifibrotic treatment and not only pirfenidone.
- No significant difference in survival was observed between the functionally improved group and the non improved one, given the small number of events in the first group.
- The strength of our study is that functional evaluation and clinical course were assessed over a long-term period and no patient was lost to follow-up.
- Main limits of the study:
  - Monocentric, small number of patients
  - Retrospective nature

# Conclusions

- Only a small number of IPF patients experienced a significant improvement in lung function in the first year of therapy and this condition prevented a deterioration in FVC over a long-term follow-up of 3 years.
- Larger studies are needed to better characterize IPF population with a great functional improvement and to identify earlier subjects who will benefit the most from antifibrotic therapy.

# Thank you for your attention