Respiration

Clinical Investigations

Respiration 2020;99:646–648
DOI: 10.1159/000508667

Received: May 9, 2020
Accepted: May 15, 2020
Published online: August 27, 2020

# Older Idiopathic Pulmonary Fibrosis Male Patients Are at a Higher Risk of Nintedanib Dose Reduction

Sergio Harari[a–c] Claudia Specchia[d] Roberto Lipsi[a] Roberto Cassandro[a] Antonella Caminati[a]

[a]Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria, Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe, MultiMedica IRCCS, Milan, Italy; [b]Department of Medical Sciences, San Giuseppe Hospital MultiMedica IRCCS, Milan, Italy; [c]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy; [d]Dipartimento di Medicina Molecolare e Translazionale, Università di Brescia, Brescia, Italy

**Keywords**
Idiopathic pulmonary fibrosis · Nintedanib · Therapy · Body mass index

**Abstract**
***Background:*** Two pharmaceutical agents have been approved for treatment of idiopathic pulmonary fibrosis (IPF): pirfenidone and nintedanib. ***Objectives:*** We investigated the need of dose reduction in consecutive patients treated with nintedanib in relation to gender and body max index, comparing the population over and under 80 years of age. ***Methods:*** We retrospectively reviewed the data of all consecutive IPF patients treated with nintedanib for at least 3 months. Data on age, gender, body max index, side effects, and duration of therapy after enrolment were recorded. ***Results:*** A total of 82 patients has been evaluated. All dose reductions were related to side effects and/or toxicities. The need for a dose reduction was significantly more frequent in patients aged 80 years or older (50 vs. 26.8%, $p = 0.039$), independently from their body mass index. A total of 52% of males >80 years and only 16% of males <80 years reduced the dose ($p = 0.002$). ***Conclusions:*** Male gender and not body mass index in IPF patients aged ≥80 years treated with nintedanib seems to influence dose reduction.



## Introduction

For treatment of idiopathic pulmonary fibrosis (IPF), 2 pharmaceutical agents have been approved: pirfenidone and nintedanib [1]. In some European countries, as in Italy, pirfenidone can be prescribed only to patients with IPF younger than 80 years of age, while nintedanib can be prescribed also to older patients. This is due to the fact that while in the pivotal trials for pirfenidone the upper age limit was 80 years, no upper limit was considered in the nintedanib studies [2–5].

The TOMORROW study was a dose finding trial, with significant positive results on the annual trend of decline of forced vital capacity (FVC) only for the dose of 150 twice daily, while the primary endpoint was not reached by the groups of patients treated with lower dosages [6].

karger@karger.com
www.karger.com/res



Sergio Harari
Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria
Ospedale San Giuseppe, MultiMedica
Via San Vittore 12, IT–20123 Milan (Italy)
sergio@sergioharari.it

This trial was followed by 2 phase III clinical studies with identical designs that investigated the efficacy and safety of nintedanib 150 mg twice daily or placebo in patients with IPF (the INPULSIS trials) [2]. The primary endpoint was the annual rate of decline in FVC: nintedanib consistently slowed disease progression by reducing the rate of decline of FVC compared with placebo [2].

However, patients randomized in clinical trial for IPF are less severe than in real life, and without any other significant associated comorbidities. Even if no upper age limit was an exclusion criterion in the randomized controlled trial (RCT) studies of nintedanib, the mean age of patients randomized in the INPULSIS and TOMORROW studies ranged from 64.8 to 67.1 years [2, 6].

In this retrospective analysis, we evaluated the need of dose reduction in consecutive patients in a real-life setting, and treated with nintedanib for at least 3 months in relation to gender and body mass index (BMI), comparing the population over and under 80 years of age.

## Methods

We retrospectively reviewed the data of all consecutive IPF patients that from June 2016 to April 2019 started nintedanib therapy at our center. San Giuseppe Hospital is a tertiary referral national center for rare pulmonary interstitial and vascular diseases. To be included in this analysis, patients had to be in treatment for at least 3 months. Data on age, gender, BMI, side effects, and duration of therapy after enrolment were recorded.

All dose reductions (from 150 mg twice daily to 100 mg twice daily) were related to side effects and/or toxicities. When possible, according to the evaluation of the physician on charge, nintedanib was up-titrated to the maximum dose of 150 mg twice daily. For the purpose of this analysis, if the reduction of the drug was only transient, the patient was considered as taking the higher tolerated dose, if the reduction was permanent, the lower.

The association between binary variables was tested using the $\chi^2$ test. A multivariable logistic regression model was used to test the interaction between gender and age.

## Results

A total of 82 patients have been treated with nintedanib for at least 3 months (average duration of therapy equal to 18 months, SD = 9 months). Sixty-five (79%) were males and 17 (21%) females, with a mean age of 75 years (SD = 7 years) and BMI of 25.5 kg/m$^2$ (SD = 3.8 kg/m$^2$). A total of 28 patients (22%) reduced the dose during treatment. The side effects reported are: diarrhea with weight loss (21 patients), nausea (8 patients), asthenia (3 patients), and drug-induced liver injury with persistent elevation of liver enzymes ≥3 times the upper limit of normal (2 patients).

**Table 1.** Nintedanib dose reduction (from 150 to 100 mg t.i.d.) among patients aged >80 years stratified by BMI level (kg/m$^2$) and gender

| | Dose reduction, *n* (%) | | *p* value |
|---|---|---|---|
| | ≥80 years | <80 years | |
| All patients | | | |
| *n* | 26 | 56 | |
| Yes | 13 (50.0) | 15 (26.8) | 0.039 |
| No | 13 (50.0) | 41 (73.2) | |
| Patients with BMI ≥25 | | | |
| *n* | 11 | 35 | |
| Yes | 5 (45.5) | 7 (20.0) | 0.094 |
| No | 6 (54.5) | 28 (80.0) | |
| Patients with BMI <25 | | | |
| *n* | 15 | 21 | |
| Yes | 8 (53.3) | 8 (38.1) | 0.36 |
| No | 7 (46.7) | 13 (61.9) | |
| Males | | | |
| *n* | 21 | 44 | |
| Yes | 11 (52.4) | 7 (15.9) | 0.002 |
| No | 10 (47.6) | 37 (84.1) | |
| Females | | | |
| *n* | 5 | 12 | |
| Yes | 2 (40.0) | 8 (66.7) | 0.31 |
| No | 3 (60.0) | 4 (33.3) | |

The need for dose reduction was significantly more frequent in patients aged 80 years or older (50 vs. 26.8%, $p = 0.039$), independently from their BMI (Table 1). The expected effect of age on dose reduction was observed only in males. A total of 52% of males aged over 80 years and only 16% of males aged <80 years reduced the dose ($p = 0.002$). The percentage of those who reduced the dose was >40% both among females who were less and those who were 80 years old (Table 1). This different effect of age on dose reduction between males and females was statistically significant ($p = 0.02$).

## Discussion

Our real-life population is much older that the ones of the TOMORROW [6] and INPULSIS studies [2], with a slightly lower BMI than the latter studies. Treated populations in real life are frequently older than in RCTs; in 3 previous national real-life studies, the mean age of IPF patients treated with antifibrotic drugs ranged from 69 ± 7.9 years [7, 8] to 70 ± 8 years [9]. The fact that nintedanib

is the only drug available in Italy for patients aged over 80 years could explain the shift to an older age of the whole population. Our study does not evaluate the efficacy of a lower dose of nintedanib in the population aged 80 years old or older, where males resulted at higher risk of dose reduction, but suggests the need for specific trials in this particular fragile subgroup of patients. We did not registered nintedanib dose reduction in women over 80 years of age; however, the number of women was too limited to make a firm conclusion. In the TOMORROW study, the dose of 100 mg twice daily did not significantly affect the rate of decline of FVC but had several positive effects on secondary endpoints, among them quality of life questionnaires [6]. Dose reduction during the INPULSIS-ON trial, as recommended for the treatment of side effects, did not affect the annual rate of decline of FVC, suggesting the long-term efficacy of nintedanib in reducing disease progression also in patients requiring dose adjustments [10]. We believe that an accurate balance between the positive effects and the possible side effects should be considered when prescribing nintedanib in older patients. In conclusion, male gender and not BMI in IPF patients aged 80 years or older treated with nintedanib seems to influence dose reduction; however, new data on this specific population are needed to confirm our findings.

## Statement of Ethics

The study obtained the authorization by the San Giuseppe Hospital Ethic Committee (EC; No. 285/2016).

## Disclosure Statement

C.S., R.L., and R.C. have no conflicts of interest to declare. S.H. and A.C. have potential competing interests outside this work.


## Funding Sources

There are no funding sources to declare.


## Author Contributions

S.H. had full access to all data used in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. A.C. assumes full responsibility for the integrity of the submission as a whole, from inception to the publication of the article. All authors contributed substantially to the study design. R.L. and R.C. contributed substantially to data collection. C.S. contributed substantially to data analysis. All authors contributed substantially to the interpretation of the data results and the writing of the manuscript. All authors read and approved this study before submission.

## References


1 Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al.; American Thoracic Society; European Respiratory society; Japanese Respiratory Society; Latin American Thoracic Association. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 Clinical practice guideline. Am J Respir Crit Care Med. 2015 Jul;192(2):e3–19.

2 Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014 May;370(22):2071–82.

3 Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al.; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011 May;377(9779):1760–9.

4 King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al.; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014 May;370(22):2083–92.

5 Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, et al.; INSTAGE Investigators. Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2018 Nov;379(18):1722–31.

6 Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011 Sep;365(12):1079–87.

7 Harari S, Caminati A, Albera C, Vancheri C, Poletti V, Pesci A, et al. Efficacy of pirfenidone for idiopathic pulmonary fibrosis: an Italian real life study. Respir Med. 2015 Jul;109(7):904–13.

8 Harari S, Caminati A, Confalonieri M, Poletti V, Vancheri C, Pesci A, et al.; ILDINET (Interstitial Lung Diseases Italian Network). The prognostic role of Gender-Age-Physiology system in idiopathic pulmonary fibrosis patients treated with pirfenidone. Clin Respir J. 2019 Mar;13(3):166–73.

9 Harari S, Caminati A, Poletti V, Confalonieri M, Gasparini S, Lacedonia D, et al.; for the ILDINET (Interstitial Lung Diseases Italian Network). A real-life multicenter national study on nintedanib in severe idiopathic pulmonary fibrosis. Respiration. 2018;95(6):433–40.

10 Crestani B, Huggins JT, Kaye M, Costabel U, Glaspole I, Ogura T, et al. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. Lancet Respir Med. 2019 Jan;7(1):60–8.