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Title: REAL LIFE COMPARISON OF PIRFENIDONE AND NINTEDANIB IN PATIENTS WITH IDIOPHATIC PULMONARY FIBROSI: A 24 MONTHS ASSESSMENT

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Abstract: Background: Real-life data on the use of pirfenidone and nintedanib to treat patients with idiopathic pulmonary fibrosis (IPF) are still scarce.
Methods: We compared the efficacy of either pirfenidone (n=78) or nintedanib (n=28) delivered over a 24-month period in patients with IPF, followed at two regional clinic centers in Italy, with a group of patients who refused the treatment (n=36), and who were considered to be controls. All patients completed regular visits at 1- to 3-month intervals, where primary [forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO)] and secondary outcomes (side effects, treatment compliance, and mortality) were recorded.
Results: Over time, the decline in FVC and DLCO was significantly higher (p=0.0053 and p=0.037, respectively) in controls when compared with the combined treated group, with no significant difference between the two treated groups. Compared to patients with less advanced disease (GAP (Gender, Age, Physiology) stage I), those in GAP stages II and III showed a significantly higher decline in both FVC and DLCO irrespective of the drug taken. Side effects were similarly reported in patients receiving pirfenidone and nintedanib (5% and 7%, respectively), whereas mortality did not differ among the three groups.
Conclusion: This real-life study demonstrated that both pirfenidone and nintedanib were equally effective in reducing the decline of FVC and DLCO versus non-treated patients after 24 months of treatment; however, patients with more advanced disease were likely to show a more rapid decline in respiratory function.

Dear Editor, dear Reviewers,

Thank you for the thoughtful and constructive review of our paper. We carefully read your comments and suggestions, and we modified the manuscript accordingly.

Please find enclosed a point-by-point response as well as a marked and clean copy of the revised manuscript.

While we hope that you will find the revised version of the manuscript acceptable for publication as "Original Article" in *Respiratory Medicine* we will be happy to respond to outstanding comments and questions, should they occur.

Best regards,

Prof. Enrico Clini

Reviewer 1

We thank the Reviewer for the precise reviewing process of our work. We have welcomed all of her/his comments and we have tried to emend the manuscript accordingly.

Major comments

Reviewer 1's comment 1

Did the authors calculate the power of the study (e.g. number of patients needed to respond to the main aim) before its start? This does not seem to be mentioned along the paper.

Answer to Reviewer 1's comment 1

We thank the Reviewer for this comment. We did not perform a sample size calculation on primary outcome due to the nature and purpose of the study that aims at exploring the real life local experience of two referral center for IPF drugs prescription. We admit that this limitation has surely underpowered the results of the study and add it in the dedicate section.

Reviewer 1's comment 2

There is no any information on what kind of treatment the control patients had. Anyone? Others than pirfenidone and nintedanib?

Answer to Reviewer 1's comment 2

We really thank the Reviewer for this comment that gave us the chance to better illustrate this point. For those patients refusing the treatment, we only provide symptom support, as needed (i.e. oxygen, HFNC, opioids etc). This was added in the Methods section: "*Their "chronic" therapy, for any other comorbidity*

was left unchanged; symptomatic intervention for dyspnea was prescribed when needed (i.e. opioids, High Flow Nasal Cannula or Oxygen".

Reviewer 1's comment 3

Discussion: the whole discussion requires editing and revision. The first 4 paragraphs at page 9 could be in part removed and in part moved to the Introduction. Discussion should better start by highlighting the results and the novelty of the results, what this paper adds to the known literature. Page 10: "Interestingly our study confirms some results of the previous ones…". References are needed. Discussion of the present results and those from the main RCT should be added.

Answer to Reviewer 1's comment 3

We agree with the Reviewer with this comment. We have thus extensively modified the Discussion section, as suggested.

Reviewer 1's comment 4

Figure 1 and Figure 2: statistical significance is missing into the figures. Figure 1 and Figure 2 seem to report data on patients with GAP Index 1? From the text the reader understands that they refer to all patients, this must be clarified.

Answer to Reviewer 1's comment 4

We thank the Reviewer for this comment and we do apologize for the mistaken figure presented. We have now produced the correctly formatted figure and we have added the p values as indicated. Figures 1 and 2 now refer to all patients. This has been now clarified: Figure 1 and 2 illustrate the time course of FVC and DLCO respectively, irrespective of the GAP index, during the 24 months time period.

Reviewer 1's comment 5

Table 1 and Table 2: IPF not treated should better be in the 3rd column.

Answer to Reviewer 1's comment 5

We thank the Reviewer for this comment. We have emended the table as indicated.

Reviewer 1's comment 6

Table 2: Were side effects statistically different?

Answer to Reviewer 1's comment 6

We thank the Reviewer for this comment. No statistical differences were found. This was added in the text (Side effects are illustrated in table 2, and no statistical difference was observed between the two treatments).

Reviewer 1's comment 7

The whole text of the paper generally should benefit of a revision/editing of the English.

Answer to Reviewer 1's comment 7

We thank the Reviewer for this suggestion. The manuscript has been edited by a professional, native English-speaking editor with 25 years' experience editing medical and science manuscripts (see in acknowledgments).

Reviewer 1's comment 8

The abstract should mention which are the main and secondary aims of the study.

Answer to Reviewer 1's comment 8

We thank the Reviewer for this suggestion. We have thus modified the abstract and indicated primary and secondary outcomes: "*All completed regular visits at 1-to 3-month intervals, where primary [forced vital capacity (FVC) and diffusing lung capacity (DLCO)] and secondary outcomes (side effects, treatment compliance, and mortality) were recorded*".

Reviewer 1's comment 9

Page 4, line 2: ".. with IPF based on.." should better read as ".. with IPF diagnosis based on..".

Answer to Reviewer 1's comment 9

We thank the Reviewer for this comment. We modified the manuscript accordingly.

Reviewer 1's comment 10

Page 4, lines 3: "Patients were naïve to one of the two drugs.." should better read as "Patients were naïve from both the 2 drugs tested".

Answer to Reviewer 1's comment 10

We thank the Reviewer for this comment. We modified the manuscript accordingly.

Reviewer 1's comment 11

Page 4, 2nd paragraph: the authors should explain that the mentioned criteria were the criteria requested for starting an anti-IPF treatment, as the reader can guess.

Answer to Reviewer 1's comment 11

We thank the Reviewer for this comment with which we agree. We have now better specified the issue (According to the Italian Health Ministry rule, criteria for starting an anti-IPF treatment were)

Reviewer 1's comment 12

Page 4, last paragraph: "The authorization to prescribe pirfenidone in Italy was…" - was this in the context of a clinical study? Authors should better explain this.

Answer to Reviewer 1's comment 12

We thank the Reviewer for this comment. We have modified the manuscript as follows: "*In Italy, at least in the first few years (depending on the geographical location) of release of Pirfenidone or Nintedanib, the local Health Care Agency, required its specific authorization to start the anti-IPF treatment in all the patients. All patients signed informed consent to enter the present study*".

Reviewer 1's comment 13

Page 5, 3rd paragraph: "The control group of the study..". The whole paragraph is difficult to read, and would need some improvement.

Answer to Reviewer 1's comment 13

We thank the Reviewer for this comment. We have modified the manuscript accordingly: *"The control group of the study was composed by 36 IPF patients that after the initial clinical evaluation decided to refuse the proposed treatment with an anti-IPF drug or had a contraindication. Specifically, 13 were not eligible due to DLCO<30% (n=4), elevated age (n=5) or FVC>90% (n=4) (this limit was removed after May 2016 by the local health agency). Eleven patients were not fully convinced by the effectiveness of the medication, mainly because lack of a clear effect on survival, 6 refused the anti-IPF treatment because of fear of side effects, 3 were not selected due to elevated value of alanine aminotransferase, aspartate aminotransferase or bilirubin, 2 dropped-out after few weeks (<12) of treatment, and 1 for unknown reason".*

Reviewer 1's comment 14

Page 5, last paragraph: the authors say that the primary outcome was the trend of lung function - was this in terms of FVC and DLCO? This seems the case from the Tables and Figures but it is not mentioned along the text nor in the abstract.

Answer to Reviewer 1's comment 14

We thank the Reviewer for this comment with which we agree. Both measurements were considered primary outcomes. This was now better specified in the abstract (see a previous point) and in the Results section. Figure 1, panel A shows the time course of FVC, irrespective of the GAP index, during the 24 month time period. A statistical significant reduction in this parameter was observed in the control group during the time course (p=0.0053); when compared to the pirfenidone and nintedanib groups the decline in the controls was statistically significant at months 12 and 24 (0.027 and 0.011 vs pirfenidone and 0.043 and 0.036 vs nintedanib, respectively).

Figure 1, panel B illustrates the time course in the treated groups, irrespective of the GAP index, according to the drug taken, and no difference was observed during the time course for both treatment, as well as between the pirfenidone and nintedanib group.

Reviewer 1's comment 15

Page 5, last line: ".. as determined through September 30, 2018" is not clear what it means.

Answer to Reviewer 1's comment 15

We thank the Reviewer for this comment. We have now deleted that statement.

Reviewer 1's comment 16

The recent retrospective observational multicentre study in Italian IPF patients (IRENE Study) by Vancheri C et al, 2019 should be cited, discussed and added amongst references.

Answer to Reviewer 1's comment 16

We thank the Reviewer for this suggestion. We have cited and discussed the indicated reference.

Reviewer 2

We really thank the Reviewer for the careful reviewing of our work. We welcome all of her/his suggestions and we have tried to modify the manuscript accordingly.

Reviewer 2's comment 1

Is FVC (pulmonary functions) decline not a surrogate marker of survival? Authors should describe more details.

Answer to Reviewer 2's comment 1

We really thank the Reviewer for this comment that gave us the chance to better illustrate this point. It has been shown that the decline in this parameter is associated with survival, but defining it surrogate it may be a bit misleading, since death in these patients may be also related to other factors, such as co-morbidities, invasive procedure or infectious complications. This has been discussed in the text.

Reviewer 2's comment 2

Baseline %FVC seems to be different among three groups in Figure 1. Authors should consider 'adjusted analysis of %FVC at baseline'.

Answer to Reviewer 2's comment 2

We thank the Reviewer for this comment with which we agree. Indeed absolute % value of FVC at baseline actually differs among groups (as now indicated in Table 1). However after having performed adjusted analysis for baseline %FVC as suggested no differences were observed among the 3 groups. This has been now better specified in text in the Results section.

Reviewer 2's comment 3

Is there a difference between the baseline FVC of the deceased patient and the baseline FVC of the surviving patient?

Answer to Reviewer 2's comment 3

We thank the Reviewer for this comment. We added the following sentence in the Results section: *Both baseline value of FVC and the rate of FVC decline over time were not statistically different between survivors and non-survivors, irrespective of the groups*.

Reviewer 2's comment 4

Are DLco decline and FVC decline equally suppressed in the same patient? If the two are separated, why?

Answer to Reviewer 2's comment 4

We thank the Reviewer for this question that strikes an interesting point. We did a statistical analysis on this point, and the two trends during the time course paralleled. This was added in the text (The changes in FVC and DLCO closely paralleled over time in the 3 groups).

Reviewer 2's comment 5

List all causes of death.

Answer to Reviewer 2's comment 5

We have appreciated the Reviewer's comment. As we stated previously in the text, we could only record the cause of death in those patients dying in the hospital, now shown on table 3. A telephone interview was done regularly to assess whether a patients was still alive or not. The cause of death reported from the family or surrogates were not often clear, and these data are usually not considered in the clinical studies, due to lack of reliability. We reported the "reliable cause" in the Methods and Results (Causes of death were recorded only when this occurred in the hospital. A telephone interview was done regularly to assess whether a patients was still alive or not. The cause of death reported from the family or surrogates were not often clear, and these data are usually not considered in the clinical studies, due to lack of reliability) (Table 3 shows the hospital cause of death in 3 groups. Data recorded during the telephone interview were not considered reliable).

Reviewer 2's comment 6

The 24 months observation period is expected to involve various prognostic factors other than 'IPF progression'. In Table 1, cardiovascular comorbidities are more in the non-treatment group. Is there any effect on the cause of death?

Answer to Reviewer 2's comment 6

We thank the Reviewer for this comment. Being the cause of death not always certain we could not provide a clear answer (see Answer to Reviewer 2's comment 5).

Reviewer 2's comment 7

Even if there is a difference in FVC decline in the comparison of control vs anti-fibrotic group, the reason why there is no difference in all cause mortality may be due to other causes of death. I want you to add some consideration.

Answer to Reviewer 2's comment 7

We thank the Reviewer for this comment with which we definitely agree. We have thus added a sentence about this important issue in the text.

Reviewer 2's comment 8

Nintenamib"? Isn't "Nintedanib" correct

Answer to Reviewer 2's comment 8

We thank the Reviewer for this comment. We have corrected the manuscript accordingly.

Reviewer 3

We really thank the Reviewer for the careful reviewing of our work. We welcome all of her/his suggestions and we have tried to modify the manuscript accordingly.

Reviewer 3's comment 1

Could you show us average exposure weeks of anti-fibrotic drugs in Table 1 ?

Answer to Reviewer 3's comment 1

We thank the Reviewer for this question. All the enrolled patients underwent 24 months of treatment for the analysis of data. This has been clarified in the text.

Reviewer 3's comment 2

Could you show information of clinical symptoms such as cough, dyspnea of each group in Table 1 ?

Answer to Reviewer 3's comment 2

We thank the Reviewer for this question. We have added the baseline value of the requested data, since a systematic collection of these data was not performed at each visit.

Reviewer 3's comment 3

Do you have information about acute exacerbation and lung cancer development of each group ?

Answer to Reviewer 3's comment 3

We have appreciated the Reviewer's question. Unfortunately it was very difficult to collect reliable data on exacerbations, especially for those patients living far from the hospital. We have however identified a clear picture of the occurrence of lung tumor. Data are reported in the Results section.

Reviewer 3's comment 4

1.In Table 1, Line Age, you had better explain (number).

Answer to Reviewer 3's comment 4

We thank the Reviewer for this comment. We have clarified number and percentage in Table 1.

Reviewer 3's comment 5

I think you had better include major functional parameters such as FVC and DLco in Table 1.

Answer to Reviewer 3's comment 5

We thank the Reviewer for this comment. We have added the function parameters as requested.

Reviewer 3's comment 6

3.You had better include mortality of each group in Table 1.

Answer to Reviewer 3's comment 6

We thank the Reviewer for this comment. We have added data on mortality of each group in Table 1 as requested.

Reviewer 3's comment 7

Regarding side effects in Table 2, difficult in concentration is quite unusual adverse reaction in pirfenidone. How about the other drug contribution of this symptom ?

Answer to Reviewer 3's comment 7

We thank the Reviewer for this comment. In the 3 patients who developed this symptom, no other drug was likely to induce the problem. We have added this in the manuscript.

Reviewer 3's comment 7

5.From Figure 1 to Figure 4, you should show statistical value such as p-value.

Answer to Reviewer 3's comment 7

We thank the Reviewer for this comment. We have added this in the Figures.

Reviewer 3's comment 8

6.Why did you repeat figure about decline of %FVC in GAP stage Ⅰ? How about the figure about decline of %FVC in GAP stage stage ⅡⅢ?

Answer to Reviewer 3's comment 8

We thank the Reviewer for this comment. It was a mistake: the first 2 figures pertain to the whole group of patients, irrespective of the GAP stage.

CONFLICT OF INTEREST STATEMENT

Manuscript: REAL LIFE COMPARISON OF PIRFENIDONE AND NINTEDANIB IN PATIENTS WITH IDIOPHATIC PULMONARY FIBROSI: A 24 MONTHS ASSESSMENT

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

FABRIZIO LUPPI received speking fee from Roche and Boheringer Ingelheim

STEFANO NAVA received speaking fee from Roche

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from Stefano Nava.

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MATTEO MONARI

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PIERLUIGI DONATELLI

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GIANPIERO BANDELLI

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ILARIA BASSI

REAL-LIFE COMPARISON OF PIRFENIDONE AND NINTEDANIB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS: A 24-MONTH ASSESSMENT

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S. Cerri and M. Monari contributed equally to the study

E. Clini and S. Nava contributed equally to the study

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Conflicts of Interest

Stefania CERRI, Matteo MONARI, Aldo GUERRIERI, Pierluigi DONATELLI, Ilaria BASSI, Martina GARUTI, Sara BETTI, Gianpiero BANDELLI, Marco CARPANO, Maria Letizia BACCHI REGGIANI, Roberto TONELLI, and Enrico CLINI declare no conflict of interest.

Stefano NAVA received speaking fees from Roche.

Fabrizio LUPPI received a speaking fee from Roche and Boehringer Ingelheim.

ABSTRACT

Background: Real-life data on the use of pirfenidone and nintedanib to treat patients with idiopathic pulmonary fibrosis (IPF) are still scarce.

Methods: We compared the efficacy of either pirfenidone (n=78) or nintedanib (n=28) delivered over a 24-month period in patients with IPF, followed at two regional clinic centers in Italy, with a group of patients who refused the treatment (n=36), and who were considered to be controls. All patients completed regular visits at 1- to 3-month intervals, where primary [forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO)] and secondary outcomes (side effects, treatment compliance, and mortality) were recorded.

Results: Over time, the decline in FVC and DLCO was significantly higher (p=0.0053 and p=0.037, respectively) in controls when compared with the combined treated group, with no significant difference between the two treated groups. Compared to patients with less advanced disease (GAP (Gender, Age, Physiology) stage I), those in GAP stages II and III showed a significantly higher decline in both FVC and DLCO irrespective of the drug taken. Side effects were similarly reported in patients receiving pirfenidone and nintedanib (5% and 7%, respectively), whereas mortality did not differ among the three groups.

Conclusion: This real-life study demonstrated that both pirfenidone and nintedanib were equally effective in reducing the decline of FVC and DLCO versus non-treated patients after 24 months of treatment; however, patients with more advanced disease were likely to show a more rapid decline in respiratory function.

Keywords: Idiopathic pulmonary fibrosis, forced vital capacity, nintedanib, pirfenidone

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, interstitial lung disease of unknown cause, and is associated with a high mortality rate [1].

In recent years, advances have been made in pharmacotherapeutic approaches to IPF, and two drugs, nintedanib and pirfenidone, have been shown to slow down the decline of Forced Vital Capacity (FVC), reduce acute exacerbations, and reduce hospitalization for respiratory events [2-6]; however, apart from a pooled meta-analyses [7], no study has clearly demonstrated an effect on mortality. More recently, a phase-2 double-blind, placebo-controlled study showed that administration of recombinant human pentraxin 2 also resulted in a slower decline in lung function over 28 weeks [8].

Pirfenidone is an anti-inflammatory and antifibrotic drug that inhibits the synthesis of collagen and reduces fibroblast proliferation, whereas nintedanib is a tyrosine kinase inhibitor that targets growth factor pathways. Both therapies are costly and may be associated with side effects [3-6].

Randomized controlled trials (RCTs) comparing the two drugs are lacking and therefore, prescription of one or other of the drugs or the time of initiation of treatment is left to the choice of the clinicians [3].

A review published in 2015 about the efficacy of the new treatments for IPF, comparing real-life experiences vs randomized clinical trials, concluded that the results from the two different study designs seem to be quite different [1]. This is because patients in the real-life scenario often have comorbidities, have more severe disease, take concomitant medications, and are likely to have a higher mortality. At the time of publication of that review, only real-life data on the use of pirfenidone were available (about 400 patients) [2–10], whereas since then, more patients using the drug have been enrolled in observational studies [11–14], and a few additional patients have been studied using nintedanib [15, 16], or a combination of the two drugs [17].

To the best of our knowledge, there is only one observational single-center study comparing the clinical effects of the two drugs [18], but unfortunately, the data presented for the non-

Tendering-group were limited to 6 months.

In our region (Emilia Romagna, Italy), as the local healthcare agency lacked information from RCTs directly comparing pirfenidone with nintedanib, the prescribing physician was free to choose between the two drugs, according to the patient's preference and the decision of the doctors. This gave us the possibility to compare the real-life efficacy of the two drugs in patients with IPF in two referral centers over a 24-month period, and to analyze the data versus a group of patients who refused this treatment, and were therefore

considered to be controls.

PATIENTS AND METHODS

Informed consent was obtained from each patient before any study activity or treatment was undertaken, after having obtained authorization from our Ethics Committee (No. 279/2016).

Eligible patients were aged 40–80 years at the start of screening, with IPF diagnosis based on the ATS/ERS/JRS/ALAT 2015 guidelines [19]. Patients were naïve to both drugs tested, and most of them had received only low doses of oral steroids in the past and/or at the start of this study.

According to the Italian Health Ministry rules, criteria for starting anti-IPF treatment were percent predicted Forced Vital Capacity (FVC %pred.) > 50%, with a Forced Expiratory Volume at one second (FEV1)/Forced Vital Capacity ratio$\geq$70%, and a percent predicted diffusing capacity of the lung for carbon monoxide (DLCO %pred.) >30% at screening.

Exclusion criteria were: alanine aminotransferase, aspartate aminotransferase or bilirubin levels higher than 1.5 times the upper limit of normal; bleeding risk or thrombosis; planned major surgery within the next 3 months including lung transplantation, major abdominal, or major intestinal surgery; myocardial infarction within the previous 6 months, or unstable angina within the last month. Combined pulmonary fibrosis and emphysema (CPFE), defined as the presence of emphysematous lesions in >10% of the affected lungs, was also considered as an exclusion criterion.

In Italy, at least in the first few years (depending on the geographical location) of release of pirfenidone or nintedanib, the local health care agency required specific authorization to start the anti-IPF treatment in all of the patients. The authorization to prescribe pirfenidone in Italy was officially started in June 2013, while nintedanib only became available in June 2016. Based on this, after June 2016, the decision to prescribe one of the two drugs was left to the attending physician, based on her/his judgment and the patient's preference. A simple and unbiased leaflet was given to the patient, while the doctor explained the mechanism of action, the clinical results, the potential side effects, and the method and timing of administration of the two drugs.

In total, 78 patients were scheduled for pirfenidone treatment and 28 received nintedanib. Pirfenidone treatment was started by gradually increasing the dose over a 2-week period from 801 mg daily to 2403 mg daily divided into three doses. Nintedanib was started at a dose of 150 mg twice daily, and eventually decreased to 100 mg twice daily if not tolerated. Subsequently, patients were followed with regular visits to the clinic at 1- to 3-month intervals with full pulmonary function testing, arterial blood gas sampling, liver function monitoring, and recording of side effects and treatment compliance.

The control group in the study was composed of 36 IPF patients who, after the initial clinical evaluation,

decided to refuse the proposed treatment with an anti-IPF drug or who had a contraindication. Specifically, 13 were not eligible due to DLCO<30% (n=4), elevated age (n=5) or FVC>90% (n=4) (after May 2016, this limit was removed by the local health care agency). Eleven patients were not fully convinced about the effectiveness of the medication, mainly because of the lack of a clear effect on survival, 6 refused the anti-IPF treatment because of fear of side effects, 3 were not selected due to elevated levels of alanine aminotransferase, aspartate aminotransferase or bilirubin, 2 dropped out after a few weeks (<12 weeks) of treatment, and 1 dropped out for an unknown reason.All were enrolled in the follow-up program, which was the same as that for all of the other IPF patients undergoing treatment. Their "chronic" therapy for any other comorbidity was left unchanged; symptomatic intervention for dyspnea was prescribed when needed (i.e. opioids, high flow nasal cannula or oxygen).

The primary outcome of this observational, non-sponsored and prospective study was to evaluate the trend of lung function parameters (FVC and DLCO) during a 24-month period and to record any side effects. Secondary outcomes were the rate of disease progression defined as a reduction in FVC ≥10% of predicted and/or diffusion capacity (DLCO) ≥15% of predicted, and the mortality rate at 6, 12, 18, and 24 months.

Forced Vital Capacity (FVC), percent predicted FVC (FVC%), forced expiratory volume in 1 s (FEV1), percent predicted FEV1 (FEV1%), and percent predicted Diffusing Capacity of the Lung for CO (DLCO%) were measured using a lung function testing device (JAEGER MasterScreen Body/Diffusion, Vyaire Medical, Plymouth, MN, United States).

The differences between post- and pre-treatment lung function parameters were tested with the Wilcoxon signed rank test. Analysis of variance (with Bonferroni test for internal comparison) was used to compare groups (i.e. pirfenidone vs nintedanib; and controls (non-treated patients) vs pirfenidone or nintedanib (treated group)).

The changes in FVC% and DLCO% were also analyzed for the two subgroups of patients (stratified by GAP (Gender, Age, Physiology) score as stage I or stage II–III).

The overall survival observed in the cohort was calculated between groups with the log rank test. *P* values <0.05 were considered to be statistically significant. Causes of death were only recorded when this occurred in hospital. Telephone interviews were performed regularly to determine whether patients were still alive. The causes of death reported by the family or surrogates were not often clear, and these data are usually not considered in clinical studies due to lack of reliability.

The statistical analysis was performed using STATA 11 (Stata-Corp 2009 Stata Statistical Software Release 11; StataCorp LP, College Station, TX, USA).

RESULTS

In total, 142 patients were included in the study, 78 in the pirfenidone group, 28 in the nintedanib group, and 36 in the control, untreated group. Table 1 lists the patients' characteristics at enrollment, grouped as "treated" (i.e. pirfenidone or nintedanib) and control patients. More patients (78 vs 28) were enrolled in the pirfenidone group, since that drug was available on the market 2 years before nintedanib.

Figures 1 and 2 illustrate the primary outcomes of the study. In particular, Figure 1A shows the time course of FVC, irrespective of the GAP index, during the 24-month time period. After adjustment for baseline differences in FVC, a statistically significant reduction in this parameter was observed in the control group during the time period when compared with the combined treated group (p=0.0053). When compared to the pirfenidone and nintedanib groups separately, the decline in the controls was statistically significant at 12 and 24 months (0.027 and 0.011 vs pirfenidone and 0.043 and 0.036 vs nintedanib, respectively). Both the baseline value of FVC and the rate of FVC decline over time were not statistically significantly different between survivors and non-survivors, irrespective of the groups considered.

Figure 1B illustrates the time course in the treated groups, irrespective of the GAP index, according to the drug taken; no significant difference was observed during the 24-month time course between the pirfenidone and nintedanib groups.

Changes in DLCO for controls and treated groups are shown in Figure 2A. After adjustment for baseline differences in DLCO, non-treated patients showed a statistically significant reduction in this parameter (p=0.037). When compared to the pirfenidone and nintedanib groups, the decline in the controls was statistically significant at month 24 (0.047 vs pirfenidone and 0.027 vs nintedanib).

Figure 2B shows that no statistically significant difference was observed between the two treated groups and that DLCO remained stable during the 24-month time period.

The changes in FVC and DLCO were broadly similar over time in the three groups.

As shown in Figure 3, FVC% stratification of patients using the GAP index at baseline revealed that, compared to patients with less advanced disease (GAP stage I, Fig. 3A), those with more advanced disease (GAP stages II and III, Fig. 3B) showed a significant decrease over time irrespective of the drug taken and without any statistically significant difference between the two groups (overall significance p=0.01). In particular, non-treated patients demonstrated a significant decrease in FVC% vs treated GAP stage II–III patients at 12 and 24 months (p=0.033 and 0.0040 for pirfenidone, and p=0.047 and 0.0017 for nintedanib, respectively).

Similar results were obtained for DLCO with the exception of the statistically significant decline in the control group in both GAP I and GAP II–III subsets of patients (p=0.018 and 0.0067, respectively).

Figure 4 shows the percentage of patients with a reduction in FVC >10% at 6, 12, and 24 months. Both drugs (pirfenidone and nintedanib) statistically significantly and similarly reduced this decrease vs no treatment, but with no significant difference between pirfenidone and nintedanib.

Most of the patients tolerated the treatments well and the dropout rate was 4/78 (5%) for pirfenidone and 2/28 (7%) for nintedanib. Side effects are listed in Table 2, and no statistically significant difference was observed between the two treatments.

In the whole patient cohort, a total of 55/142 (39%) patients died in the 24-month period. In the control group, mortality from all causes was 44% (16/36 patients), compared with 37% (29/78 patients) of those patients treated with pirfenidone, and 36% (10/28 patients) of those treated with nintedanib. Table 3 shows the causes of death of the hospitalized patients in the three groups. Data recorded during the telephone interviews were not considered reliable. The occurrence of lung tumors was 4/36 (11%), 5/78 (6.4%), and 1/28 (3.5%) for the control, pirfenidone, and nintedanib groups, respectively; however, there were no statistically significant differences between the results (p=0.5).

DISCUSSION

In the present observational investigation, we have demonstrated that both pirfenidone and nintedanib are equally effective in reducing the decline of FVC and DLCO versus non-treated patients over a 24-month period; however, patients with more advanced disease (i.e. those in GAP stages II and III) were likely to show a more rapid decline in respiratory function. Among the secondary outcomes, side effects were similar in patients receiving the anti-IPF treatments, whereas mortality rates did not differ among the three groups.

The present study is unique in that it compares the pulmonary function and survival rate not only in the two groups of patients receiving either pirfenidone or nintedanib, but also in a relatively large control group of individuals who, for various reasons, refused to be treated, despite the fact that they met the inclusion criteria for both drugs. This investigation also shows that a relatively high number of the non-treated patients (>20% if we exclude those patients with elevated levels of alanine aminotransferase, aspartate aminotransferase or bilirubin) refused to undergo one of the two proposed treatments, mainly because they were dissuaded by the possible side effects or were not fully convinced of the efficacy of the drugs, some of them after having received the opinion of their family doctor.

These results highlight the importance of improving the educational models (i.e. with a dedicated website, training and education of general practitioners), to convince the more skeptical patients about the safety and efficacy of the available treatments.

As for all of the RCTs, rigorous inclusion and exclusion criteria were applied per protocol when assessing the efficacy of pirfenidone or nintedanib, so that many patients who were potential candidates for treatment were excluded. Just as an example, 37% and 44% of the patients screened for two RCTs assessing the efficacy of nintedanib and pirfenidone, respectively, were not enrolled [20, 24].

Clearly, all these exclusion criteria were not applied by the regulatory agencies of European countries, so that, as described by Harari and Caminati in their review [1], in real-life studies, comorbidities were frequent, particularly overweight/obesity and pulmonary hypertension. Indeed, the stages of the disease, as assessed with the GAP index were different.

To our knowledge, there is only one single-center study comparing the 6-month outcomes of IPF patients undergoing treatment with pirfenidone or placebo [23], but this very short timeframe did not allow the authors to reach a firm conclusion; indeed, a control group was lacking.

Our study demonstrated once more that both pirfenidone and nintedanib significantly slowed disease

progression, as assessed by the decline in FVC and DLCO. Our results are also in line with RCTs and real-life observational studies that showed a favorable safety profile and generally good tolerance of both drugs over the long term. Indeed, to our knowledge, this is the first long-term direct comparison between the two available treatments for IPF, and confirms what has already been suggested in the literature, that both drugs are equally effective in reducing the functional decline.

Interestingly, earlier observational studies with nintedanib enrolled patients with more advanced disease than those in the present study (FVC ≤ 50% and/or DLCO ≤ 35%), so that our study expands our knowledge on individuals with less severe IPF. This allowed us to compare the two drugs in patients with similar stages of disease.

As also demonstrated by several earlier investigations, the rate of decline of FVC or DLCO was higher in patients with more advanced disease, even when they were undergoing therapy [7, 25, 26], and therefore it is important to identify IPF patients in the early stage of their disease, and in whom treatment may be more successful in slowing down the progression of the disease.

This is also the first study to assess the mortality rate in patients treated with either pirfenidone or nintedanib, and with the rate in an untreated control group. A recent retrospective analysis of 379 Italian patients treated with pirfenidone demonstrated that the decline in FVC and the safety profile were consistent with findings observed in Phase III pirfenidone clinical trials and with similar side effects compared with our study [27].

In our cohort, the 24-month mortality rate was not statistically significantly different among the groups, despite the fact that survival was somehow higher in the controls. As already stated, only a meta-analysis was able to demonstrate a survival improvement vs placebo using pirfenidone [20], but this had the obvious limitations of such kinds of investigation. We were not able to record all of the causes of mortality in all of our patients, since most died in hospitals, while others died at home, thus making it difficult to assess the real cause of death. The hospital deaths were mainly, but not exclusively, due to respiratory failure which may or may not have been the result of acute exacerbations, since other significant causes of death were cardiac problems or tumors. Thus, the recording of FVC in these patients was probably not the best indicator of mortality.

Our study has several major limitations. First, it was not a randomized controlled trial; however, at this time, we are not aware of any ongoing study enrolling three arms of patients (placebo, pirfenidone, and nintedanib), so it may be considered novel and original, being the first one, despite being non-randomized. Indeed, our ethics committee felt that it would be unethical to approve a placebo arm, considering the favorable results already available on pulmonary function in patients treated with both drugs.

Second, we did not perform a sample size calculation based on primary outcome, and the study population was relatively small and non-homogeneous among the groups. It was not possible to improve sample size and homogeneity because of the different timing of approval of the two active drugs; however, the number of patients enrolled was in keeping with most of the real-life studies reported, in which, very rarely, a threshold of 100 patients was achieved.

In conclusion, our real-life study demonstrated for the first time that both pirfenidone and nintedanib are equally effective in reducing the decline of FVC and DLCO in a 24-month period compared with non-treated patients. Patients with more advanced disease were likely to show a more rapid decline in respiratory function. The mortality rate was similar in the treated and non-treated groups, but this trial was not randomized. Notwithstanding this, our findings may launch the call for a large multicenter, randomized trial with parallel groups using either one of the available drugs and compared with a placebo arm.

Acknowledgments

We would like to thank Colin Woodham at Alpha Science Editors for language editing.

Legend to Figures

Figure 1. Time course of FVC over 24 months showing the trend in the whole population, comparing the three study groups (panel A) and the two treatment groups (nintedanib and pirfenidone) (panel B).

Figure 2. Time course of DLCO over 24 months showing the trend in the whole population comparing the three study groups (panel A) and the two treatment groups (nintedanib and pirfenidone) (panel B).

Figure 3. Time course of FVC over 24 months in the three study groups divided according to GAP I (panel A) and GAP II–III (panel B) score.

Figure 4. Proportion of patients in the three study groups showing a decline in FVC >10% from baseline after 6, 12, and 24 months.

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REAL-LIFE COMPARISON OF PIRFENIDONE AND NINTEDANIB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS: A 24-MONTH ASSESSMENT

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Conflicts of Interest

Stefania CERRI, Matteo MONARI, Aldo GUERRIERI, Pierluigi DONATELLI, Ilaria BASSI, Martina GARUTI, Sara BETTI, Gianpiero BANDELLI, Marco CARPANO, Maria Letizia BACCHI REGGIANI, Roberto TONELLI, and Enrico CLINI declare no conflict of interest.

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Stefano NAVA received speaking fees from Roche.

Fabrizio LUPPI received a speaking fee from Roche and Boehringer Ingelheim.

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ABSTRACT

Background: Real-life data on the use of pirfenidone and nintedanib to treat patients with idiopathic pulmonary fibrosis (IPF) are still scarce.

Methods: We compared the efficacy of either pirfenidone (n=78) or nintedanib (n=28) delivered over a 24-month period in patients with IPF, followed at two regional clinic centers in Italy, with a group of patients who refused the treatment (n=36), and who were considered to be controls. ~~All patients completed regular visits at 1- to 3-month intervals, where primary [forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO)] and secondary outcomes (side effects, treatment compliance, and mortality) were recorded.~~ All patients completed regular visits at 1- to 3-month intervals, where primary [forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO)] and secondary outcomes (side effects, treatment compliance, and mortality) were recorded.

Results: Over time, the decline in FVC and DLCO was significantly higher (p=0.0053 and p=0.037, respectively) in controls when compared with the combined treated group, with no significant difference between the two treated groups. Compared to patients with less advanced disease (GAP (Gender, Age, Physiology) stage I), those in GAP stages II and III showed a significantly higher decline in both FVC and DLCO irrespective of the drug taken. Side effects were similarly reported in patients receiving pirfenidone and nintedanib (5% and 7%, respectively), whereas mortality did not differ among the three groups.

Conclusion: This real-life study demonstrated that both pirfenidone and nintedanib were equally effective in reducing the decline of FVC and DLCO versus non-treated patients after 24 months of treatment; however, patients with more advanced disease were likely to show a more rapid decline in respiratory function.

Keywords: Idiopathic pulmonary fibrosis, forced vital capacity, nintedanib, pirfenidone

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INTRODUCTION

~~Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, interstitial lung disease of unknown cause, and is associated with a high mortality rate [1].~~

~~In recent years, advances have been made in pharmacotherapeutic approaches to IPF, and two drugs, nintedanib and pirfenidone, have been shown to slow down the decline of Forced Vital Capacity (FVC), reduce acute exacerbations, and reduce hospitalization for respiratory events [2-6]; however, apart from a pooled meta-analyses [7], no study has clearly demonstrated an effect on mortality. More recently, a phase-2 double-blind, placebo-controlled study showed that administration of recombinant human pentraxin 2 also resulted in a slower decline in lung function over 28 weeks [8].~~

~~Pirfenidone is an anti-inflammatory and antifibrotic drug that inhibits the synthesis of collagen and reduces fibroblast proliferation, whereas nintedanib is a tyrosine kinase inhibitor that targets growth factor pathways. Both therapies are costly and may be associated with side effects [3-6].~~

~~Randomized controlled trials (RCTs) comparing the two drugs are lacking and therefore, prescription of one or other of the drugs or the time of initiation of treatment is left to the choice of the clinicians [3].~~

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Randomized controlled trials (RCTs) comparing the two drugs are lacking and therefore, prescription of one or other of the drugs or the time of initiation of treatment is left to the choice of the clinicians [3].

A review published in 2015 about the efficacy of the new treatments for IPF, comparing real-life experiences vs randomized clinical trials, concluded that the results from the two different study designs

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seem to be quite different [1]. This is because patients in the real-life scenario often have comorbidities, have more severe disease, take concomitant medications, and are likely to have a higher mortality. At the time of publication of that review, only real-life data on the use of pirfenidone were available (about 400 patients) [2–10], whereas since then, more patients using the drug have been enrolled in observational studies [11–14], and a few additional patients have been studied using nintedanib [15, 16], or a combination of the two drugs [17].

To the best of our knowledge, there is only one observational single-center study comparing the clinical effects of the two drugs [18], but unfortunately, the data presented for the non-

Tendering-group were limited to 6 months.

In our region (Emilia Romagna, Italy), as the local healthcare agency lacked information from RCTs directly comparing pirfenidone with nintedanib, the prescribing physician was free to choose between the two drugs, according to the patient's preference and the decision of the doctors. This gave us the possibility to compare the real-life efficacy of the two drugs in patients with IPF in two referral centers over a 24-month period, and to analyze the data versus a group of patients who refused this treatment, and were therefore considered to be controls.

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PATIENTS AND METHODS

Informed consent was obtained from each patient before any study activity or treatment was undertaken, after having obtained authorization from our Ethics Committee (No. ~~227985~~/2016).

Eligible patients were aged 40–80 years at the start of screening, ~~with IPF diagnosis based on the ATS/ERS/JRS/ALAT 2015 guidelines [19]. Patients were naïve to both drugs tested, and most of them had received only low doses of oral steroids in the past and/or at the start of this study.~~ with IPF diagnosis based on the ATS/ERS/JRS/ALAT 2015 guidelines [19]. Patients were naïve to both drugs tested, and most of them had received only low doses of oral steroids in the past and/or at the start of this study.

According to the Italian Health Ministry rules, ~~criteria for starting anti-IPF treatment were~~ criteria for starting anti-IPF treatment were percent predicted Forced Vital Capacity (FVC %pred.) > 50%, with a Forced Expiratory Volume at one second (FEV1)/Forced Vital Capacity ratio≥70%, and a percent predicted diffusing capacity of the lung for carbon monoxide (DLCO %pred.) >30% at screening.

Exclusion criteria were: alanine aminotransferase, aspartate aminotransferase or bilirubin levels higher than 1.5 times the upper limit of normal; bleeding risk or thrombosis; planned major surgery within the next 3 months including lung transplantation, major abdominal, or major intestinal surgery; myocardial infarction within the previous 6 months, or unstable angina within the last month. Combined pulmonary fibrosis and emphysema (CPFE), defined as the presence of emphysematous lesions in >10% of the affected lungs, was also considered as an exclusion criterion.

~~In Italy, at least in the first few years (depending on the geographical location) of release of pirfenidone or nintedanib, the local health care agency required specific authorization to start the anti-IPF treatment in all of the patients.~~ In Italy, at least in the first few years (depending on the geographical location) of release of pirfenidone or nintedanib, the local health care agency required specific authorization to start the anti-IPF treatment in all of the patients. The authorization to prescribe pirfenidone in Italy was officially started in June 2013, while nintedanib only became available in June 2016. Based on this, after June 2016, the decision to prescribe one of the two drugs was left to the attending physician, based on her/his judgment and the patient's preference. A simple and unbiased leaflet was given to the patient, while the doctor explained the mechanism of action, the clinical results, the potential side effects, and the method and timing of administration of the two drugs.

In total, 78 patients were scheduled for pirfenidone treatment and 28 received nintedanib. Pirfenidone treatment was started by gradually increasing the dose over a 2-week period from 801 mg daily to 2403 mg daily divided into three doses. Nintedanib was started at a dose of 150 mg twice daily, and eventually

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decreased to 100 mg twice daily if not tolerated. Subsequently, patients were followed with regular visits to the clinic at 1- to 3-month intervals with full pulmonary function testing, arterial blood gas sampling, liver function monitoring, and recording of side effects and treatment compliance.

~~The control group in the study was composed of 36 IPF patients who, after the initial clinical evaluation, decided to refuse the proposed treatment with an anti-IPF drug or who had a contraindication~~ The control group in the study was composed of 36 IPF patients who, after the initial clinical evaluation, decided to refuse the proposed treatment with an anti-IPF drug or who had a contraindication. Specifically, 13 were not eligible due to DLCO<30% (n=4), elevated age (n=5) or FVC>90% (n=4) (after May 2016, this limit was removed by the local health care agency). ~~Eleven patients were not fully convinced about the effectiveness of the medication, mainly because of the lack of a clear effect on survival, 6 refused the anti-IPF treatment because of fear of side effects, 3 were not selected due to elevated levels of alanine aminotransferase, aspartate aminotransferase or bilirubin, 2 dropped out after a few weeks (<12 weeks) of treatment, and 1 dropped out for an unknown reason.~~ Eleven patients were not fully convinced about the effectiveness of the medication, mainly because of the lack of a clear effect on survival, 6 refused the anti-IPF treatment because of fear of side effects, 3 were not selected due to elevated levels of alanine aminotransferase, aspartate aminotransferase or bilirubin, 2 dropped out after a few weeks (<12 weeks) of treatment, and 1 dropped out for an unknown reason.All were enrolled in the follow-up program, which was the same as that for all of the other IPF patients undergoing treatment. ~~Their "chronic" therapy for any other comorbidity was left unchanged; symptomatic intervention for dyspnea was prescribed when needed (i.e. opioids, high flow nasal cannula or oxygen).~~ Their "chronic" therapy for any other comorbidity was left unchanged; symptomatic intervention for dyspnea was prescribed when needed (i.e. opioids, high flow nasal cannula or oxygen).

The primary outcome of this observational, non-sponsored and prospective study was to evaluate the trend of lung function parameters (FVC and DLCO) during a 24-month period and to record any side effects. Secondary outcomes were the rate of disease progression defined as a reduction in FVC ≥10% of predicted and/or diffusion capacity (DLCO) ≥15% of predicted, and the mortality rate at 6, 12, 18, and 24 months.

Forced Vital Capacity (FVC), percent predicted FVC (FVC%), forced expiratory volume in 1 s (FEV1), percent predicted FEV1 (FEV1%), and percent predicted Diffusing Capacity of the Lung for CO (DLCO%) were measured using a lung function testing device (JAEGER MasterScreen Body/Diffusion, Vyaire Medical, Plymouth, MN, United States).

The differences between post- and pre-treatment lung function parameters were tested with the Wilcoxon signed rank test. Analysis of variance (with Bonferroni test for internal comparison) was used to compare groups (i.e. pirfenidone vs nintedanib; and controls (non-treated patients) vs pirfenidone or nintedanib

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(treated group)).

The changes in FVC% and DLCO% were also analyzed for the two subgroups of patients (stratified by GAP (Gender, Age, Physiology) score as stage I or stage II–III).

~~The overall survival observed in the cohort was calculated between groups with the log rank test. *P* values <0.05 were considered to be statistically significant. Causes of death were only recorded when this occurred in hospital. Telephone interviews were performed regularly to determine whether patients were still alive. The causes of death reported by the family or surrogates were not often clear, and these data are usually not considered in clinical studies due to lack of reliability.~~

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The statistical analysis was performed using STATA 11 (Stata-Corp 2009 Stata Statistical Software Release 11; StataCorp LP, College Station, TX, USA).

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RESULTS

In total, 142 patients were included in the study, 78 in the pirfenidone group, 28 in the nintedanib group, and 36 in the control, untreated group. Table 1 lists the patients' characteristics at enrollment, grouped as "treated" (i.e. pirfenidone or nintedanib) and control patients. More patients (78 vs 28) were enrolled in the pirfenidone group, since that drug was available on the market 2 years before nintedanib.

~~Figures 1 and 2 illustrate the primary outcomes of the study. In particular, Figure 1A shows the time course of FVC, irrespective of the GAP index, during the 24-month time period.~~ Figures 1 and 2 illustrate the primary outcomes of the study. In particular, Figure 1A shows the time course of FVC, irrespective of the GAP index, during the 24-month time period. After adjustment for baseline differences in FVC, a statistically significant reduction in this parameter was observed in the control group during the time period when compared with the combined treated group (p=0.0053). When compared to the pirfenidone and nintedanib groups separately, the decline in the controls was statistically significant at 12 and 24 months (0.027 and 0.011 vs pirfenidone and 0.043 and 0.036 vs nintedanib, respectively). ~~Both the baseline value of FVC and the rate of FVC decline over time were not statistically significantly different between survivors and non-survivors, irrespective of the groups considered.~~ Both the baseline value of FVC and the rate of FVC decline over time were not statistically significantly different between survivors and non-survivors, irrespective of the groups considered.

Figure 1B illustrates the time course in the treated groups, irrespective of the GAP index, according to the drug taken; no significant difference was observed during the 24-month time course between the pirfenidone and nintedanib groups.

~~Changes in DLCO for controls and treated groups are shown in Figure 2A~~ Changes in DLCO for controls and treated groups are shown in Figure 2A. After adjustment for baseline differences in DLCO, non-treated patients showed a statistically significant reduction in this parameter (p=0.037). When compared to the pirfenidone and nintedanib groups, the decline in the controls was statistically significant at month 24 (0.047 vs pirfenidone and 0.027 vs nintedanib).

Figure 2B shows that no statistically significant difference was observed between the two treated groups and that DLCO remained stable during the 24-month time period.

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As shown in ~~Figure 3~~ Figure 3, FVC% stratification of patients using the GAP index at baseline revealed that,

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compared to patients with less advanced disease (GAP stage I, ~~Fig. 3A~~ Fig. 3A), those with more advanced disease (GAP stages II and III, ~~Fig. 3B~~ Fig. 3B) showed a significant decrease over time irrespective of the drug taken and without any statistically significant difference between the two groups (~~overall significance p=0.01~~overall significance p=0.01). In particular, non-treated patients demonstrated a significant decrease in FVC% vs treated ~~GAP stage II–III~~ GAP stage II–III patients at 12 and 24 months (p=0.033 and 0.0040 for pirfenidone, and p=0.047 and 0.0017 for nintedanib, respectively).

Similar results were obtained for DLCO with the exception of the statistically significant decline in the control group in both GAP I and GAP II–III subsets of patients (p=0.018 and 0.0067, respectively).

Figure 4 shows the percentage of patients with a reduction in FVC >10% at 6, 12, and 24 months. Both drugs (~~pirfenidone and nintedanib~~pirfenidone and nintedanib) statistically significantly and similarly reduced this decrease vs ~~no treatment~~ no treatment, but with no significant difference between pirfenidone and nintedanib.

Most of the patients tolerated the treatments well and the dropout rate was 4/78 (5%) for pirfenidone and 2/28 (7%) for nintedanib. Side effects are listed in Table 2, ~~and no statistically significant difference was observed between the two treatments.~~ and no statistically significant difference was observed between the two treatments.

In the whole patient cohort, a total of 55/142 (39%) patients died in the 24-month period. In the control group, mortality from all causes was 44% (16/36 patients), compared with 37% (29/78 patients) of those patients treated with pirfenidone, and 36% (10/28 patients) of those treated with nintedanib. Table 3 shows the causes of death of the hospitalized patients in the three groups. Data recorded during the telephone interviews were not considered reliable. ~~The occurrence of lung tumors was 4/36 (11%), 5/78 (6.4%), and 1/28 (3.5%) for the control, pirfenidone, and nintedanib groups, respectively; however, there were no statistically significant differences between the results (p=0.5).~~ The occurrence of lung tumors was 4/36 (11%), 5/78 (6.4%), and 1/28 (3.5%) for the control, pirfenidone, and nintedanib groups, respectively; however, there were no statistically significant differences between the results (p=0.5).

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DISCUSSION

~~In the present observational investigation, we have demonstrated that both pirfenidone and nintedanib are equally effective in reducing the decline of FVC and DLCO versus non-treated patients over a 24-month period; however, patients with more advanced disease (i.e. those in GAP stages II and III) were likely to show a more rapid decline in respiratory function. Among the secondary outcomes, side effects were similar in patients receiving the anti-IPF treatments, whereas mortality rates did not differ among the three groups.~~

~~The present study is unique in that it compares the pulmonary function and survival rate not only in the two groups of patients receiving either pirfenidone or nintedanib, but also in a relatively large control group of individuals who, for various reasons, refused to be treated, despite the fact that they met the inclusion criteria for both drugs. This investigation also shows that a relatively high number of the non-treated patients (>20% if we exclude those patients with elevated levels of alanine aminotransferase, aspartate aminotransferase or bilirubin) refused to undergo one of the two proposed treatments, mainly because they were dissuaded by the possible side effects or were not fully convinced of the efficacy of the drugs, some of them after having received the opinion of their family doctor.~~

~~These results highlight the importance of improving the educational models (i.e. with a dedicated website, training and education of general practitioners), to convince the more skeptical patients about the safety and efficacy of the available treatments.~~

~~As for all of the RCTs, rigorous inclusion and exclusion criteria were applied per protocol when assessing the efficacy of pirfenidone or nintedanib, so that many patients who were potential candidates for treatment were excluded. Just as an example, 37% and 44% of the patients screened for two RCTs assessing the efficacy of nintedanib and pirfenidone, respectively, were not enrolled [20, 24].~~

~~Clearly, all these exclusion criteria were not applied by the regulatory agencies of European countries, so that, as described by Harari and Caminati in their review [1], in real-life studies, comorbidities were frequent, particularly overweight/obesity and pulmonary hypertension. Indeed, the stages of the disease, as assessed with the GAP index were different.~~

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To our knowledge, there is only one single-center study comparing the 6-month outcomes of IPF patients undergoing treatment with pirfenidone or placebo [23], but this very short timeframe did not allow the authors to reach a firm conclusion; indeed, a control group was lacking.

Our study demonstrated once more that both pirfenidone and nintedanib significantly slowed disease progression, as assessed by the decline in FVC and DLCO. Our results are also in line with RCTs and real-life observational studies that showed a favorable safety profile and generally good tolerance of both drugs over the long term. Indeed, to our knowledge, this is the first long-term direct comparison between the two available treatments for IPF, and confirms what has already been suggested in the literature, that both drugs are equally effective in reducing the functional decline.

Interestingly, earlier observational studies with nintedanib enrolled patients with more advanced disease than those in the present study (FVC ≤ 50% and/or DLCO ≤ 35%), so that our study expands our knowledge

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on individuals with less severe IPF. This allowed us to compare the two drugs in patients with similar stages of disease.

~~As also demonstrated by several earlier investigations, the rate of decline of FVC or DLCO was higher in patients with more advanced disease, even when they were undergoing therapy [7, 25, 26], and therefore it is important to identify IPF patients in the early stage of their disease, and in whom treatment may be more successful in slowing down the progression of the disease.~~

~~This is also the first study to assess the mortality rate in patients treated with either pirfenidone or nintedanib, and with the rate in an untreated control group. A recent retrospective analysis of 379 Italian patients treated with pirfenidone demonstrated that the decline in FVC and the safety profile were consistent with findings observed in Phase III pirfenidone clinical trials and with similar side effects compared with our study [27].~~

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In our cohort, the 24-month mortality rate was not statistically significantly different among the groups, despite the fact that survival was somehow higher in the controls. As already stated, only a meta-analysis was able to demonstrate a survival improvement vs placebo using pirfenidone [20], but this had the obvious limitations of such kinds of investigation. ~~We were not able to record all of the causes of mortality in all of our patients, since most died in hospitals, while others died at home, thus making it difficult to assess the real cause of death. The hospital deaths were mainly, but not exclusively, due to respiratory failure which may or may not have been the result of acute exacerbations, since other significant causes of death were cardiac problems or tumors. Thus, the recording of FVC in these patients was probably not the best indicator of mortality.~~ We were not able to record all of the causes of mortality in all of our patients, since most died in hospitals, while others died at home, thus making it difficult to assess the real cause of death. The hospital deaths were mainly, but not exclusively, due to respiratory failure which may or may not have been the result of acute exacerbations, since other significant causes of death were cardiac

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Our study has several major limitations. First, it was not a randomized controlled trial; however, at this time, we are not aware of any ongoing study enrolling three arms of patients (placebo, pirfenidone, and nintedanib), so it may be considered novel and original, being the first one, despite being non-randomized. Indeed, our ethics committee felt that it would be unethical to approve a placebo arm, considering the favorable results already available on pulmonary function in patients treated with both drugs.

Second, ~~we did not perform a sample size calculation based on primary outcome~~ we did not perform a sample size calculation based on primary ~~, and the study population was relatively small~~ outcome, and the study population was relatively small and non-homogeneous among the groups. It was not possible to improve sample size and homogeneity because of the different timing of approval of the two active drugs; however, the number of patients enrolled was in keeping with most of the real-life studies reported, in which, very rarely, a threshold of 100 patients was achieved.

In conclusion, our real-life study demonstrated for the first time that both pirfenidone and nintedanib are equally effective in reducing the decline of FVC and DLCO in a 24-month period compared with non-treated patients. Patients with more advanced disease were likely to show a more rapid decline in respiratory function. The mortality rate was similar in the treated and non-treated groups, but this trial was not randomized. Notwithstanding this, our findings may launch the call for a large multicenter, randomized trial with parallel groups using either one of the available drugs and compared with a placebo arm.

~~*Acknowledgments*~~

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Legend to Figures

~~Figure 1. Time course of FVC over 24 months showing the trend in the whole population, comparing the three study groups (panel A) and the two treatment groups (nintedanib and pirfenidone) (panel B).~~

~~Figure 2. Time course of DLCO over 24 months showing the trend in the whole population comparing the three study groups (panel A) and the two treatment groups (nintedanib and pirfenidone) (panel B).~~

~~Figure 3. Time course of FVC over 24 months in the three study groups divided according to GAP I (panel A) and GAP II–III (panel B) score.~~

~~Figure 4. Proportion of patients in the three study groups showing a decline in FVC >10% from baseline after 6, 12, and 24 months.~~

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***Highlights (for review)**

- Pirfenidone and nintedanib are the mostly used anti-fibrotic drugs for idiopathic pulmonary fibrosis (IPF)
- Face to face, randomized controlled and real life studies are lacking
- In this real life study, both drugs were effective in reducing the decline of Forced Vital Capacity and Diffusing Lung Capacity versus non-treated patients at 24-month
- Sicker patients in both groups were likely to show a more rapid decline in respiratory function

Tables

Table 1

	Total of patients	Pirfenidone	Nintedanib	No treatment	P
Patients, n	142	78	28	36	
Male, n (%)	113 (78%)	64 (82%)	22 (78%)	27 (75%)	0.7
Age, years (SD)	73,3 (9)	73 (8)	72 (7)	75 (7)	0.25
Current or former smokers, n (%)	118 (82%)	65 (83%)	24 (85%)	29 (80%)	0.8
FVC, %pred (SD)	80.9 (17.7)	75 (17)	84 (16)	87 (18)	0.01
DLCO, %pred (SD)	53 (16.3)	50 (13)	45 (19)	55 (15)	0.029
GAP Index II-III, n (%)	71 (50%)	41 (53%)	15 (54%)	15 (43%)	0.5
GERD, n (%)	61 (43%)	34 (43%)	12 (44%)	15 (43%)	0.9
Cardiovascular comorbidities, n (%)	69 (48%)	37 (48%)	12 (44%)	20 (56%)	0.6
Dyspnea at baseline, Borg score (SD)	2.13 (1.6)	1.95 (1.9)	2.54 (2.12)	2.23 (1.04)	0.3
Presence of cough, n (%)	92 (64.7%)	50 (64%)*	18 (64%)**	24 (66%) ***	0.9
Mortality, n (%)	90 (63.4%)	46 (59%)	15 (54%)	29 (81%)	0.04

Table 1

Patients' characteristics at enrollment, divided as "treated" (i.e. pirfenidone or nintedanib) and control.

Legend. FVC= Forced Vital Capacity. DLCO= Lung Tissue Diffuse for Carbon Dioxide. GAP Index = Gender, Age and Physiology Index. GERD = Gastro-Esophageal Reflux Disease. SD= Standard Deviation. *=2 patients missing, **=5 patient missing, ***=2 patients missing.

Table 2

Side effect	Pirfenidone	Nintedanib	No treatment
Total, n (%)	26 (33%)	13 (46%)	5 (14%)
Diarrhea, n (%)	0 (0%)	9 (32%)	2 (5%)
Nausea, n (%)	3 (4%)	0 (0%)	2 (5%)
Dyspepsia, n (%)	12 (15%)	0 (0%)	0 (0%)
Headache, n (%)	0 (0%)	0 (0%)	1 (3%)
Involuntary weight loss, n (%)	0 (0%)	4 (14%)	0 (0%)
Transaminase elevation, n (%)	0 (0%)	3 (11%)	0 (0%)
Loss of appetite, n (%)	3 (4%)	0 (0%)	0 (0%)
Phototoxic reactions, n (%)	4 (5%)	0 (0%)	0 (0%)
Difficulty in concentration, n (%)	4 (5%)	0 (0%)	0 (0%)

Table 2

Side effects in the 3 groups of patients.

No statistically significant difference among groups was found for the variables investigated.

Table 3

Death cause	Pirfenidone (32)	Nintedanib (8)	No treatment (18)
Acute respiratory failure, n (%)	18 (56%)	5 (62%)	11 (61%)
Lung cancer	2 (6%)	0 (0%)	3 (17%)
Lung infection	2 (6%)	0 (0%)	3 (17%)
Stroke	2 (6%)	0 (0%)	0 (0%)
Acute hearth disease	4 (12%)	0 (0%)	0 (0%)
Liver failure	0 (0%)	2 (25%)	0 (0%)
Cancer other than lung	3 (9%)	1 (13%)	1 (6%)
Post surgical complications	1 (3%)	0 (0%)	0 (0%)

Table 3

Death causes in the 3 groups of patients.

Figure 1

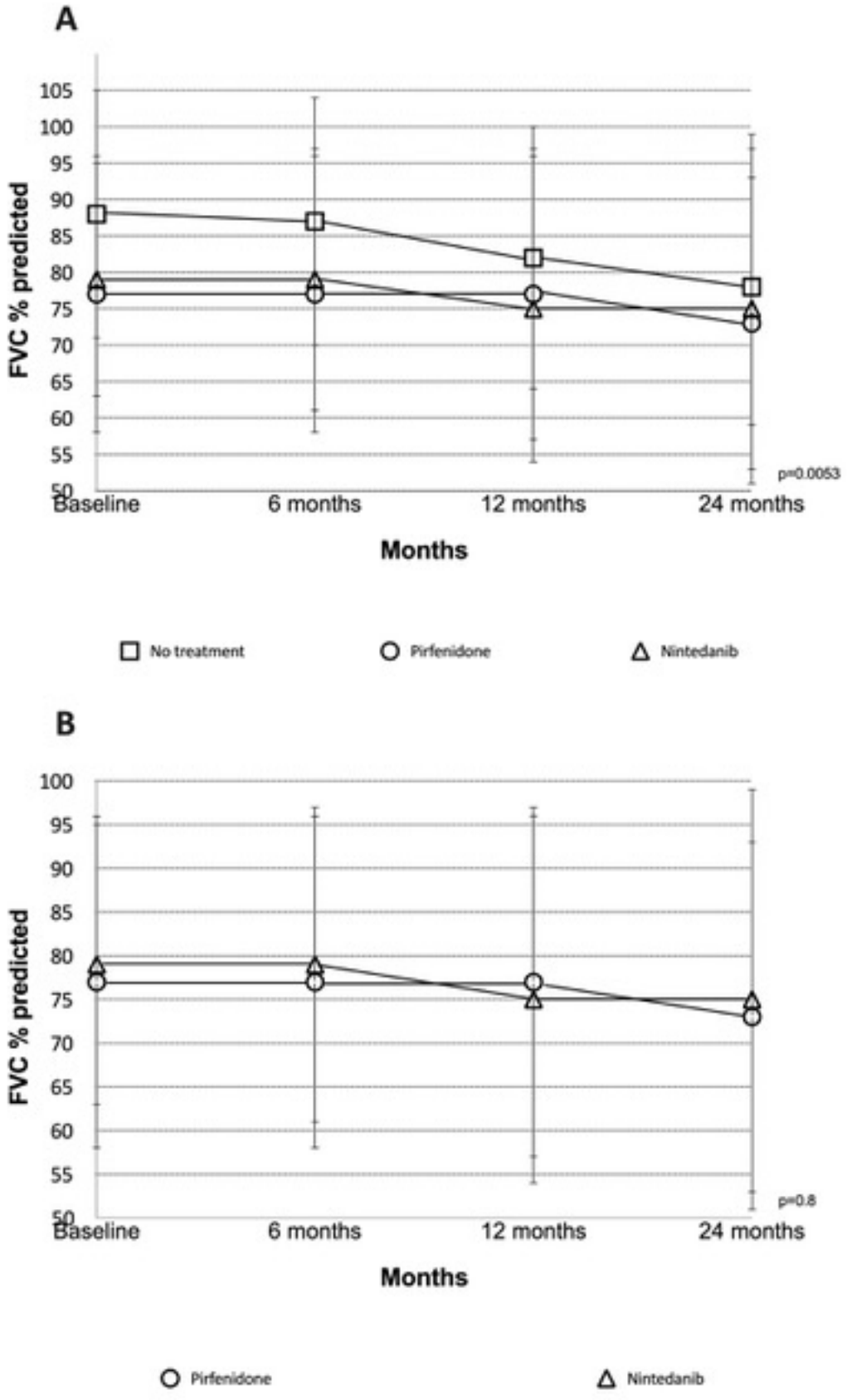
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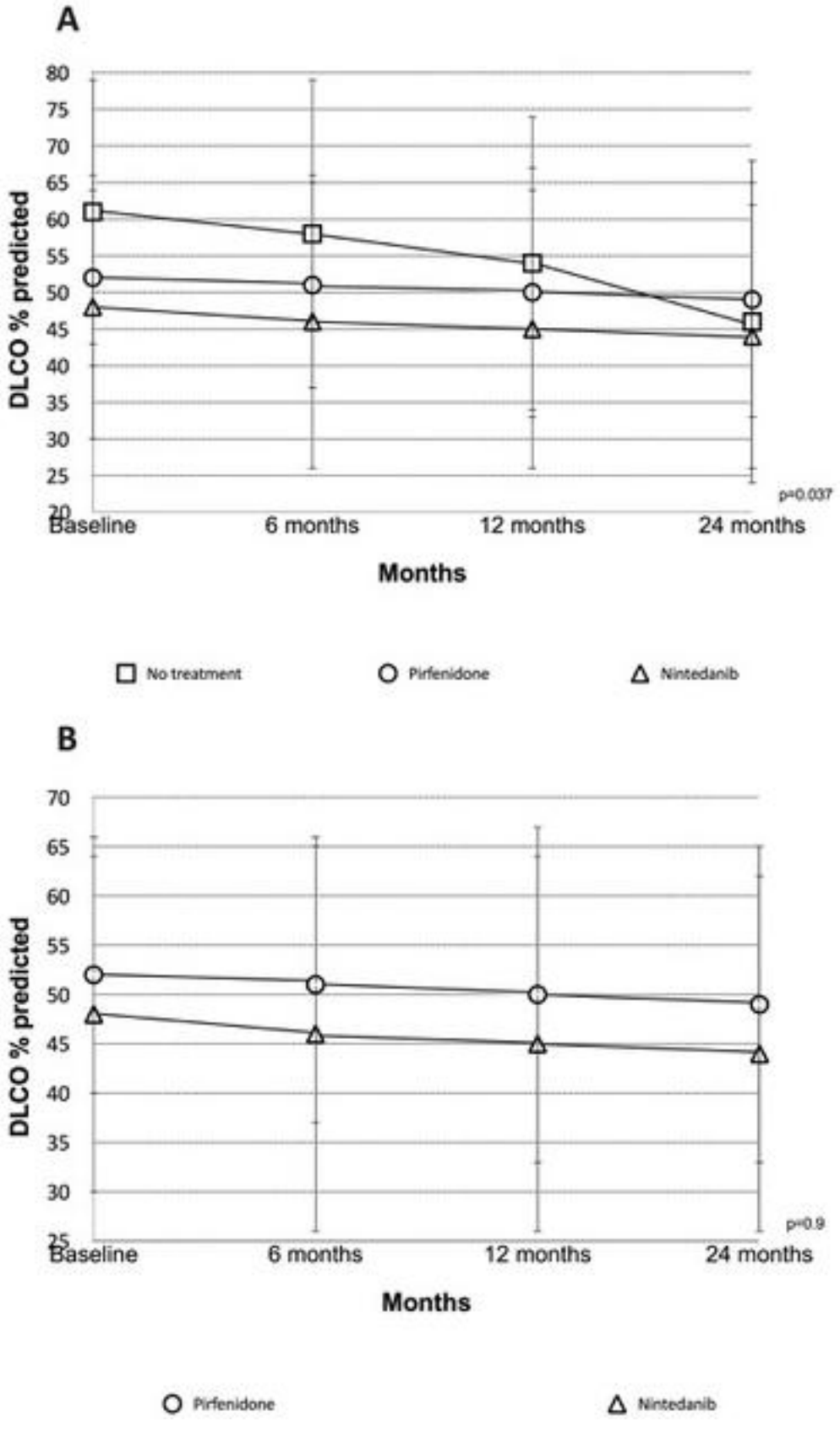
Figure 2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45
40
35
30
25
p=0.9
Baseline
6 months
12 months
24 months
Months
Pirfenidone
Nintedanib

Figure 3

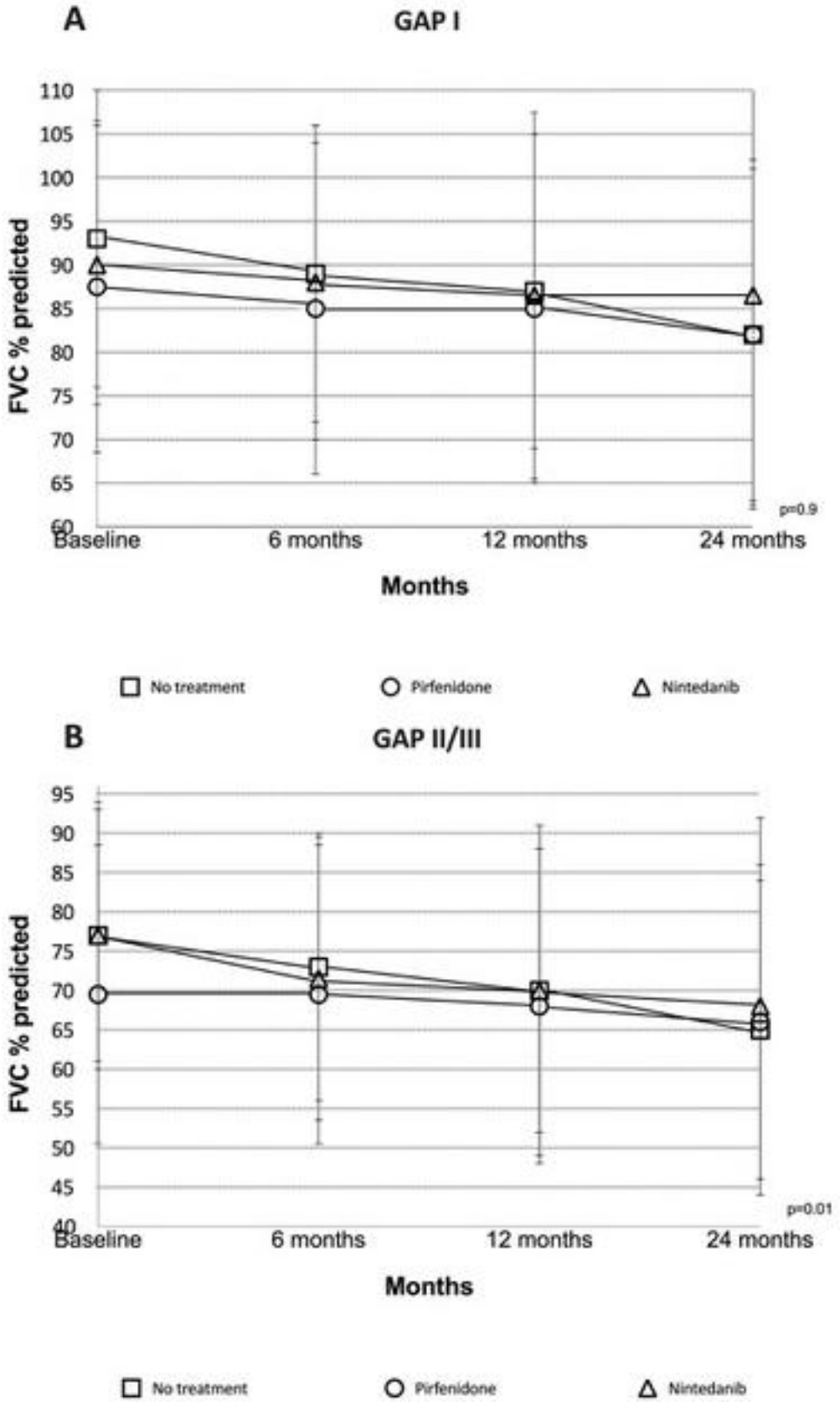
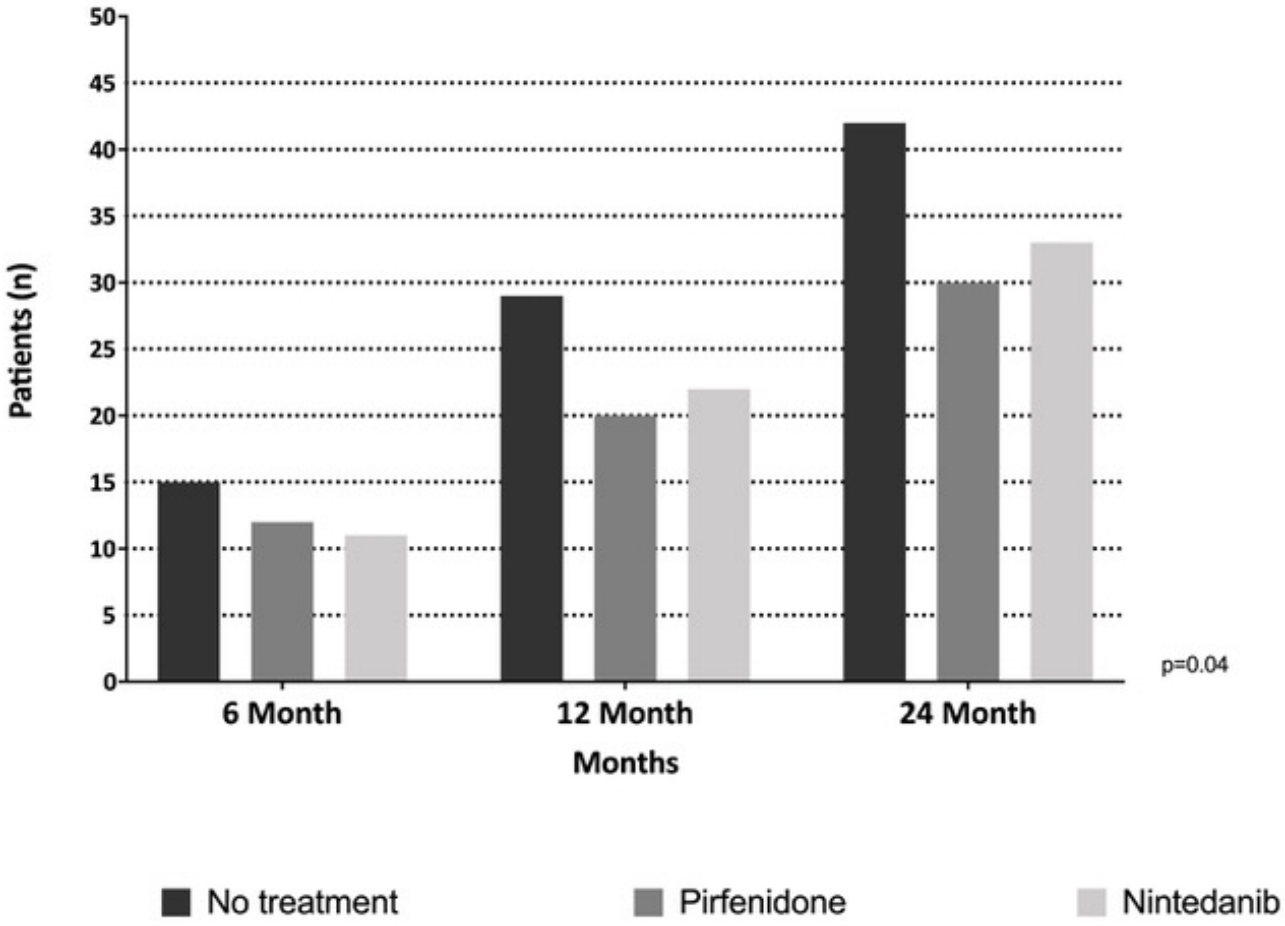

A
GAP I
FVC % predicted
110
105
100
95
90
85
80
75
70
65
60
p=0.9
Baseline
6 months
12 months
24 months
Months
No treatment
Pirfenidone
Nintedanib
B
GAP II/III
FVC % predicted
95
90
85
80
75
70
65
60
55
50
45
40
p=0.01
Baseline
6 months
12 months
24 months
Months
No treatment
Pirfenidone
Nintedanib

Figure 4


50
45
40
35
30
25
20
15
10
5
0
Patients (n)
6 Month
12 Month
24 Month
Months
p=0.04
No treatment
Pirfenidone
Nintedanib

Legend to figures

Figure 1- Time course of FVC over 24 month. Trend in the whole population comparing the three study groups (panel A) and the two groups of treatment (nintedanib and pirfinidone) (panel B).

Figure 2- Time course of DLCO over 24 month. Trend in the whole population comparing the three study groups (panel A) and the two groups of treatment (nintedanib and pirfinidone) (panel B).

Figure 3- Time course of FVC over 24 month in the three study groups divided according to the GAP I (panel A) and GAP II-III (panel B) score.

Figure 4- Proportion of patients in the three groups showing a decline in FVC >10% from baseline after 6, 12, and 24 months.

Author Agreement/Declaration

All authors have seen and approved the final version of the manuscript being submitted (REAL LIFE COMPARISON OF PIRFENIDONE AND NINTEDANIB IN PATIENTS WITH IDIOPHATIC PULMONARY FIBROSI: A 24 MONTHS ASSESSMENT)

They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.