Clinical Investigations

Respiration

Respiration
DOI: 10.1159/000485933

Received: July 6, 2017
Accepted: November 29, 2017
Published online: February 28, 2018

Real-World Experience with Nintedanib in Patients with Idiopathic Pulmonary Fibrosis

Eva Brunnemer[a, b] Julia Wälscher[a, b] Svenja Tenenbaum[a, b]
Julia Hausmanns[a, b] Karen Schulze[a, b] Marianne Seiter[a, b]
Claus Peter Heussel[b, c, e] Arne Warth[b, d] Felix J.F. Herth[a, b] Michael Kreuter[a, b]

[a]Centre for Interstitial and Rare Lung Diseases, Department of Pneumology and Respiratory Critical Care Medicine, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; [b]Translational Lung Research Centre Heidelberg (TLRC), Member of the German Centre for Lung Research (DZL), Heidelberg, Germany; [c]Department of Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; [d]Institute of Pathology, University of Heidelberg, Heidelberg, Germany; [e]Department of Diagnostic and Interventional Radiology, University Hospital of Heidelberg, Heidelberg, Germany

Keywords
Idiopathic pulmonary fibrosis · Nintedanib · Real-world experience

Abstract
Background: Nintedanib, an oral tyrosine kinase inhibitor, has been shown to slow down the progression of idiopathic pulmonary fibrosis (IPF) in two randomised placebo-controlled trials by reducing the annual decline in forced vital capacity (FVC). However, real-world experience is limited. ***Objective:*** To assess the efficacy and safety of nintedanib in a large cohort of patients treated at a tertiary referral site for interstitial lung diseases. ***Methods:*** The records of patients with a confirmed diagnosis of IPF were reviewed. Full medical history, pulmonary function, and adverse events (AEs) were recorded from each clinic visit. Disease progression was defined as a reduction in FVC ≥5% and/or in diffusing capacity of the lung for carbon monoxide ≥15% according to recent publications. Only patients with a treatment duration ≥3 months were included in the efficacy evaluation. ***Results:*** A total of 64 patients were treated. Mean ± standard deviation (SD) FVC was 71 ± 21% predicted, and the mean time from diagnosis to initiation of nintedanib treatment was 23.8 months. Nearly half of patients (n = 30, 47%) had received prior pirfenidone treatment. The mean duration of follow-up was 11 months. At 6 months following initiation of nintedanib, 67% of the patients were stable. The mean ± SD change in percent predicted FVC from baseline was 0.2 ± 7.8% at 3 months, –1.3 ± 7.9% at 6 months, and –2.1 ± 9% at 9 months. Diarrhoea was the most common AE experienced by 33% of patients and was generally manageable. ***Conclusion:*** The results from this real-world clinical setting support findings from previously conducted clinical trials and show that nintedanib is effective for the management of IPF and is associated with disease stabilisation. Nintedanib is generally well tolerated.

KARGER

E-Mail karger@karger.com
www.karger.com/res

Michael Kreuter
Centre for Interstitial and Rare Lung Diseases
Department of Pneumology and Respiratory Critical Care Medicine
Thoraxklinik, University of Heidelberg, German Centre for Lung Research
Röntgenstrasse 1, DE–69126 Heidelberg (Germany)
E-Mail michael.kreuter@med.uni-heidelberg.de

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease leading to deterioration of respiratory function and ultimately the patient's death. The average life expectancy following diagnosis is approximately 3 years, as this is the worst of all idiopathic interstitial pneumonias. The disease significantly affects health-related quality of life [1] and is also associated with a large number of comorbidities, which further add to the burden of disease associated with the condition [2, 3]. The requirement of those comorbidities for concomitant treatment may also affect the course of the illness [4–6].

Until relatively recently, there was no effective pharmacological intervention available for the treatment of IPF, although there are now two approved options: pirfenidone and nintedanib. Currently, therapy is aimed at reducing the decline in lung function associated with IPF, but cannot stop the course of the disease [7, 8]. Nintedanib is an intracellular small-molecule tyrosine kinase inhibitor that targets multiple tyrosine kinases, including the vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor receptors [9]. The receptors inhibited by nintedanib have been shown to be involved in the development of lung fibrosis, and simultaneous inhibition of these receptors with nintedanib has been shown to be effective in animal models of pulmonary fibrosis [10].

A phase 2 trial (TOMORROW) [11] and two replicate 52-week, randomised, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) [12] evaluated the efficacy and safety of 150 mg nintedanib twice daily compared with placebo; in both studies nintedanib significantly reduced the decline in forced vital capacity (FVC) compared to placebo (the primary endpoint) and had positive effects on the time to first acute exacerbations, both of which are consistent with a slowing of disease progression. Based on these results, nintedanib was approved for the treatment of IPF by the FDA in 2014 and by the European Commission in 2015. Nintedanib treatment is generally well tolerated and the most frequently reported adverse event (AE) is diarrhoea [12]. The updated ATS/ERS/JRS/ALAT clinical practice guidelines for the treatment of IPF recommend nintedanib as a treatment option, with consideration of individual patient needs [13].

In addition to data from controlled clinical trials, there is now a high demand for long-term evidence and real-world clinical experience in order to gain further insight into the use of nintedanib in IPF. Results recently published in abstract form from the ongoing INPULSIS®-ON extension study have confirmed the long-term benefit of nintedanib in reducing disease progression and the long-term safety and tolerability profile of nintedanib in patients suffering from IPF [14]. Only minimal data of patients treated in the real-world setting have been published so far and include data from a cohort of 62 patients treated with nintedanib as part of the German compassionate use programme with a mean treatment duration 14 months [15] and data from a cohort of 124 patients treated with nintedanib in the UK in which the average length of treatment was around 9 months [16]. These findings confirmed the results of controlled trials.

The aim of the current analysis was to assess the efficacy and safety of a large cohort of IPF patients treated with nintedanib at a tertiary referral site for interstitial lung diseases in a real-world setting.

Methods

Patients

We retrospectively analysed the clinical records of all patients with IPF treated with nintedanib outside of a study context at our tertiary referral centre for interstitial lung diseases in Germany [17]. The ethics committee of the University of Heidelberg approved the retrospective analyses of our patient cohort (S-318/2013, University of Heidelberg). Patient data was anonymised prior to analysis.

To be eligible for treatment and inclusions in our analyses, patients were required to have a confirmed multidisciplinary team diagnosis of IPF in accordance with the ATS/ERS/JRS/ALAT consensus guidelines [18] and the German guideline for diagnosis and treatment of IPF [19].

Nintedanib Treatment

The decision to start nintedanib treatment was based on a multidisciplinary confirmed diagnosis of IPF, shared decision making with the patient based on disease severity, the presence of comorbidities and its drug treatments, the individual history of the patient, and patient preferences. In our clinical practice, disease progression is defined as worsening of symptoms and a decline in FVC predicted >10% and/or radiological progression. For patients previously treated with pirfenidone, these criteria were also used as the reason for switching from pirfenidone to nintedanib. In case of intolerability to pirfenidone despite supportive measures, a switch to nintedanib was offered. All patients provided informed consent to initiate treatment.

Nintedanib was given as continuous oral treatment in accordance with the manufacturer's recommendations. Treatment schedules were collected with the following standard: treatment was started at a dose of 150 mg twice daily; dose reduction to 100 mg twice daily was undertaken for the management of AEs with the intention to re-titrate to 150 mg twice daily permitted upon resolution of the event. A dose reduction below 100 mg twice daily was not performed. Temporary interruption of treatment for the management of AEs was clinical practice, as were concomitant

medications, provided they were given in accordance with the manufacturer's instructions. In case of ongoing or recurrent AEs, the decision to stop the treatment with nintedanib was discussed with the patient.

Clinical Evaluation

At the time of diagnosis, a full medical history was obtained, including previous and concomitant medication use and details of comorbidities. Prior to the initiation of nintedanib, pulmonary function tests were performed assessing FVC, forced expiratory volume in 1 s, single-breath diffusing capacity of the lung for carbon monoxide (DL_{CO}), 6-min walk test, and high-resolution computed tomography [20]. The details of all previous treatments for IPF were recorded, along with reasons for switching to nintedanib if applicable.

Following treatment initiation, all patients were routinely evaluated according to the standard of care in our department, which includes a first follow-up visit 4 weeks after treatment initiation followed by regular clinic follow-up visits every 3 months. Full pulmonary function testing including DL_{CO} was performed every 3 months along with arterial blood gas sampling. Liver function monitoring was conducted on a monthly basis during the first 3 months after treatment initiation and at least every 3 months thereafter in line with the manufacturer's recommendations. Information on oxygen requirement, treatment-related AEs and severe AEs, treatment compliance, interruptions for any reason, and hospitalisations were also recorded at each treatment visit.

Acute exacerbations of IPF were defined based on the criteria proposed by Collard et al. [21].

Data Analysis and Evaluation

All patients were required to have a follow-up and/or intake of nintedanib ≥3 months to be included in the efficacy evaluation. Patients without a follow-up visit following diagnosis were also excluded from additional analysis. Disease progression under nintedanib was defined as an absolute decline in FVC predicted ≥5% and/or an absolute decline in DL_{CO} ≥15% at any time point according to du Bois et al. [22].

Normal data distribution was tested using the Shapiro-Wilk normality test with data presented as mean ± standard deviation (SD). The GraphPad Prism 6 software (San Diego, CA, USA) was used for statistical analysis.

Results

Patients

A total of 64 patients with IPF received treatment with nintedanib at our centre over the course of this evaluation between June 2014 and November 2016; all patients returned for follow-up visits and had post-baseline follow-up data available for analysis. Patient demographics and baseline clinical characteristics are shown in Table 1. The majority of patients were male (n = 55, 86%) and ex-smokers (n = 44, 69%). There was a high level of comorbidity, most commonly hypertension (n = 28, 44%). Pulmonary function was restrictive: mean ± SD FVC was

Table 1. Patient demographics and baseline clinical characteristics (n = 64)

Characteristic	
Sex	
Male	55 (85.9%)
Female	9 (14.1%)
Age, years	70.3 (6.8)
Body mass index	27.5 (4.3)
Time since diagnosis (range), months	23.8 (0–103)
Smoking status	
Ex-smoker	44 (68.8%)
Non-smoker	20 (31.3%)
Comorbidities	
Arterial hypertension	28 (43.8%)
Coronary artery disease	21 (32.8%)
Diabetes mellitus II	16 (25.0%)
Gastroesophageal reflux disease	21 (32.8%)
Pulmonary hypertension	5 (7.8%)
Obstructive sleep apnoea syndrome	9 (14.1%)
Stroke	2 (3.1%)
Transient ischemic attack	1 (1.6%)
Peripheral artery disease	4 (6.3%)
Atrial fibrillation	7 (10.9%)
Emphysema	9 (14.1%)
Concomitant medication at baseline	
Antihypertensive drugs	28 (43.8%)
Proton pump inhibitors	22 (34.4%)
Acetylsalicylic acid monotherapy	18 (28.1%)
Metformin/insulin	10 (15.6%)
Anticoagulants	7 (10.9%)
Statins	20 (31.3%)
N-acetylcysteine	5 (7.8%)
Acetylsalicylic acid + anticoagulants	3 (4.7%)
Prior treatments for IPF	
Pirfenidone	29 (45.3%)
N-acetylcysteine monotherapy	26 (40.6%)
Corticosteroids	10 (15.6%)
Immunosuppressants	5 (7.8%)
Trial medication	3 (4.7%)
N-acetylcysteine and pirfenidone	1 (1.6%)
None	19 (29.7%)
Baseline lung function	
Forced vital capacity, % predicted	71 (21)
DL_{CO}, % predicted	37 (10)
Computed tomography diagnosis	
UIP pattern present	51 (79.7%)
UIP pattern present and emphysema	10 (15.6%)
Possible UIP pattern present	13 (20.3%)
Biopsy	
Video-assisted thoracoscopic	24 (37.5%)
Cryo	4 (6.3%)
Baseline 6-min walk distance, m	390 (99)

Values are presented as n (%) or mean (standard deviation), unless indicated otherwise. DL_{CO}, diffusing capacity of the lung for carbon monoxide; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

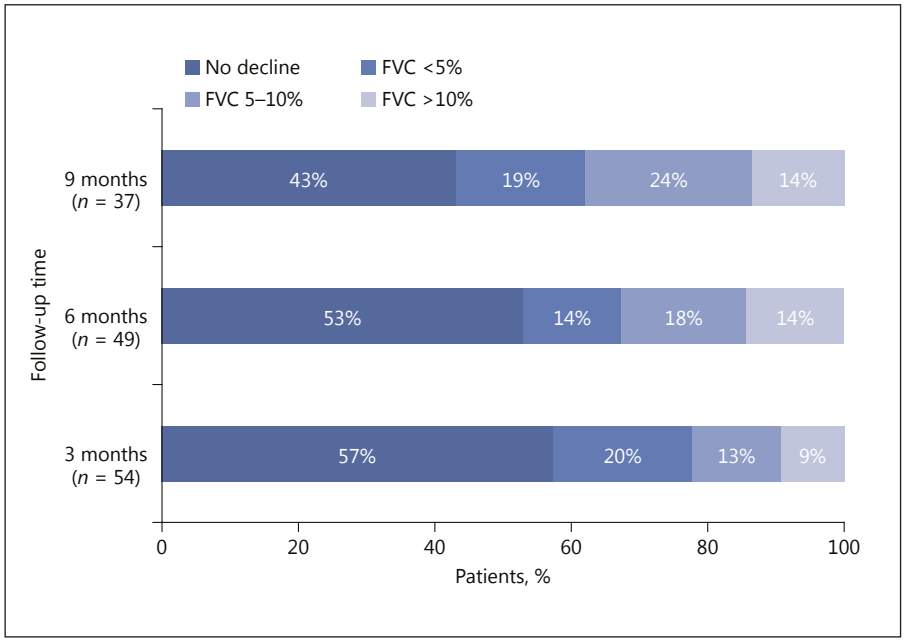

Fig. 1. Categorical change in forced vital capacity (FVC) at different follow-up time points. *n* represents the number of patients with data at that time point.

71 ± 21% predicted with a moderate reduction in DL_{CO} of 37 ± 21% predicted. The mean time from diagnosis to initiation of nintedanib treatment was 23.8 months.

Before initiating treatment with nintedanib, almost half of patients (*n* = 30, 47%) had been treated with pirfenidone. The reasons for discontinuation of previous pirfenidone treatment included intolerability (*n* = 21, 33%) or disease progression (as defined above) under pirfenidone (*n* = 9, 14%). Previous treatment with N-acetylcysteine was also common (*n* = 27, 42%), with 1 patient having previously received N-acetylcysteine in combination with pirfenidone. Nineteen patients (30%) were treatment-naïve at the start had of nintedanib therapy.

Nintedanib Treatment

The mean duration of follow-up after initiating nintedanib treatment was 11 months and ranged from 1 month to 29 months. At the time of this analysis, 46 patients (72%) remained on nintedanib. Eighteen patients (28%) had permanently discontinued treatment; 11 patients had died while on treatment (disease progression: *n* = 10, 16%; AEs: *n* = 1, 2%), and 7 patients had discontinued treatment due to AEs. AEs leading to discontinuation included diarrhoea (*n* = 5, 8%), disease progression (*n* = 1, 2%), and development of small-cell lung cancer (*n* = 1, 2%).

The majority of patients (*n* = 56, 88%) received treatment at the recommended dose of 150 mg nintedanib twice daily, while 8 patients (13%) required a permanent dose reduction to 100 mg nintedanib twice daily due to diarrhoea and anorexia. Temporary interruption of treatment was required in 5 patients due to AEs (diarrhoea: *n* = 4, 6%; liver enzyme elevations: *n* = 1, 2%). No concomitant treatment with pirfenidone was given, although 5 patients receiving N-acetylcysteine at baseline continued to receive N-acetylcysteine treatment while receiving nintedanib.

Disease Outcome under Nintedanib Treatment

The data of 10 patients were not included in the analysis as duration of treatment was <3 months. Reasons for treatment duration <3 months included insufficient follow-up period reached (*n* = 1, 2%), discontinuation of treatment (*n* = 3, 5%), and death (*n* = 6, 9%). Of the 64 patients treated with nintedanib in this retrospective analysis, FVC data were available for 54 patients (84%) at 3 months post treatment, 49 patients (77%) at 6 months post treatment, and 37 patients (58%) at 9 months post treatment.

The categorical change in FVC at 3, 6, and 9 months after the initiation of nintedanib therapy is shown in Figure 1. At 6 months following initiation of nintedanib, 33 of 49 patients (67%) were classified as having stable disease as defined by a decline in FVC <5% from baseline; the majority of these patients (*n* = 26, 53%) experienced no decline in FVC at 6 months. The remaining 16 patients

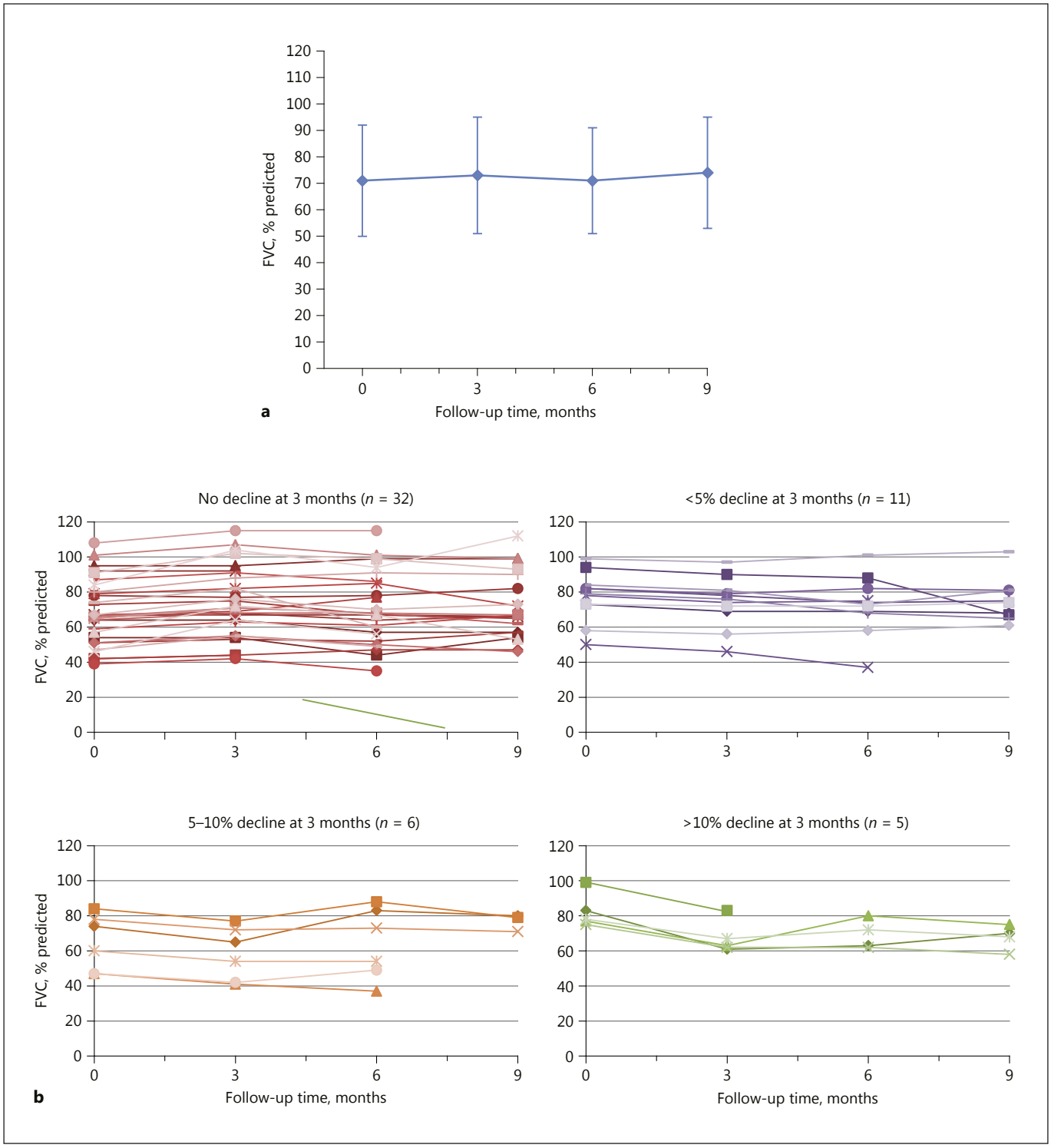

Fig. 2. Mean change in percent predicted forced vital capacity (FVC) over the course of treatment in all patients (n = 54) (**a**) and by disease status at 3 months (**b**). Data are presented as means ± SD.

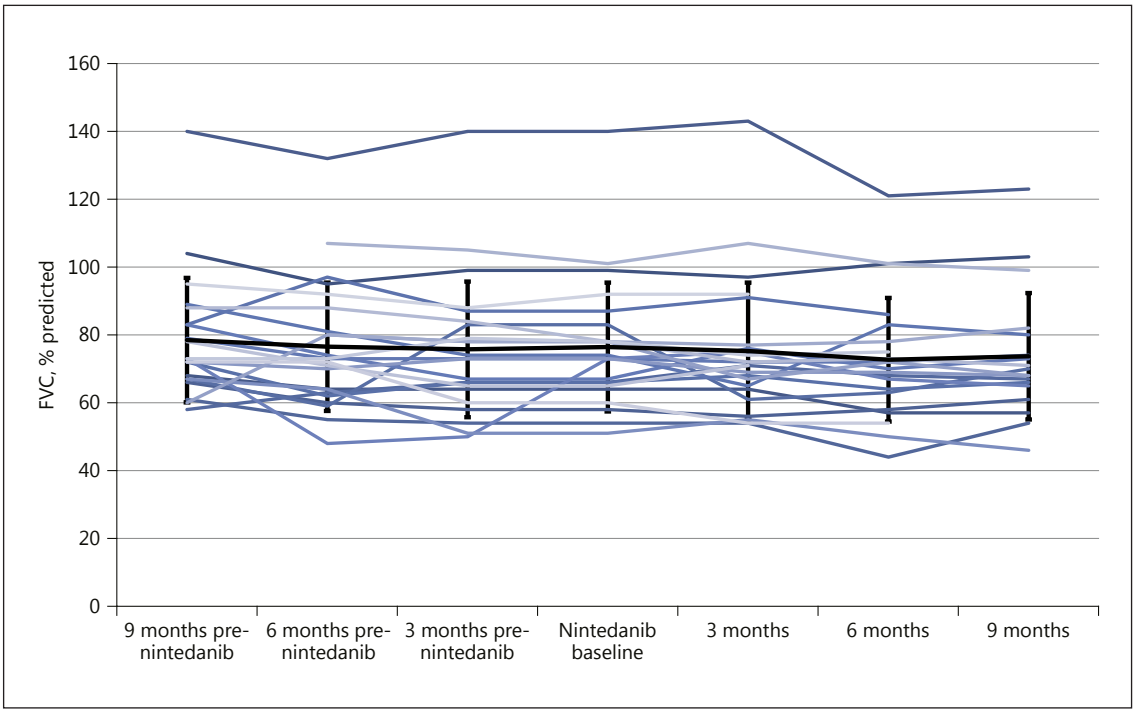

Fig. 3. Change in percent predicted forced vital capacity (FVC) for patients previously treated with pirfenidone. The black line represents the mean ± standard deviation for all patients.

(33%) were classified as experiencing disease progression. At 9 months following initiation of nintedanib, the proportion of patients with stable disease remained high (n = 23 of 37, 62%).

The course of pulmonary function after initiation of treatment with nintedanib measured using FVC is shown in Figure 2a. FVC decline was grouped into four categories according to data previously published by Nathan et al. [23] and Richeldi et al. [24] (Fig. 2b). The mean ± SD change in percent predicted FVC from baseline was 0.2 ± 7.8% at 3 months, –1.3 ± 7.9% at 6 months, and –2.1 ± 9.0% at 9 months. Similar results were observed in the subgroup of patients who received prior treatment with pirfenidone (n = 30). In these patients the mean ± SD change in percent predicted FVC from baseline was –0.7 ± 6.6% at 3 months, –2.8 ± 7.4% at 6 months, and –2.3 ± 6.8% at 9 months.

The pretreatment data for patients previously receiving pirfenidone are shown in Figure 3; disease stabilisation was achieved on an individual patient basis. The mean change in FVC in patients receiving concomitant treatment with anticoagulants was 1.1 ± 8.5% at month 3, –1.9 ± 8.5% at month 6, and –3.7 ± 11.8% at month 9, and in patients receiving concomitant treatment with statins it was 0.7 ± 15.9% at month 3, –0.3 ± 15% at month 6, and –1.5 ± 20.5% at month 9. Patients with coronary artery disease had a slightly slower decline in FVC compared to those without coronary artery disease after 3 months (0.2 ± 8.7 vs. 0.3 ± 7.7%), 6 months (–0.9 ± 6.8 vs. –1.4 ± 8.4%), and 9 months (0.1 ± 11.8 vs. –2.9 ± 8.4%). Similar to this, patients with arterial hypertension had a slightly slower decline in FVC compared to patients without arterial hypertension at 3 months (1.4 ± 10.7 vs. –0.4 ± 5%), 6 months (0.8 ± 7.8 vs. –2.6 ± 7.8%), and 9 months (–1.1 ± 10.8 vs. –2.7 ± 8.5%).

Patients with IPF and coexistent emphysema had a more extensive smoking history (22.5 ± 14.6 pack-years) compared to patients without emphysema (14.9 ± 20.8 pack-years). Comparison of pulmonary function data at the initiation of nintedanib treatment showed slightly higher mean FVC (77.3%) and lower mean DL_{CO} (32.1%) parameters compared to patients without emphysema. Of the 10 patients with emphysema, 2 died before the first follow-up at 3 months and 8 had no decline in FVC at 3 months.

Table 2. Adverse events reported over the period of observation

Adverse event	
Any adverse event	27 (42.2%)
Diarrhoea	21 (32.8%)
Nausea	2 (3.1%)
Weight loss	5 (7.8%)
AST/ALT increase >3× ULN	1 (1.6%)
Dizziness	1 (1.6%)
Bleeding (hematoma)[1]	1 (1.6%)

Values are presented as *n* (%). ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal. [1] Bleeding occurred under continued treatment with acetylsalicylic acid and anticoagulants.

Tolerability of Nintedanib Treatment

AEs reported over the period of observation are shown in Table 2. At least one AE was reported by 42% of patients. Diarrhoea was the most common AE experienced by 21 patients (33%). Diarrhoea was managed by temporary discontinuation in 4 cases, dose reduction to 100 mg twice daily in 8 cases, or concomitant therapy with loperamide on a regular or occasional basis.

Serious AEs reported during the observation period included 11 patients (17%) who experienced acute exacerbations of IPF. All acute exacerbations required hospitalisation and were treated with high doses of corticosteroids and antibiotics. One patient died as a result of acute exacerbation of IPF. One patient with a pulmonary embolism required hospitalisation, and 1 patient with a non-ST elevation myocardial infarction required percutaneous transluminal coronary angioplasty. Additional reasons for hospitalisation included pneumonia (n = 2), lower respiratory tract infection (n = 2), requirement for palliative care (n = 3), and small-cell lung cancer (n = 2).

Discussion

The findings from this large cohort of patients with IPF treated in the real-world setting suggest that nintedanib treatment is associated with disease stabilisation, as measured by FVC, in the majority of IPF patients, including those with cardiovascular and other comorbidities. Treatment was generally well tolerated with a manageable AE profile.

Real-world data provide important insight into the value of treatments in clinical practice, supplementing data collected in controlled clinical trials, and help provide insight into the many areas of uncertainty [25]. The demographic characteristics of the patients reported in this study, including age, sex distribution, and smoking history, were broadly similar to those reported in the previous INPULSIS trials [11] as well as to those reported in other real-world reports [15, 16], reflecting the typical patient demographic characteristics of patients with IPF. Subgroup analyses of the INPULSIS trials have shown that the treatment effects of nintedanib are consistent across patient subgroups, including sex, age, smoking status, and baseline respiratory functions measured using baseline percent predicted FVC [26]. However, baseline respiratory function was markedly lower (nearly 10%) in our patient cohort than in the INPULSIS studies. As such, our data provide support for the benefits of nintedanib in a patient population with more severe disease at baseline; nintedanib treatment was associated with stable disease at 6 months, as measured by FVC, in the majority (67%) of patients. The baseline respiratory function reported in our real-world cohort was similar to that in patients treated in other real-world analyses [15, 16].

In contrast to the patient population treated in the INPULSIS studies, a substantial proportion of our study population had clinically relevant comorbid conditions requiring specific concomitant medications; nearly half of the patients had hypertension, and one-third had coronary artery disease. Changes in FVC in patients with coronary artery disease and arterial hypertension suggest that these patients also benefit from treatment.

The coexistence of upper lobe emphysema in patients with IPF is increasingly recognised and is associated with especially poor lung function [27]. The proportion of patients with coexistent radiological features of IPF and emphysema in our study was 16% and was similar to that reported previously in a cohort of patients treated with pirfenidone at our centre [17], although lower than reported in the INPULSIS studies (39%) [28]. Patients with emphysema treated with nintedanib in our study had no decline in FVC over the course of treatment, although the follow-up period was perhaps too short to draw conclusions. Further parameters such as DL_{CO}, 6-min walk test, capillary blood gas analysis, or radiological findings complementary to FVC are useful to assess disease stability and progression. However, post hoc analyses from the INPULSIS trials had shown that the clinical benefit of nintedanib is independent of the presence of emphysema at baseline [26].

Acute exacerbations of IPF were more commonly reported in our cohort (17%) than previously reported with

nintedanib treatment in either the German compassionate use programme (11%) [15], the INPULSIS studies (5%) [12], or the ranges typically reported in treated and untreated patient populations (8–15%) [26]. The increased rate of acute exacerbations reported here is most probably the results of more advanced disease in our patient population than in previous studies, as indicated by a longer time since first diagnosis (33 months). Additionally, the majority of patients in our study initiated treatment during the winter period, and subsequently a higher risk of infection at this time may have triggered acute exacerbations.

As would be expected, the tolerability profile reported here is based on the known tolerability profile of nintedanib. The overall reported rates of AEs were typically lower than those reported in the INPULSIS studies, but this would be expected based on differences in the methodologies for collecting such data. In agreement with results from clinical trials and other real-world reports, the most frequent events were gastrointestinal in nature, most commonly diarrhoea, although diarrhoea does not commonly lead to discontinuation of treatment and is manageable with dose reduction and treatment interruption. The tolerability profile in this cohort of patients, which had substantially higher rates of comorbidity and concomitant medication use than patients treated in controlled trials, provides further reassurance for the use on nintedanib in clinical practice. Importantly, given the presence of substantial cardiovascular morbidity in this patient cohort, the rates of major adverse cardiovascular events, bleeding, and pulmonary embolism were very low.

Our data provide growing support for the clinical use of nintedanib as a treatment option for patients with IPF from a relatively large cohort of patients with IPF treated in the real-world setting. However, the findings of our study need to be considered in the context of study limitations which include the retrospective nature of data collection and the heterogeneous patient population that included patients with and without prior antifibrotic treatment exposure. Furthermore, it should be noted that information on treatment compliance was not available. It should also be noted that 5 patients included in this study were also included in the previously reported analysis of 62 patients with IPF treated with nintedanib within a compassionate use programme [15]; however, the follow-up time of these patients reported here was substantially longer and thus previous provided justification for their inclusion.

Conclusion

The results from the real-world clinical setting support findings from previously conducted clinical trials that nintedanib is associated with disease stabilisation while on treatment in patients with IPF and is generally well tolerated. Importantly, serious AEs such as bleeding and major adverse cardiovascular events were low in this real-world setting in a diverse patient population with diverse comorbidities and concomitant medications.

Acknowledgements

The authors would like to acknowledge Suzanne Patel who provided editorial assistance, supported by an unrestricted grant from Boehringer Ingelheim, prior to submission of this article. The authors were responsible for data collection and analysis; Boehringer Ingelheim did not have access to the data, and the authors did not discuss the data with them during the development of the manuscript.

Financial Disclosure and Conflicts of Interest

M. Kreuter has received grants and fees for consulting from Boehringer Ingelheim and Roche/InterMune. The other authors report no conflicts of interest.

Author Contributions

All authors contributed patient data, critically reviewed the manuscript drafts, provided comments, and read and approved the final manuscript.

References

1 Kreuter M, Swigris J, Pittrow D, Geier S, Klotsche J, Prasse A, Wirtz H, Koschel D, Andreas S, Claussen M, Grohe C, Wilkens H, Hagmeyer L, Skowasch D, Meyer JF, Kirschner J, Glaser S, Herth FJF, Welte T, Neurohr C, Schwaiblmair M, Held M, Bahmer T, Frankenberger M, Behr J: Health related quality of life in patients with idiopathic pulmonary fibrosis in clinical practice: INSIGHTS-IPF registry. Respir Res 2017;18:139.

2 Kreuter M, Ehlers-Tenenbaum S, Palmowski K, Bruhwyler J, Oltmanns U, Muley T, Heussel CP, Warth A, Kolb M, Herth FJ: Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. PLoS One 2016;11:e0151425.

3 Kreuter M, Ehlers-Tenenbaum S, Schaaf M, Oltmanns U, Palmowski K, Hoffmann H, Schnabel PA, Heussel CP, Puderbach M, Herth FJ, Warth A: Treatment and outcome of lung cancer in idiopathic interstitial pneumonias. Sarcoidosis Vasc Diffuse Lung Dis 2015;31:266–274.
4 Kreuter M, Bonella F, Maher TM, Costabel U, Spagnolo P, Weycker D, Kirchgaessler KU, Kolb M: Effect of statins on disease-related outcomes in patients with idiopathic pulmonary fibrosis. Thorax 2017;72:148–153.
5 Kreuter M, Wijsenbeek MS, Vasakova M, Spagnolo P, Kolb M, Costabel U, Weycker D, Kirchgaessler KU, Maher TM: Unfavourable effects of medically indicated oral anticoagulants on survival in idiopathic pulmonary fibrosis. Eur Respir J 2016;47:1776–1784.
6 Kreuter M, Wuyts W, Renzoni E, Koschel D, Maher TM, Kolb M, Weycker D, Spagnolo P, Kirchgaessler KU, Herth FJ, Costabel U: Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. Lancet Respir Med 2016;4:381–389.
7 Tzouvelekis A, Bonella F, Spagnolo P: Update on therapeutic management of idiopathic pulmonary fibrosis. Ther Clin Risk Manag 2015;11:359–370.
8 Kreuter M, Bonella F, Wijsenbeek M, Maher TM, Spagnolo P: Pharmacological treatment of idiopathic pulmonary fibrosis: current approaches, unsolved issues, and future perspectives. Biomed Res Int 2015;2015:329481.
9 Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Rettig WJ: BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68:4774–4782.
10 Woodcock HV, Molyneaux PL, Maher TM: Reducing lung function decline in patients with idiopathic pulmonary fibrosis: potential of nintedanib. Drug Des Devel Ther 2013;7:503–510.
11 Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Kluglich M, du Bois RM: Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365:1079–1087.
12 Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR; INPULSIS Trial Investigators: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–2082.
13 Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, Johkoh T, Martinez FJ, Myers J, Protzko SL, Richeldi L, Rind D, Selman M, Theodore A, Wells AU, Hoogsteden H, Schunemann HJ; 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;192:e3–e19.
14 Crestani B, Quaresma M, Kaye M, Stansen W, Stowasser S, Kreuter M: Long-term treatment with nintedanib in patients with IPF: an update from INPULSIS®-ON. Eur Respir J 2016;48:OA4960.
15 Bonella F, Kreuter M, Hagmeyer L, Neurohr C, Keller C, Kohlhaeufl MJ, Muller-Quernheim J, Milger K, Prasse A; German Nintedanib Compassionate Use Consortium: Insights from the German compassionate use program of nintedanib for the treatment of idiopathic pulmonary fibrosis. Respiration 2016;92:98–106.
16 Hughes G, Toellner H, Morris H, Leonard C, Chaudhuri N: Real world experiences: pirfenidone and nintedanib are effective and well tolerated treatments for idiopathic pulmonary fibrosis. J Clin Med 2016;5:E78.
17 Oltmanns U, Kahn N, Palmowski K, Trager A, Wenz H, Heussel CP, Schnabel PA, Puderbach M, Wiebel M, Ehlers-Tenenbaum S, Warth A, Herth FJ, Kreuter M: Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. Respiration 2014;88:199–207.
18 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788–824.
19 Behr J, Gunther A, Ammenwerth W, Bittmann I, Bonnet R, Buhl R, Eickelberg O, Ewert R, Glaser S, Gottlieb J, Grohe C, Kreuter M, Kroegel C, Markart P, Neurohr C, Pfeifer M, Prasse A, Schonfeld N, Schreiber J, Sitter H, Theegarten D, Theile A, Wilke A, Wirtz H, Witt C, Worth H, Zabel P, Muller-Quernheim J, Costabel U: German guideline for diagnosis and management of idiopathic pulmonary fibrosis (in German). Pneumologie 2013;67:81–111.
20 Csernus R, Wiebel M, Godeny M, Herth FJ, Kauczor HU, Heussel CP: Hypoxic respiratory failure in chronic lung disease (in German). Med Klin Intensivmed Notfmed 2017;112:149–155.
21 Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, Noth I, Olman MA, Raghu G, Roman J, Ryu JH, Zisman DA, Hunninghake GW, Colby TV, Egan JJ, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kondoh Y, Lynch DA, Muller-Quernheim J, Myers JL, Nicholson AG, Selman M, Toews GB, Wells AU, Martinez FJ: Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176:636–643.
22 du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, King TE Jr, Lancaster L, Noble PW, Sahn SA, Thomeer M, Valeyre D, Wells AU: Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med 2011;184:1382–1389.
23 Nathan SD, Albera C, Bradford WZ, Costabel U, du Bois RM, Fagan EA, Fishman RS, Glaspole I, Glassberg MK, Glasscock KF, King TE Jr, Lancaster L, Lederer DJ, Lin Z, Pereira CA, Swigris JJ, Valeyre D, Noble PW, Wells AU: Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax 2016;71:429–435.
24 Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, Elicker BM, Jones KD, King TE Jr, Ryu JH, Collard HR: Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. Thorax 2012;67:407–411.
25 Funke-Chambour M, Azzola A, Adler D, Barazzone-Argiroffo C, Benden C, Boehler A, Bridevaux PO, Brutsche M, Clarenbach CF, Hostettler K, Kleiner-Finger R, Nicod LP, Soccal PM, Tamm M, Geiser T, Lazor R: Idiopathic pulmonary fibrosis in Switzerland: diagnosis and treatment. Respiration 2017;93:363–378.
26 Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, Azuma A: Efficacy of nintedanib in idiopathic pulmonary fibrosis across prespecified subgroups in INPULSIS. Am J Respir Crit Care Med 2016;193:178–185.
27 Papaioannou AI, Kostikas K, Manali ED, Papadaki G, Roussou A, Kolilekas L, Borie R, Bouros D, Papiris SA: Combined pulmonary fibrosis and emphysema: the many aspects of a cohabitation contract. Respir Med 2016;117:14–26.
28 Pfeifer M, Cottin V, Taniguchi H, Richeldi L, Collard HR, Kaye M, Hansell DM, Bailes Z, Schlenker-Herceg R, Raghu G: Effect of baseline emphysema on reduction in FVC decline with nintedanib in the INPULSIS™ trials. Pneumologie 2015;69:P254.