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Insights from the German Compassionate Use Program of Nintedanib for the Treatment of Idiopathic Pulmonary Fibrosis

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Key Words

Idiopathic pulmonary fibrosis · Nintedanib ·
Compassionate use

Abstract

Background: Nintedanib is approved for the treatment of idiopathic pulmonary fibrosis (IPF) and has been shown to slow disease progression by reducing annual lung function decline. **Objective:** To evaluate the results of a large cohort of IPF patients treated with nintedanib within a compassionate use program (CUP) in Germany (9 centers). **Methods:** Patients (≥ 40 years) were required to have a confirmed diagnosis of IPF, a forced vital capacity (FVC) $\geq 50\%$ predicted (pred.) and a carbon monoxide diffusing capacity (DLCO) 30–79% pred. and not to be eligible for pirfenidone treatment. Clinical data, pulmonary function tests and adverse events were recorded up to July 2015. **Results:** Sixty-two patients

(48 male/14 female) with moderate IPF (FVC $64 \pm 17\%$ pred. and DLCO $40 \pm 10\%$ pred.) were treated with nintedanib. 77% of patients switched from pirfenidone (mean treatment duration 14 ± 2 months) mostly due to disease progression (mean decline in FVC $7.4 \pm 3\%$ pred. in the 6 months prior to nintedanib intake). Initiation of nintedanib treatment occurred 69 ± 29 months after IPF diagnosis, and mean treatment duration was 8 ± 4 months. Most patients (63%) stabilized 6 months after treatment start (mean FVC decline 3 ± 1 vs. $-17 \pm 2\%$ in patients with disease progression; $p < 0.01$). The most common adverse events were diarrhea (63%) and weight loss (50%). Dose reduction occurred in 34% of cases and treatment discontinuation in 10%. **Conclusion:** Nintedanib treatment was generally well tolerated and was associated with FVC stabilization in the majority of IPF patients in this CUP setting where most patients were not treatment naïve. Our data are in agreement with the previously published data.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and finally lethal lung disease with a frequency of 2.8–9.3 per 100,000 per year in Europe and North America [1]. The deterioration of respiratory function over time and IPF-related complications heavily affect the quality of life of IPF patients [2]. There are two approved antifibrotic drugs for IPF, which cannot stop the disease course, but can considerably reduce the decline of lung function: nintedanib and pirfenidone [3, 4].

Nintedanib has been investigated in three international phase II (TOMORROW) and phase III clinical trials (INPULSIS[®]-1 and INPULSIS[®]-2) including almost 1,500 patients with IPF [5, 6]. In both INPULSIS[®] trials, the primary outcome was achieved, with a reduction in the annual rate of forced vital capacity (FVC) decline of approximately 50% in the nintedanib group compared to placebo [6]. The most frequently reported adverse event (AE) in these trials was diarrhea, which was reported in 62% of patients treated with nintedanib compared to 18% in the placebo group. Diarrhea events were mild to moderate in intensity in the vast majority of patients and led to premature treatment discontinuation in fewer than 5% of nintedanib-treated patients [6].

The twin phase III INPULSIS[®] trials and the phase II TOMORROW study were all followed by open-label extension trials to provide ongoing treatment options to patients who completed the studies and to assess long-term safety and tolerability of nintedanib treatment [7–9]. More than 90% of eligible patients ($n = 734/807$) chose to continue to receive open-label nintedanib in the ongoing INPULSIS[®]-ON extension trial, following completion of the INPULSIS[®] trials [7, 8]. Interim results from this study have recently been reported and confirmed the long-term safety and tolerability profile of nintedanib in IPF [7, 8]. Recently, a phase II study assessed the safety, tolerability, and pharmacokinetic profile of nintedanib when given alone or in addition to pirfenidone treatment in Japanese patients [10]. In addition, 2 open-label trials investigating the long-term safety and tolerability of the combination nintedanib plus pirfenidone are ongoing (www.clinicaltrials.gov identifier No. NCT01417156 and NCT02598193).

Whereas data and subgroup analyses from patients treated with nintedanib in clinical trials have been reported, the use of nintedanib in real-life settings has not been reported in detail. Compassionate use programs (CUP) are intended to facilitate the availability of new treatment options under development to patients before they are

available commercially [11] and allow for data to be collected on use of products under conditions of clinical practice. The nintedanib CUP was offered by Boehringer Ingelheim GmbH (Ingelheim, Germany) in May 2014 to enable early access to nintedanib for patients with IPF after publication of the results from the pivotal INPULSIS trials in May 2014. Here, we report the efficacy and safety of a large cohort of IPF patients who received nintedanib within a CUP in Germany.

Patients and Methods

The Compassionate Use Program

To be eligible for treatment with nintedanib in the CUP, patients were required to be over 40 years of age, with a confirmed diagnosis of IPF in accordance with international guidelines [12]. Carbon monoxide diffusing capacity (DLCO) had to be 30–79% predicted (pred.) based on international standards, and FVC $\geq 50\%$ pred. based on institutional standards [13, 14]. Patients were required to be judged as not eligible for treatment with pirfenidone, based on disease severity and/or intolerability, by the treating clinician, and the decision to prescribe nintedanib was based on clinician's judgement. Key exclusion criteria included alanine aminotransferase (ALT)/aspartate aminotransferase (AST) or bilirubin levels greater than 1.5 times the upper limit of normal (ULN); risk of bleeding or thrombosis; planned major surgery within the next 3 months, including lung transplantation, major abdominal, or major intestinal surgery; myocardial infarction within the last 6 months, or unstable angina within the last month. All patients were assessed for study eligibility by central review.

All patients provided written informed consent, and the required regulatory authorities (Federal Institute for Drugs and Medical Devices and regional authorities) were informed; as this was a CUP, ethics committee approval was not required. The CUP was conducted in accordance with the Ordinance on Medicinal Products for Compassionate Use [15]. It was initiated in May 2014 and stopped upon market availability of nintedanib for the treatment of IPF in Germany (February 2015) as applicable by German law.

Drug Intake

Nintedanib was given as continuous oral treatment at a starting dose of 150 mg twice daily. Dose interruption or reduction of the 150 mg twice daily to 100 mg twice daily was allowed for the management of AEs. The dose could be retitrated to 150 mg twice daily upon resolution of the AE. Dose reductions below 100 mg twice daily were not permitted. Hepatic transaminases (AST and ALT) monitoring was recommended on a monthly basis during the first 3 months after treatment initiation and at least every 3 months thereafter. Recommendations for the management of diarrhea and elevated levels of liver enzymes were provided.

Patients were required to permanently discontinue nintedanib if they experienced significant liver function impairment or recurrent grade 3/4 diarrhea. Concomitant medications to allow adequate care of the patient were permitted as clinically necessary; concomitant therapies that were not permitted during the study are given in online supplemental table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000448288).

Table 1. Patient characteristics (n = 62)

Gender	
Male	48 (77)
Female	14 (23)
Age, years	71±8
Body mass index	26±4
Smoking status	
Ex-smoker	38 (61)
Non-smoker	24 (39)
Time since IPF diagnosis, months	69±29
Medical co-morbidity	
Arterial hypertension	19 (31)
Type 2 diabetes	9 (14.5)
Coronary heart disease	8 (13)
Gastroesophageal reflux disease	7 (11)
Obstructive sleep apnea syndrome	4 (6)
Other	3 (5)
Prior treatments for IPF	
Pirfenidone (any)	48 (77)
Monotherapy	37 (60)
Combination with	
N-acetylcysteine and/or steroids	11 (17)
N-acetylcysteine, alone or in combination	9 (14.5)
Immunosuppressive, alone or in combination	8 (13)
None	9 (14.5)
Duration of pirfenidone treatment, months	13.5±1.6
Reasons for discontinuation of previous pirfenidone treatment (n = 48; 100%)	
Tolerability	27 (56)
Disease progression	21 (44)
Concomitant medications at baseline	
ACE inhibitors/ARB/diuretics	19 (31)
Proton pump inhibitors	16 (26)
Acetylsalicylic acid	12 (19)
Metformin/meglitinides	8 (13)
Beta-blockers	8 (13)
Allopurinol	5 (8)
N-acetylcysteine	5 (8)
Anticoagulants	2 (3)
Others	<3 (5)
Baseline lung function	
FVC, % predicted	64±17
DLCO, % predicted	40±10
PaO ₂ , mm Hg	67±0
Long-term oxygen treatment at start	5 (8)

Data are presented as n (%) or mean ± SEM. ACE = Angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

Data Collection

Participating clinicians were asked to retrospectively provide data for each patient treated in the CUP including: demographics and baseline characteristics (gender, age, comorbidities, disease history and prior and concomitant medications); pulmonary function tests at 6 months prior to initiation of therapy, at nintedanib treatment baseline and 6 months after start of treatment; FVC, maximum vital capacity and DLCO and radiological assessment. Patients were followed-up for as long as possible prior to the end of the CUP; for patients treated with nintedanib for longer than 6 months, additional follow-up visits were conducted as appropriate. Blood gas analysis results were also collected as well as information on long-term oxygen requirement at baseline and follow-up. Patient self-reported symptoms were also collected at each follow-up. Information on AEs, including nonserious, serious, AEs of special interest, AEs leading to treatment discontinuation or dose reduction/interruption of nintedanib were required to be centrally reported to Boehringer Ingelheim.

Clinical Definitions

Patients were required to have a follow-up and/or intake of nintedanib ≥3 months to be included in the efficacy analysis. Disease progression was defined as an absolute decline in FVC pred. ≥5% from baseline over 6 months. Patients with a decline in FVC pred. <5% from baseline were classified as having stable disease provided they had no worsening of symptoms or radiological findings. Other outcomes included change of self-reported respiratory symptoms and IPF-related radiological findings over time. These outcomes were considered exploratory as there was no standardization of data collection (symptom reporting was ad hoc, and criteria for radiological evaluation were not defined).

Statistics

The Kolmogorov-Smirnov test was used to test variable distribution. Continuous normally distributed variables are expressed as mean ± standard error of the mean, while non-normally distributed data are expressed by median and interquartile range. Paired t test was used to compare lung function tests over time. Differences in proportions of subjects showing a change of %FVC before and after treatment were analyzed using the McNemar χ^2 test. A p value <0.05 was considered significant for all analyses. All analyses were conducted using IBM[®] SPSS[®] statistic software (version 21).

Results

Patients

A total of 83 patients with IPF received treatment with nintedanib as part of the CUP. Here, we report data on 62 patients treated at 9 centers across Germany who began treatment between May 2014 and January 2015; data on the remaining 21 patients were not provided by the treating centers. All data from treatment initiation to the cut-off date of 31 July 2015 were collected.

Patient demographics and baseline clinical characteristics are shown in table 1. The majority of patients were male (77%) and ex-smokers (61%) with moderate func-

Table 2. Reasons for treatment discontinuation/interruption and AEs reported during the observation period (n = 62)

Permanent discontinuation of treatment	7 (11)
Death	3 (5)
Adverse events	2 (3)
Disease progression	2 (3)
Temporary discontinuation	18 (29)
Adverse events	
Diarrhea	10 (16)
Liver enzyme elevations	2 (3)
Progression	6 (10)
Adverse events requiring dose reduction	21 (34)
Diarrhea	19 (31)
Liver enzyme elevations	2 (3)
Any adverse events	47 (75.8)
Gastrointestinal adverse events	42 (67.7)
Diarrhea	39 (62.9)
Anorexia	24 (38.7)
Nausea	16 (25.8)
Heartburn	4 (6.5)
AST/ALT increase >3× ULN	5 (8.1)
Weight loss	31 (50.0)
Mean weight loss, kg	3.2±1
Fatigue	24 (38.7)
Cough worsening	9 (14.5)
Skin rash	6 (9.7)
Dizziness	4 (6.5)
Headache	3 (4.8)
Ischemic stroke	2 (3)
Other	<3 (<4.8)

Data are presented as n (%) or mean ± SEM. No bleeding events were reported.

tional impairment at the start of treatment (FVC of $64 \pm 17\%$, DLCO $40 \pm 10\%$ pred.). Five patients were on long-term oxygen treatment.

Patients were 71 years old on average, and the diagnosis of IPF was made 69 ± 29 months prior to the start of nintedanib treatment. The most frequent observed comorbidity was arterial hypertension (31%) followed by type 2 diabetes (15%).

Before starting treatment with nintedanib, the majority of patients (n = 48, 77%) had been receiving treatment with pirfenidone, either alone or in combination with other IPF treatments, for a mean duration of 14 ± 2 months (table 1). Fourteen patients (23%) were not receiving pirfenidone at the time of starting nintedanib treatment due to: comorbidity (n = 1); patient reluctance to take pirfenidone due to concerns about the general tolerability profile (n = 2) or possible phototoxic effects (n =

5); tolerability issues with previous pirfenidone treatment (n = 3); failure of previous pirfenidone (n = 1), or unknown reasons (n = 2).

Duration of Treatment and Compliance

The follow-up duration in the CUP ranged from 2 to 14 months, with a mean follow-up of 9 ± 2.4 months. Exposure to nintedanib ranged from 0.5 to 14 months with a mean of 8 ± 4 months. As of the cutoff date (31 July 2015), 7 patients (11%) had permanently discontinued treatment with nintedanib, and a further 18 patients (29%) had required a temporary treatment interruption. The reasons for permanent and temporary treatment discontinuation are shown in table 2. The average time to treatment discontinuation was 106 (range 3–327) days after treatment initiation. The median (range) duration of temporary discontinuation was 17 (1–91) days.

Disease Outcome under Nintedanib Treatment

Decline in FVC

Of the 62 patients treated within the CUP, FVC data were available for 48 patients at 6 months and for 36 at the last follow-up visit; data on 14 patients were excluded from the analysis due to missing data at follow-up (n = 4) or too short (<3 months) nintedanib intake (n = 10).

In the 6 months prior to initiating therapy with nintedanib, the mean change in FVC had been $-7.4 \pm 3\%$ pred. The change in FVC 6 months prior to nintedanib initiation was significantly lower in patients who had been receiving pirfenidone (n = 42) than in those who did not receive antifibrotic therapy (n = 13) (-5.2 ± 3.9 vs. $-17.6 \pm 3.7\%$ pred.; p = 0.027).

At 6 months following the initiation of nintedanib, 30 patients (63%) were classified as having stable disease as defined by a decline in FVC of <5% from baseline; the remaining 18 patients (37%) were classified as experiencing disease progression. Figure 1 shows the course of pulmonary function measured using FVC before and after initiation of treatment with nintedanib in patients based on whether or not they suffered from stable or progressive disease at 6 months. The mean change in FVC at 6 months was $3.1 \pm 1.2\%$ from baseline in stable patients compared to $-17 \pm 2\%$ in patients with disease progression (p < 0.01). A similar pattern of pulmonary function was also observed at the last follow-up visit (average 8 ± 0.5 months after first intake of nintedanib) at which time 64% of patients were classified as having stable disease and 36% of patients were classified as having disease progression; the mean change in FVC was 1.6 ± 1.2 versus $-13.3 \pm 1.8\%$, respectively (p < 0.01).

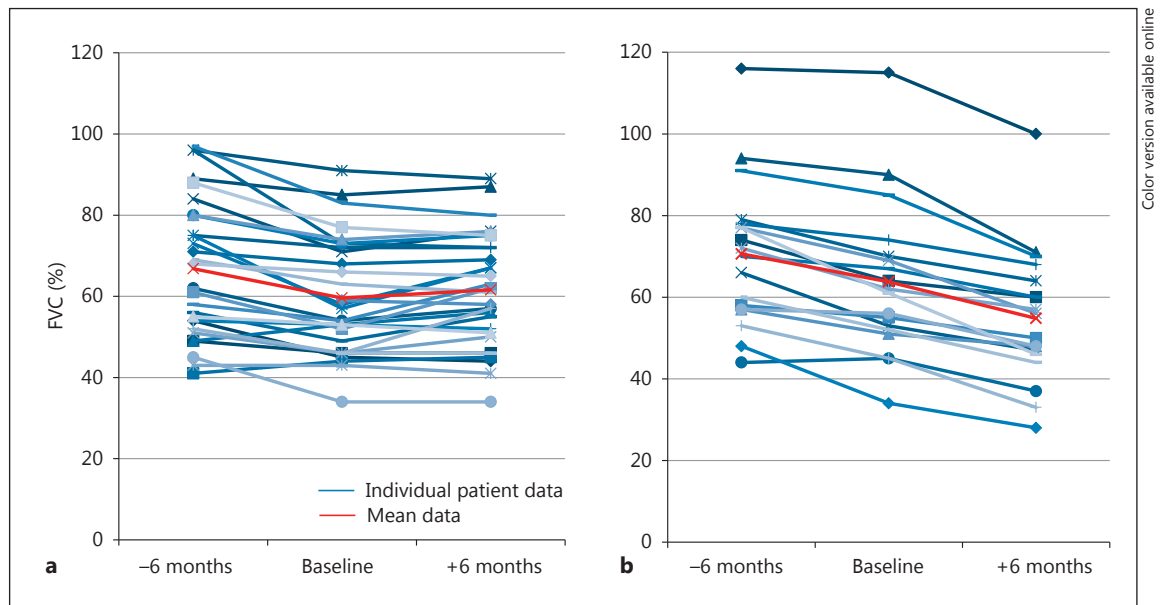


Fig. 1. FVC before and after initiation of treatment with nintedanib in patients with stable disease (n = 30; **a**) and disease progression (n = 18; **b**) with nintedanib.

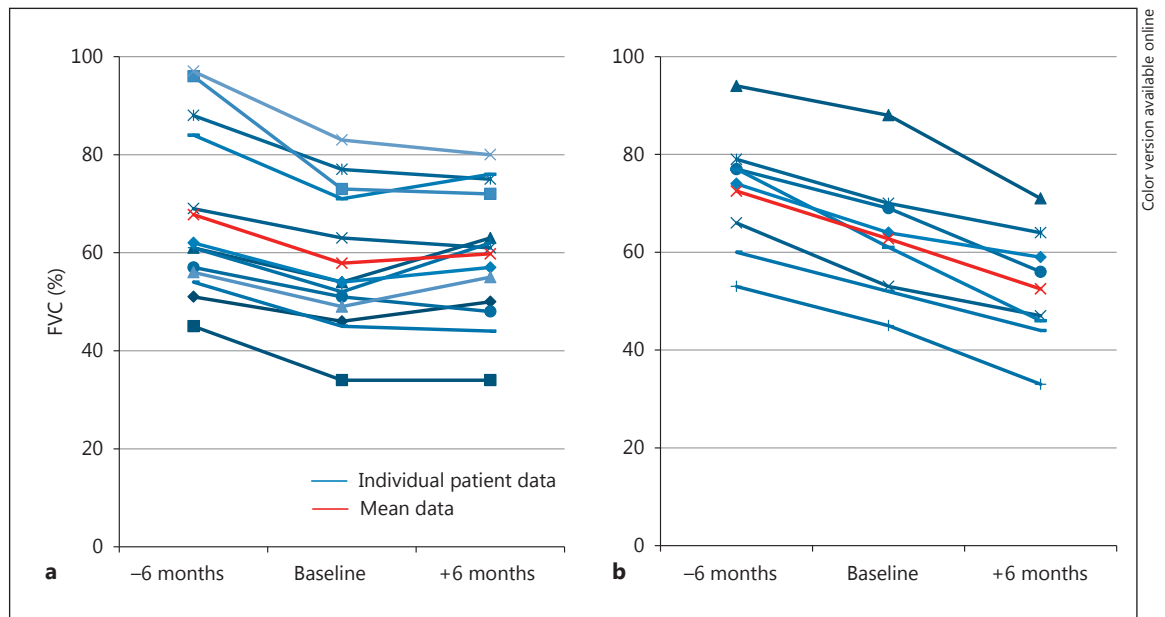


Fig. 2. FVC before and after initiation of treatment with nintedanib in patients with stable disease (n = 13; **a**) and disease progression (n = 8; **b**) under pirfenidone prior to entering the CUP.

In the patients who had progressed while on pirfenidone (n = 21), the change in FVC was $-17.3 \pm 6\%$ pred. in the 6 months prior to entering the CUP. Among those patients, 13 (62%) stabilized (FVC change $-18.2 \pm 6\%$ pred. before treatment compared to $2 \pm 1.8\%$ pred. after

treatment) and 8 (38%) continued to progress (FVC change $-15.7 \pm 4\%$ pred. before treatment compared to $-18 \pm 11\%$ pred. after treatment) (fig. 2). Among the patients who were stable under pirfenidone but did not tolerate it, 12 (70%) remained stable (FVC change $7 \pm 8\%$

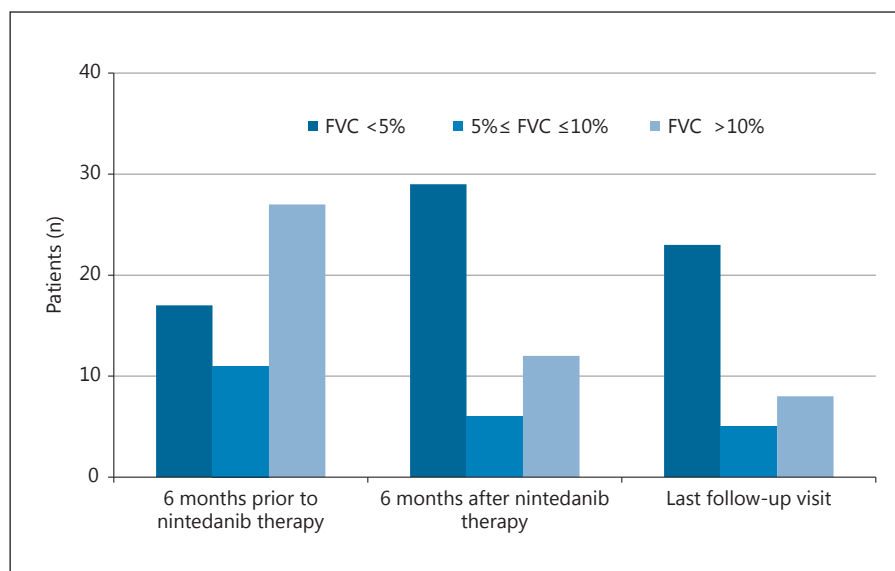


Fig. 3. Categorical decline in FVC 6 months before and after nintedanib treatment and at last follow-up visit. $p = 0.008$, variation in the frequency of response categories over all time points (χ^2 test).

Table 3. Treatment outcome at 6 months and at last follow-up visit

	FVC	DLCO	Radiological assessment	Symptomatic assessment
Six-month follow-up				
Stable disease	30 (62.5)	18 (50.0)	36 (85.7)	22 (57.9)
Progression	18 (37.5)	18 (50.0)	6 (14.3)	16 (42.1)
Missing data	14	26	20	24
Last follow-up visit				
Stable disease	23 (63.9)	15 (78.9)	26 (74.3)	17 (65.4)
Progression	13 (36.0)	4 (21.1)	9 (25.7)	9 (34.6)
Missing data	26	43	27	36

Data are presented as n (%). Stable disease was defined as: FVC decline <5%; DLCO decline <15%, and based on investigator assessment (radiological assessment), and on self-reported symptoms (symptomatic assessment).

pred. before treatment compared to $3 \pm 2\%$ pred. after treatment) and 5 (30%) had progression (FVC change $-18 \pm 20\%$ pred. before treatment compared to $-21 \pm 2\%$ pred. after treatment) under nintedanib.

Figure 3 shows the categorical change in FVC 6 months before and after initiation of nintedanib therapy. After 6 months of nintedanib therapy, more patients had an FVC decline <5% than in the 6 months prior to nintedanib (60 vs. 30%). There was no association between the decline in FVC in the 6 months prior to nintedanib treatment and outcome at 6 months ($p = 0.718$) or at the last follow up visit ($p = 0.417$). The decline in FVC did not differ in patients receiving nintedanib plus N-acetylcysteine from those receiving nintedanib alone (data not shown).

Decline in DLCO

DLCO data were available for 36 patients at 6 months and 19 patients at the last follow-up visit. The outcome of patients is summarized in table 3. At 6 months following initiation of nintedanib, 18 patients (50%) were classified as having stable disease as defined by a decline in DLCO of <15% from baseline. A similar trend for less decline in mean DLCO in patients with stable disease compared to those with disease progression was seen, but no significance was reached due to the low number of measurements available in the follow-up (online suppl. fig. 1).

Additional Outcomes

Radiological outcomes and results from patient-reported symptomatic assessment are shown in table 3. Stable disease, based on radiological assessment by the investigator, was reported in 86% (n = 36/42) of patients at 6 months after treatment and 74% (n = 26/35) of patients at the last visit.

At initiation of nintedanib treatment, the majority of patients (n = 47/56; 84%) had reported a worsening of dyspnea and/or cough within the previous 6 months. Following 6 months of nintedanib treatment, 61% (n = 22/38) of patients considered these symptoms to be stable.

During the observation period, 7 patients experienced acute exacerbations, all of which were classified as 'suspected acute' exacerbation on the basis of proposed criteria [16]. Seven patients died during the observation period; 3 deaths were due to acute exacerbation of IPF, 3 due to pneumonia and 1 had an unknown cause.

Tolerability of Nintedanib Treatment

Side Effects

AEs reported over the observation period are shown in table 2. At least one AE was reported by 76% of patients, while 24% did not report any AE. No severe AEs were reported.

Gastrointestinal AEs were reported by 67% of patients, the most common of which was diarrhea (63%), followed by anorexia (39%) and nausea (26%). As per guidelines provided for the management of AEs, patients experiencing diarrhea were prescribed loperamide. Twenty-six patients (42%) were prescribed loperamide 2 mg on a regular basis for the management of diarrhea. The average loperamide use was 5 tablets (each of 2 mg) per week (range 1–20). Weight loss was reported in half of all patients, with a mean decrease of 3.2 ± 1 (range 0–21) kg over 6 months in those who experienced weight loss.

Elevations in AST/ALT greater than 3 times the ULN were reported in 5 patients (8%). Following temporary treatment discontinuation, these elevations generally returned to within-normal limits, and nintedanib treatment was restarted at a reduced dose without further AST/ALT elevations. Two patients suffered an ischemic stroke during the study period; no other cardiovascular events were reported. No bleeding events were reported.

No significant difference in the incidence of side effects or drug discontinuation was seen in patients who received N-acetylcysteine plus nintedanib versus nintedanib alone (data not shown).

Dose Reduction

In total, 21 patients (34%) required a dose reduction due to AEs; AEs leading to dose reduction are shown in table 2. Of the 21 patients that required dose reduction, 12 had a dose reduction after temporary interruption of treatment and remained at the reduced dose until the end of follow-up; 7 patients had a dose reduction and then permanently discontinued treatment, and 2 patients had a temporary dose reduction followed by a rechallenge to the full dose.

Discussion

To our knowledge, this is the first report on a prospective cohort of patients with IPF treated with nintedanib in the real-life setting. Patients treated within the CUP typically had more advanced IPF than patients treated in clinical trials, and they were older. Nintedanib treatment was associated with disease stabilization within 6 months, as measured by FVC, in the majority (63%) of IPF patients; disease stabilization also occurred in two thirds of patients who previously had progression under pirfenidone (n = 13/21). Nintedanib was generally well tolerated with a manageable AE profile.

Clinical trials are an essential part of drug development, yet the strict inclusion and exclusion criteria employed often result in a patient population that differs from that seen in clinical practice. While there were similarities in the eligibility criteria between the CUP and the INPULSIS clinical trials, there were also important differences. In our cohort, for example, treatment was started on average 5.8 years after IPF diagnosis in comparison to 1.6 years in the INPULSIS trials [6]. Respiratory function at baseline also differed, with mean FVC markedly lower than in INPULSIS (64 vs. 80% pred., respectively) and mean DLCO about 7% lower than in INPULSIS (40 vs. 47% pred., respectively). This clinical setting is also related to the fact that the majority of CUP patients had received a number of previous treatments for IPF, the majority of them had pirfenidone for longer than 1 year, and had a significant decline in the 6 months prior to the start of nintedanib. Patients in the CUP were also permitted to receive N-acetylcysteine treatment, which was an exclusion criterion in INPULSIS. With regard to comorbidities, another important difference is that cardiac disease was present in 13% of patients in the CUP, consistent with previous data in this patient population [17]; the INPULSIS trials specifically excluded patients with myocardial infarction within 6 months or unstable angina within 1

month of randomization. A further comparison between the CUP and INPULSIS cohorts with regard to comorbidities is not possible since the details of comorbidities were not given in the INPULSIS publication.

Although the CUP cohort consisted of patients with moderate/advanced IPF in the majority of patients (63%), FVC stabilized under treatment with nintedanib within 6 months. The reduction in the decline in FVC reported in the CUP cohort was ~58% (reduction from 7.4% before treatment to 3% after 6 months) in patients who stabilized; a ~50% reduction at 12 months was observed in the INPULSIS trials.

Patient self-reporting of symptom improvement and radiological findings were consistent with FVC findings. We did not observe any influence of concomitant medication, especially N-acetylcysteine, or comorbidities on the decline in FVC or disease outcome.

In our cohort, acute exacerbations of IPF (AE-IPF) occurred in 11% of patients compared to 4.9% of patients treated with nintedanib in INPULSIS [6] and were responsible for 42% of deaths during the follow-up period. As we know from the results of the INPULSIS trials, AE-IPF tend to be more frequent in IPF patients with FVC \leq 70% pred. with a frequency ranging from 8 to 15% [18] in treated and untreated patients, respectively. The incidence of AE-IPF in our cohort appears to be in line with these data.

Nintedanib was well tolerated, with most side effects being mild to moderate in intensity. Similar to the results from clinical trials, the most frequent events were gastrointestinal, most commonly diarrhea (62%); this is also in agreement with results from postmarketing surveillance of the safety and tolerability of nintedanib in >3,500 patients treated in the United States [19]. Diarrhea led to treatment discontinuation in 11% of patients treated in the CUP compared to 5% in the INPULSIS trials [6]. The safety profile seen in the CUP is also consistent with a recent communication on a cohort of 20 IPF patients treated with nintedanib from Spain [20], although 7 patients in this dataset had participated in the INPULSIS trials and therefore may have been affected by selection bias. We observed weight loss in 50% of patients (3 kg, on average, over 6 months). The number of patients with weight loss is much higher than observed with nintedanib treatments in the INPULSIS trials (8–11%), although it is similar to the Spanish experience in which 40% of patients (n = 8/20) reported weight loss [20]. Since we observed no significant correlation between weight loss and patient characteristics, previous treatment or response to nintedanib, the potential reasons for this difference are unknown.

With regard to AEs of special interest, the tolerability profile was similar to that previously reported in clinical trials [5, 6], and no new safety signals were detected in this real-world setting; specifically liver enzyme elevations were manageable with dose reductions, and treatment interruptions and monitoring intervals were adequate. It should be considered that patients entering the CUP were required to be ineligible for pirfenidone treatment based on disease severity and/or tolerability potentially resulting in a selection bias towards patients prone to tolerability issues.

There are several limitations to this study. Firstly, as the aim of the CUP was to provide nintedanib to those patients for whom no further approved treatment option was available, comprehensive and structured data collection was not achievable; hence, data were missing for a number of patients, and additional information that may have been of interest was not available. For example, just over three quarters of patients entering the CUP (n = 48) switched from pirfenidone. While patients were required to be ineligible for treatment with pirfenidone, based on disease severity and/or intolerance, the specific reasons for this switch were not documented; however, FVC data suggest that nearly half of these patients (n = 21) experienced disease progression while on pirfenidone. Secondly, we did not use questionnaires to quantify symptoms or changes in quality of life, thus limiting the reliability of our results. In addition, data from 7 patients treated in one center, which have been reported previously [21], have not been excluded from the analysis.

Conclusion

Our results from the real-life clinical setting support findings from previously conducted clinical trials and confirm that nintedanib is effective at slowing disease progression in patients with IPF and is well tolerated.

Members of the German Nintedanib Compassionate Use Consortium

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References

- 1 Hutchinson J, Fogarty A, Hubbard R, McKeever T: Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J* 2015;43:795–806.
- 2 Poletti V, Ravaglia C, Buccioli M, Tantalocco P, Piciocchi S, Dubini A, Carloni A, Chilosi M, Tomassetti S: Idiopathic pulmonary fibrosis: diagnosis and prognostic evaluation. *Respiration* 2013;86:5–12.
- 3 Tzouveleki A, Bonella F, Spagnolo P: Update on therapeutic management of idiopathic pulmonary fibrosis. *Ther Clin Risk Manag* 2015;11:359–370.
- 4 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.
- 5 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.
- 6 Richeldi L, du Bois RM, Raghu G, Azuma A, et al: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
- 7 Crestani B, Ogura T, Pelling K, Quaresma M, Coeck C, Kaye M: Safety and tolerability of nintedanib in patients with IPF: interim analysis from an open-label extension of the INPULSIS® Trials (INPULSIS®-ON). *Am Thorac Soc Int Conf Abstracts* 2015;257:A1020–A1020.
- 8 Crestani B, Ogura T, Pelling K, Coeck C, Quaresma M, Kreuter M, Kaye M: Interim analysis of nintedanib in an open-label extension of the INPULSIS® trials (INPULSIS®-ON). *Eur Respir J* 2015;46.
- 9 Richeldi L, Costabel U, Selman M, Xu Z, Kimura T, Stowasser S, Hallmann C, Du Bois RM: Efficacy and safety of nintedanib in patients with IPF beyond week 52: data from the phase II TOMORROW trial. *Am Thorac Soc Int Conf Abstracts* 2015;257:A1019–A1019.
- 10 Ogura T, Taniguchi H, Azuma A, Inoue Y, Kondoh Y, Hasegawa Y, Bando M, Abe S, Mochizuki Y, Chida K, Kluglich M, Fujimoto T, Okazaki K, Tadayasu Y, Sakamoto W, Sugiyama Y: Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2015;45:1382–1392.
- 11 European Medicines Agency: Guideline on compassionate use of medicinal products, pursuant to article 83 of regulation (EC) No 726/2004. Doc Ref: EMEA/27170/2006.
- 12 Raghu G, Collard HR, Egan JJ, Martinez FJ, et al: 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.
- 13 Standardized lung function testing. Official statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:1–100.
- 14 Clinical exercise testing with reference to lung diseases: Indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. *Eur Respir J* 1997;10:2662–2689.
- 15 Federal Institute for Drugs and Medical Devices (BfArM): Ordinance on the placing on the market of unauthorised medicinal products for compassionate use. *Federal Law Gazette* 2010; part 1 No 37.
- 16 Collard HR, Yow E, Richeldi L, Anstrom KJ, Glazer C: Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respir Res* 2013;14:73.
- 17 Vancheri C, Cottin V, Kreuter M, Hilberg O: IPF, comorbidities and management implications. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;32(suppl 1):17–23.
- 18 Costabel U, Inoue Y, Richeldi L, Collard HR, Tschöpe 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.
- 19 Noth I: Safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis (IPF): data from post-marketing surveillance in the United States (abstract). PFF Summit 2015, Washington, November 12–14, 2015.
- 20 Valenzuela C, Molina M, Diaz Chantar F, Alonso T, Rodriguez Portal JA, Rodriguez Nieto MJ, Laporta R, Linares MJ, Ancochea J: Initial clinical experience with nintedanib for treatment of idiopathic pulmonary fibrosis (IPF): about 20 cases. *Eur Respir J* 2015;46.
- 21 Milger K, Kneidinger N, Neurohr C, Reichenberger F, Behr J: Switching to nintedanib after discontinuation of pirfenidone due to adverse events in IPF. *Eur Respir J* 2015;46:1217–1221.