

# Nintedanib in the management of idiopathic pulmonary fibrosis: clinical trial evidence and real-world experience

Pilar Rivera-Ortega, Conal Hayton, John Blaikley, Colm Leonard and Nazia Chaudhuri 

*Ther Adv Respir Dis*

2018, Vol. 12: 1–13

DOI: 10.1177/  
1753466618800618

© The Author(s), 2018.

Article reuse guidelines:  
sagepub.com/journals-  
permissions

**Abstract:** Idiopathic pulmonary fibrosis (IPF) is a fibrotic interstitial lung disease associated with significant morbidity and mortality. Previously, IPF has been managed using immunosuppressive therapy; however, it has been shown that this is associated with increased mortality. In the last 5 years, two disease-modifying agents have been licensed for use in IPF, namely pirfenidone and nintedanib. Nintedanib is a tyrosine kinase inhibitor with antifibrotic properties that has also been shown to significantly reduce the progression of the disease. The scientific evidence shows that nintedanib is effective and well tolerated for the treatment of IPF in mild, moderate and severe stages of the disease. Real-world experiences also support the findings of previously conducted clinical trials and show that nintedanib is effective for the management of IPF and is associated with reducing disease progression. Gastrointestinal events, mainly diarrhoea, are the main adverse events caused by the treatment. Recent real-world studies also suggest that nintedanib stabilizes lung function till lung transplantation, with no increased surgical complications or postoperative mortality after lung transplantation. In this review, we will discuss the clinical trial evidence and real-world experience for nintedanib in the management of IPF.

**Keywords:** antifibrotic, idiopathic pulmonary fibrosis, interstitial lung disease, nintedanib

Received: 10 June 2018; revised manuscript accepted: 3 August 2018.

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic respiratory disease characterized by progressive fibrotic change to the lung parenchyma leading to loss of function and eventual respiratory failure. It is the most common form of interstitial lung disease with an estimated incidence of 2.8–9.3 per 100,000 per year in Europe and North America.<sup>1</sup> It is associated with high morbidity, manifesting as symptoms of breathlessness and cough frequently leading to significant disability and dependence. Mortality in IPF is high with a reported median survival of approximately 3 years although the clinical course is recognized to be extremely variable.<sup>2,3</sup> The diagnosis should be made by a multi-disciplinary team and requires the presence of a usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT) or surgical lung biopsy and the exclusion of Interstitial lung

disease (ILD) of known cause (e.g. occupational or connective tissue disease related).<sup>4</sup>

The treatment of IPF has evolved considerably in the last decade. Historically, management of IPF primarily involved immunosuppression, with evidence suggesting a combination therapy with prednisolone, azathioprine and N-acetylcysteine as an effective treatment strategy.<sup>5</sup> However, the landmark PANTHER study highlighted that this regimen was associated with poor outcomes in comparison with placebo.<sup>6</sup> Over the past 5 years, the introduction of novel antifibrotic agents in the form of pirfenidone and nintedanib has changed the landscape of IPF and provided hope of improving disease outcomes. In this review, we will discuss the clinical trial evidence and real-world experience for nintedanib in the management of IPF.

Correspondence to:

**Nazia Chaudhuri**  
North West Interstitial  
Lung Disease Unit,  
Manchester University  
NHS Foundation Trust,  
Wythenshawe Hospital,  
Southmoore Road,  
Manchester M23 9LT, UK  
[nazia.chaudhuri@uhsm.nhs.uk](mailto:nazia.chaudhuri@uhsm.nhs.uk)

**Pilar Rivera-Ortega**  
**Conal Hayton**  
**John Blaikley**  
**Colm Leonard**  
North West Interstitial  
Lung Disease Unit,  
Manchester University  
NHS Foundation Trust,  
Manchester, UK

**Nintedanib: efficacy evidence**

Nintedanib (BIBF 1120) is a tyrosine kinase inhibitor which displays anti-angiogenesis properties through blockade of the vascular endothelial growth factor (VEGF) pathway.<sup>7</sup> Initially developed as an anti-tumour agent, it was subsequently recognized that nintedanib possessed antifibrotic activity.<sup>8</sup> The mechanism of action of nintedanib in IPF is thought to be through inhibition of profibrotic mediators including platelet-derived growth factor, fibroblast growth factor and transforming growth factor (TGF)- $\beta$  as well as VEGF, reducing fibroblast activity.<sup>9</sup>

The phase II TOMORROW (To Improve Pulmonary Fibrosis with BIBF 1120) study provided early evidence for the efficacy of nintedanib in IPF patients.<sup>10</sup> This was a multinational randomized placebo-controlled trial assessing the safety and efficacy of nintedanib at four different doses (50 mg once daily, 50 mg twice daily, 100 mg twice daily and 150 mg twice daily) in patients with IPF over a 12-month period. Patients with a diagnosis of IPF as per international consensus guidelines,<sup>4</sup> were included if they were over 40 years of age, had a forced vital capacity (FVC) of 50% or greater and diffusion capacity of the lung for carbon monoxide (DL<sub>CO</sub>) between 30% and 79% predicted. The primary endpoint was annual rate of decline of FVC, with 432 patients randomized. FVC decline in patients receiving highest dose nintedanib (150 mg twice daily) was lower compared with patients receiving placebo (0.06 l *versus* 0.19 l) however failed to reach statistical significance. The rate of FVC decline for the other doses of nintedanib was similar to placebo. Several secondary endpoints in the study did reach clinical significance at the 150 mg twice daily nintedanib dose. These included fewer patients suffering an FVC decline of 10% or 200 ml (23.8% in nintedanib group *versus* 44% in placebo group), improved quality of life (as measured using the St George Respiratory Questionnaire (SGRQ)) and incidence of acute exacerbations.

Following the promising results of the TOMORROW study, two identical phase III studies were performed.<sup>11</sup> The INPULSIS-1 and INPULSIS-2 were multicentre randomized double-blind placebo-controlled trials of nintedanib at a dose of 150 mg twice daily over a 52-week period. Eligibility criteria were similar to that for the TOMORROW study as was the primary endpoint. A total of 1066 patients were

randomized in both studies. In both studies there was a significant reduction in the rate of FVC decline in the nintedanib group compared with placebo. A prespecified pooled analysis of the primary endpoint showed a significant treatment effect with a mean difference of 109.9 ml/year (-113.6 ml/year nintedanib *versus* -223.5 ml/year placebo). The pooled analysis also showed that significantly fewer patients suffered 5% or 10% deterioration in FVC after 52 weeks in the nintedanib group. In contrast with the TOMORROW study, INPULSIS-1 and the pooled analysis failed to show a treatment effect related to acute exacerbations, although in INPULSIS-2 the time to first acute exacerbation and proportion of patients reporting one or more exacerbation was lower in the nintedanib group. Similarly, while INPULSIS-1 and 2 differed in health-related quality of life results, the pooled analysis did not suggest a treatment effect. No significant mortality benefit was noted, although the study was not powered to investigate this.

A pooled meta-analysis of the data for 723 patients taking nintedanib at a dose of 150 mg twice daily in both the TOMORROW trial and INPULSIS trials confirmed a significant treatment effect with annual rate of decline for FVC at -112.4 ml/year for nintedanib and -223.3 ml/year for placebo.<sup>12</sup> There were marginal treatment effects on time to first acute exacerbation and mean change from baseline SGRQ score. There was a trend towards reduction in all-cause mortality and respiratory mortality, but these results were not significant, likely reflecting the insufficient power to assess this as an endpoint in a 12-month period. *Post-hoc* analysis suggests nintedanib use is associated with a lower incidence of acute exacerbations of IPF (as confirmed by an adjudication committee) but no impact on the risk of mortality following an exacerbation.<sup>13</sup> Early evidence from the open label extension of the TOMORROW and INPULSIS studies suggest that the beneficial effects of nintedanib are maintained beyond 12 months.<sup>14,15</sup> It had also been suggested that dose reduction to 100 mg twice daily does not have a significant impact on the efficacy of nintedanib.<sup>16,17</sup>

A prespecified subgroup analysis identified that the efficacy of nintedanib was independent of age (<65 *versus*  $\geq$ 65), gender, smoking status and baseline FVC % predicted ( $\leq$ 70% *versus* >70%).<sup>18</sup>

Efficacy was also noted to be equivalent in patients of white or Asian ethnicity.<sup>18,19</sup> Only two patients of black/African-American ethnicity were included in the INPULSIS trials, although ethnicity data collection from France was not permitted. Additional *post-hoc* analysis indicated patients with preserved lung function (FVC > 90%) receive equal benefit from nintedanib as those with poorer lung function (FVC ≤ 90%).<sup>20</sup> A placebo-controlled trial (ClinicalTrials.org identifier: NCT02788474) recruiting exclusively IPF patient with an FVC ≥ 80% may add further validity to these findings. Additional analysis from INPULSIS-ON, the open label extension of the INPULSIS studies, suggests that nintedanib is equally effective in patients with an FVC of less than 50% predicted, although only 24 such patients were included.<sup>21</sup> Another *post-hoc* study investigated the impact of nintedanib based on diagnostic criteria.<sup>22</sup> The INPULSIS trials included some patients with a possible usual interstitial pneumonia (UIP) pattern on HRCT; traction bronchiectasis and reticulation without honeycombing. A total of 338 patients with possible UIP without surgical lung biopsy were compared with 723 patients with honeycombing on HRCT or confirmation by surgical lung biopsy. The results indicated that the treatment effect of nintedanib was not different between the two subgroups. Similarly, there were no differences in adverse events. A further *post-hoc* analysis examined the impact of statin use on the efficacy of nintedanib in the INPULSIS trials.<sup>23</sup> The treatment effect of nintedanib was consistent between patients receiving and not receiving statins.

### Nintedanib: safety data

Adverse events (AEs) were reported in 95.5% of patients taking nintedanib and 89.6% of patients taking placebo in the INPULSIS trials.<sup>24</sup> Diarrhoea was the most common AE reported with 62.4% of patients in the nintedanib group suffering this. In the TOMORROW study 55.3% of patients receiving nintedanib at 150 mg twice daily suffered diarrhoea.<sup>10</sup> Other commonly reported AEs in the INPULSIS trials included nausea (24.5%), vomiting (11.6%) and weight loss (9.7%).<sup>24</sup> A higher proportion of patients suffered a rise in alanine transaminase (ALT) or aspartate transaminase (AST) above the upper limit of normal (ULN) in the group taking nintedanib compared with placebo with 5% suffering a rise ≥ 3 times ULN compared with 0.7% of

patients taking placebo. The manufacturers advise dose reduction or interruption in this situation. Bleeding events were noted in 10.3% of patients taking nintedanib and 7.8% of patients taking placebo but serious bleeding events were similar. However, patients taking full dose anticoagulation or high-dose antiplatelets were excluded from the INPULSIS trials, so manufacturer recommendations are that nintedanib is used with caution in these patients. Cardiac disorder AEs were similar in both groups (10% in nintedanib *versus* 10.6% for placebo) but myocardial infarction was marginally higher in the nintedanib group (2.7% *versus* 1.2%). The manufacturer suggests caution in patients with a history of ischaemic heart disease. Overall, a higher proportion of patients in the nintedanib group required a dose reduction compared with placebo (27.9% *versus* 3.8%) and 19.3% of patients taking nintedanib discontinued the medication due to AEs compared with 13% of placebo.

Analysis of the pharmacokinetics of nintedanib from the pooled data of the TOMORROW and INPULSIS trials identified that age, body weight, smoking status and Asian ethnicity influence exposure to nintedanib.<sup>25</sup> Exposure does not appear to influence diarrhoea, however a weak association with ALT/AST rise was noted.<sup>26</sup> Nintedanib undergoes substantial first pass metabolism and so a recent phase I pharmacokinetic study examined the safety of nintedanib in patients with liver impairment.<sup>27</sup> This included patients with Child-Pugh A and Child-Pugh B liver impairment and healthy participants. Participants were given 100 mg daily of nintedanib. Nintedanib exposure was two-fold higher in patients with Child-Pugh A and eight-fold higher in patients with Child-Pugh B liver impairment. Manufacturer recommendations are that nintedanib should not be prescribed for patients with moderate to severe liver impairment (Child-Pugh B and C) and a reduced dose of 100 mg twice daily should be used in patients with Child-Pugh A liver impairment. Additional work has examined co-administration of nintedanib with inhibitors and inducers of p-glycoprotein (P-gp).<sup>28</sup> Nintedanib is a substrate of P-gp and exposure levels were analyzed in the presence of ketoconazole, a P-gp inhibitor, and rifampicin, a P-gp inducer. Nintedanib exposure was increased through co-administration with ketoconazole and decreased in the presence of rifampicin. The manufacturers advise close monitoring if nintedanib is

given with P-gp inhibitors and to avoid P-gp inducers if possible. The nintedanib capsule contains lectin so the manufacturers recommend that it not be used in patients who have a soya or peanut allergy.

### Real-world experiences with nintedanib

There are growing data regarding clinical experiences with nintedanib in the real world, in a patient population that are generally older, comorbid and who may not fit the stringent criteria required for clinical trial inclusion. The Compassionate Use Programs (CUP) across Europe facilitated earlier treatment with nintedanib, prior to widespread availability and provided an early opportunity to collect real-world data for IPF patients. Bonella and colleagues<sup>29</sup> observed 62 patients who were enrolled into a German CUP across nine centres. The mean age was 71 (SD  $\pm$  8) with a baseline FVC% predicted of 64 ( $\pm$ 17). The majority of patients had previously been treated with pirfenidone. Patients received treatment for a mean period of 8 ( $\pm$ 4) months. Most patients (63%) receiving nintedanib maintained disease stability at 6 months, defined as  $<$ 5% absolute decline in FVC% predicted from baseline, although data was not available for 14 patients. In keeping with the clinical trials, gastrointestinal symptoms were the most commonly observed AE with 67% of patients reporting these. Diarrhoea was experienced by 63% of patients, anorexia by 39%, nausea by 26% and weight loss in 50%. While the proportion of patients with weight loss was higher than reported in the clinical trials, similar numbers were reported in a small Spanish cohort study.<sup>30</sup> A Greek CUP study involving 94 patients identified similar rates of AEs with diarrhoea (55.3%) the most commonly reported event followed by weight loss (20.2%).<sup>31</sup> 21.2% of patients discontinued the treatment due to AEs. A UK study examined the early experience of nintedanib via a manufacturer-funded 'patient in need' scheme prior to National Institute for Health and Care Excellence (NICE) approval.<sup>32</sup> A retrospective review was performed of 187 patients with multidisciplinary diagnosis of IPF across three centres. Patients in this cohort had a slightly higher baseline FVC% predicted (81.1  $\pm$  19.8), reflecting prescribing restrictions enforced by NICE in the UK. Treatment duration with nintedanib ranged from 6–492 days. Self-reported AEs were common with 72% of patients reporting at least one.

The most frequently reported AE was diarrhoea with 50% of patients reporting at least one episode, followed by nausea (36%), reduced appetite (24%), tiredness (20%) and gastro-oesophageal reflux (18%). The majority of AEs did not require any change to treatment (64%), while 21% resulted in a dose reduction and 13% required treatment discontinuation. Lung function data suggested significantly fewer patients suffered disease progression (defined as  $>$ 5% decline in FVC at 12 months) following initiation of nintedanib, however serial measurements were only available in a selection of patients. An Italian study assessing the impact of another nintedanib CUP recruited patients with significant disease severity.<sup>33</sup> Patients were included in the program if they were ineligible for pirfenidone due to severity of lung function impairment (FVC  $\leq$  50% or DL<sub>CO</sub>  $\leq$  35%). A total of 41 patients were recruited in this retrospective study which was primarily aimed at assessing the efficacy of nintedanib in slowing lung function decline. A significant reduction in the rate of decline of absolute and % predicted DL<sub>CO</sub> at 6 months was observed although there did not appear to be any significant impact on FVC. The authors predicted a 1-year survival of 79% in this cohort.

After licence, two retrospective studies have demonstrated ongoing evidence for the efficacy and safety of nintedanib in a real-world setting. A German study of 64 patients demonstrated that 67% of patients had stable FVC at 6 months following initiation of nintedanib.<sup>34</sup> While diarrhoea remained the most commonly reported AE, a lower proportion of patients (33%) reported the side effect compared with the clinical trials and other real-world studies.<sup>10,11,29,32</sup> A United States (US)-based retrospective study of 57 IPF patients prescribed nintedanib, found that AE rates and drug tolerability were similar in their cohort compared with those previously reported in clinical trials, despite being older, reporting more comorbidities and significant respiratory impairment.<sup>35</sup> They observed discontinuation rates of 26.3% for nintedanib. They performed multivariate analysis to assess predictors of discontinuation of both antifibrotics, of which age  $>$ 70 years [odds ratio (OR): 2.21, 95% confidence interval (CI): 1.04–4.69,  $p$  = 0.04] and history of congestive cardiac failure (OR: 4.54, 95% CI: 1.41–14.55,  $p$  = 0.01) were the only predictive characteristics. They found no association between body mass index (BMI) and antifibrotic discontinuation, however

there is increasing evidence that low BMI is associated with drug intolerance and early treatment termination.<sup>36</sup>

Table 1 summarizes the clinical characteristics and reported adverse outcomes from the published real-world studies. The growing evidence from these studies is that nintedanib is well tolerated and efficacious, similar to that of clinical trials with no new safety signals. These findings are promising as IPF patients in the real-world setting are distinctly different to those enrolled in clinical trials; being older, having more comorbidities and greater lung function impairment at initiation of therapy.

### Nintedanib and lung transplantation

Despite advances in treatment in recent years, lung transplantation remains the only curative option in patients with IPF and this cohort represent the largest group on the transplant waiting list.<sup>37</sup> The safety of nintedanib in the context of lung transplantation has been questioned, with concerns regarding impairment of postoperative healing and risk of bleeding complications. Evidence from recent case series and retrospective cohort studies suggest that concerns are unwarranted. In an examination of a cohort of nine IPF patients, of which two were receiving nintedanib preoperatively, no significant postoperative wound, anastomotic or bleeding complications were reported.<sup>38</sup> An Italian case series of nine patients, all of which were treated with nintedanib, described similar findings.<sup>39</sup> One patient suffered bronchial anastomotic stenosis 4 months after transplant; however significant bleeding and wound healing complications were not observed. In a retrospective German study, 30 patients treated with antifibrotics (7 with nintedanib), were compared with 32 untreated IPF patients undergoing lung transplantation.<sup>40</sup> There were no significant differences in postsurgical revision rates due to bleeding or impaired wound healing between the two groups, while two of the untreated patients suffered anastomotic insufficiency. Most recently, a retrospective analysis of patients attending two European centres assessed outcomes in IPF patients receiving bilateral lung transplants.<sup>41</sup> The authors found no difference in complication rates between IPF patients treated preoperatively with nintedanib ( $n = 10$ ), pirfenidone ( $n = 23$ ) or steroid monotherapy ( $n = 31$ ). The results of these studies are reassuring,

although limited by small cohort sizes and retrospective data collection, and suggest that continued treatment with nintedanib would be advised to preserve lung function while patients await lung transplantation.

### Future directions

Moving forward, ongoing research is focussing on the wider applications of nintedanib in IPF and ILD. One question is whether combination antifibrotic therapy using both nintedanib and pirfenidone may be an option, particularly in patients declining on a single agent. A Japanese phase II double-blind placebo-controlled dose-finding study compared nintedanib alone or in combination with pirfenidone across a range of doses.<sup>42</sup> AEs were slightly more common in the nintedanib 150 mg twice daily/pirfenidone group compared with nintedanib 150 mg twice daily alone, particularly nausea and vomiting, although all AEs were mild to moderate in intensity. The exposure of nintedanib appeared to be reduced by combination with pirfenidone while the pirfenidone exposure was unaffected. Lung function remained stable across all groups. More recently the INJOURNEY study, an exploratory study primarily aimed at investigating the safety and tolerability of combination therapy, has been published.<sup>43</sup> Patients with IPF and an FVC  $\geq 50\%$  were treated with nintedanib at a dose of 150 mg twice daily for 4–5 weeks before being randomized to receive either open label pirfenidone at a dose of 801 mg three times daily or to continue on nintedanib alone for 12 weeks. The primary endpoint was the percentage of patients with on-treatment gastrointestinal AEs with exploratory secondary endpoints assessing change from baseline FVC. Overall, 105 patients were randomized. A total of 34 of the 53 patients receiving combination therapy completed the planned treatment period and 42 of the 51 receiving nintedanib alone. Gastrointestinal side effects were reported in 69.8% of patients with nintedanib and add-on pirfenidone compared with 52.9% of nintedanib alone. Nintedanib dose reduction and discontinuation rates were similar between the two groups. Overall, 35.8% of patients taking pirfenidone required a dose reduction and 35.8% had to discontinue pirfenidone. The total AEs were similar between the two groups (88.7% *versus* 88.2%) with nausea (41.5% *versus* 11.8%) and vomiting (28.3% *versus* 11.8%) being more commonly reported in the add-on

**Table 1.** Real-world studies in IPF patients with nintedanib treatment.

Variables	Real-world studies					
	America			Europe		
	USA	UK	Germany	Greece	Italy	
	Galli and colleagues (n = 57)	Toellner and colleagues (n = 187)	Bonella and colleagues (n = 62)	Brunner and colleagues (n = 64)	Tzouveleki and colleagues (n = 94)	Harari and colleagues (n = 41)
<b>Clinical characteristics</b>						
Male, n (%)	34 (59.6)	142 (76)	48 (77)	55 (85.9)	72 (76.6)	34 (83)
Age-years, mean (SD)	71 (8)	72 (8)	71 (8)	70.3 (6.8)	73.8 (7.8)	70 (8)
Smoking status, n (%)						
• Never smoker	16 (28.1)	35 (28)	24 (39)	20 (31.2)	24 (25.5)	11 (27)
• Former smoker	39 (68.4)	83 (67)	38 (61)	44 (68.8)	70 (94.6) <sup>a</sup>	28 (68)
• Active smoker	2 (3.5)	3 (2)	0 (0)	0 (0)	0 (0)	2 (5)
<b>Comorbidities, n (%)</b>						
• Arterial hypertension	-	56 (30)	19 (31)	28 (43.8)	41 (43.6)	-
• Coronary artery disease	14 (24.6)	43 (23)	8 (13)	21 (32.8)	20 (21.3)	-
• Diabetes mellitus	15 (26.3)	37 (20)	9 (14.5)	16 (25.0)	18 (19.1)	-
• Gastroesophageal reflux disease	31 (54.4)	19 (10)	7 (11)	21 (32.8)	38 (40.4)	-
• Pulmonary hypertension	11 (19.3)	-	-	5 (7.8)	16 (17.0)	-
• Obstructive sleep apnoea syndrome	-	-	4 (6)	9 (14.1)	-	-

Table 1. (Continued)

Variables	Real-world studies						
	America		Europe			Italy	
	USA	UK	Germany	Greece	Italy		
	Galli and colleagues (n = 57)	Toellner and colleagues (n = 187)	Bonella and colleagues (n = 62)	Tzouveleki and colleagues (n = 94)	Harari and colleagues (n = 41)		
• Stroke/transient ischaemic attack	-	-	-	3 (4.7)	-	-	-
• Peripheral artery disease	-	-	-	4 (6.3)	-	-	-
• Atrial fibrillation	-	-	-	7 (10.9)	-	-	-
• Emphysema	12 (21.1) <sup>&amp;</sup>	-	-	9 (14.1)	-	-	-
Concomitant medication at baseline, n (%)							
• Antihypertensive drugs	-	-	19 (31)	28 (43.8)	-	-	-
• Proton pump inhibitors/H <sub>2</sub> blocker	37 (64.9)	-	16 (26)	22 (34.4)	-	-	-
• Acetylsalicylic acid	-	-	12 (19)	18 (28.1)	-	-	-
• Metformin/insulin	-	-	8 (13)	10 (15.6)	-	-	-
• Anticoagulants	7 (12.3)	-	2 (3)	7 (10.9)	-	-	-
• Statins	-	-	-	20 (31.3)	-	-	-
• Acetylsalicylic acid + anticoagulants	-	-	-	3 (4.7)	-	-	-
Oxygen therapy, n (%)	37 (64.9)	43 (35)	5 (8)	-	-	-	-
Prior treatment for IPF, n (%)							
• Pirfenidone	-	-	37 (60)	29 (45.3)	-	-	7 (17.1)
• NAC monotherapy	-	-	9 (14.5)	26 (40.6)	5 (4.7)	5 (12)	

(Continued)

Table 1. (Continued)

Variables	Real-world studies							
	America				Europe			
	USA	UK	Germany	Greece	Italy	Italy	Greece	Italy
	Galli and colleagues (n = 57)	Toellner and colleagues (n = 187)	Bonella and colleagues (n = 62)	Brunner and colleagues (n = 64)	Tzouveleki and colleagues (n = 94)	Harari and colleagues (n = 41)		
• Steroids	10 (17.5)	-	-	10 (15.6)	6 (5.6) <sup>b</sup>	24 (59)		
• Immunosuppressants	5 (8.8)	-	8 (13)	5 (7.8)	4 (3.8)	-		
• Trial medication	-	-	-	3 (4.7)	-	-		
• NAC and pirfenidone	-	-	11 (17) <sup>&amp;&amp;</sup>	1 (1.6)	-	-		
• None	-	-	9 (14.5)	19 (29.7)	-	-		
Time since IPF diagnosis-years, mean (SD)	2.0 (1.6)	-	5.7(2.4)	-	-	1.7 (2.3)		
<b>Baseline lung function</b>								
• FVC%, mean (SD)	66 (17)	81.1 (19.8)	64 (17)	71 (21)	68.1 (18.3)	60.6 (14.6)		
• DL <sub>c0</sub> %, mean (SD)	35 (13)	43.9 (15)	40 (10)	37 (10)	44.4 (14.5)	26.5 (5.7)		
<b>Chest computed tomography pattern</b>								
• Definite UIP pattern, n (%)	18 (31.6)	-	-	51 (79.7)	-	26 (63)		
• Possible UIP pattern, n (%)	15 (26.3)	-	-	13 (20.3)	-	15 (37)		
<b>Histopathology</b>								
• Surgical biopsy, n (%)	10 (17.5)	-	-	24 (37.5)	-	-		



Table 1. (Continued)

Variables	Real-world studies						
	America		Europe			Italy	
	USA	UK	Germany	Greece	Italy		
Galli and colleagues (n = 57)		Toellner and colleagues (n = 187)	Bonella and colleagues (n = 62)	Brunnemer and colleagues (n = 64)	Tzouveleki and colleagues (n = 94)	Harari and colleagues (n = 41)	
• Cryobiopsy, n (%)	-	-	-	4 (6.3)	-	-	-
<b>Adverse events</b>							
• Diarrhoea, n (%)	30 (52.6)	93 (49.7)	39 (62.9)	21 (32.8)	52 (55.3)	-	-
• Nausea/vomiting, n (%)	20 (33.3)	84 (36.4)	16 (25.8)	2 (3.1)	29 (30.8)	-	-
• Weight loss, n (%)		27 (14.4)	31 (50)	5 (7.8)	19 (20.2)	-	-
• Elevated transaminases, n (%)	3 (5.3)	18 (9.6)	5 (8.1)	1 (1.6)	5 (5.3)	-	-
• Dyspepsia/abdominal pain, bloating and wind, n (%)	3 (5.3)	45 (24.1)	4 (6.5)	-	9 (9.5)	-	-
• Reduced appetite/anorexia, n (%)	3 (5.3)	44 (23.5)	24 (38.7)	-	18 (19.1)	-	-
• Bleeding, n (%)	1 (1.8)##	13 (7)	0 (0)	1 (1.6)	2 (2.1)	-	-
• Myocardial infarction, n (%)	0 (0)	21 (0.5)	-	1 (1.6)	2 (2.1)	-	-
Dose reduction, n (%)	12 (21.1)	22 (12)	21 (34)	8 (13)	-	-	-
Drug discontinuation, n (%)	15 (26.3)	39 (21)#	25 (40)**	-	20 (21.2)	-	-

(Continued)

Table 1. (Continued)

Variables	Real-world studies					
	America	Europe			Italy	
	USA	UK	Germany	Greece	Italy	
	Galli and colleagues (n = 57)	Toellner and colleagues (n = 187)	Bonella and colleagues (n = 62)	Brunnemer and colleagues (n = 64)	Tzouveleki and colleagues (n = 94)	Harari and colleagues (n = 41)
Acute exacerbation on therapy, n (%)	6 (10.5)	-	-	11 (17)	-	-
Time to first acute exacerbation-days, mean (SD)	294 (179)	-	-	-	-	-

#30 patients (16%) stopped permanently and 9 patients (9%) paused treatment temporarily.  
 &Combined pulmonary fibrosis and emphysema.  
 #Severe bleeding (bleeding event requiring emergency department evaluation, hospitalization or blood transfusion).  
 &Pirfenidone in combination with NAC or steroids.  
 \*\*Permanent discontinuation of treatment was 7 (11%) and temporary discontinuation was 18 (29%).  
<sup>a</sup>Current smokers or ex-smokers.  
<sup>b</sup>Low dose of prednisolone plus NAC.  
 DL<sub>CO</sub>, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; NAC, N-acetylcysteine; SD, standard deviation; UIP, usual interstitial pneumonia; UK, United Kingdom; USA, United States of America.

group. Rise in ALT/AST > three times ULN was seen in 5.7% of patients receiving add-on therapy but not seen in the nintedanib-only group. Promising efficacy data were observed with an absolute change in FVC of -13.3 ml seen in the add-on group and -40.9 ml in the nintedanib-only group. This was not placebo-controlled and not powered to assess efficacy but suggests that larger studies are warranted.

Active research is investigating the role of nintedanib in other forms of fibrotic ILD. Early murine models suggest a beneficial role for nintedanib in rheumatoid and systemic sclerosis related fibrosis.<sup>44,45</sup> A phase III clinical trial (ClinicalTrials.org identifier: NCT02597933) to assess the efficacy of nintedanib in systematic-sclerosis-related ILD is actively recruiting.<sup>46</sup> In addition the progressive fibrosing ILD Trial (ClinicalTrials.org identifier: NCT02999178) is assessing the efficacy of nintedanib in non-IPF fibrotic ILD including idiopathic nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis, occupational ILD, and connective tissue disease-associated ILD.<sup>47</sup> There is early evidence that nintedanib reduces radiation-induced fibrosis in mice.<sup>48</sup>

### Conclusion

Both clinical trial and real-world data have demonstrated the efficacy and tolerability of nintedanib in the treatment of IPF. Reassuringly real-world data have not demonstrated any new signals such as cardiovascular and bleeding risk. In the limited series, nintedanib appears efficacious and tolerated in patients with severe IPF and poses no increased risk after lung transplantation. The potential role of nintedanib in combination with pirfenidone is the subject of ongoing research and we eagerly await the results of clinical trials in other fibrotic lung diseases.

### Acknowledgements

PR-O and CH wrote the first draft of the manuscript. NC reviewed and edited the manuscript. JB and CL provided proofreading and editing. All authors approved the final version of the manuscript.


### Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### Conflict of interest statement

The authors declare that there is no conflict of interest.

### ORCID iD

Nazia Chaudhuri  <https://orcid.org/0000-0003-3325-6996>

### References

1. Hutchinson J, Fogarty A, Hubbard R, *et al.* Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J* 2015; 46: 795–806.
2. Bjraker JA, Ryu JH, Edwin MK, *et al.* Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998; 157: 199–203.
3. Ley B, Collard HR and King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.
4. Raghu G, Collard HR, Egan JJ, *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.
5. Demedts M, Behr J, Buhl R, *et al.* High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005; 353: 2229–2242.
6. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, *et al.* Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; 366: 1968–1977.
7. Hilberg F, Roth GJ, Krssak M, *et al.* BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res* 2008; 68: 4774–4782.
8. Wollin L, Maillet I, Quesniaux V, *et al.* Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. *J Pharmacol Exp Ther* 2014; 349: 209–220.
9. Wollin L, Wex E, Pautsch A, *et al.* Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 1434–1445.
10. Richeldi L, Costabel U, Selman M, *et al.* Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; 365: 1079–1087.

11. Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
12. Richeldi L, Cottin V, du Bois RM, *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS((R)) trials. *Respir Med* 2016; 113: 74–79.
13. Collard HR, Richeldi L, Kim DS, *et al.* Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. *Eur Respir J* 2017; 49.
14. Richeldi L, Kreuter M, Selman M, *et al.* Long-term treatment of patients with idiopathic pulmonary fibrosis with nintedanib: results from the TOMORROW trial and its open-label extension. *Thorax* 2018; 73: 581–583.
15. Crestani B, Quaresma M, Kaye M, *et al.* Long-term treatment with nintedanib in patients with IPF: An update from INPULSIS®-ON. *Eur Respir J* 2016; 48.
16. Huggins J, Meyer K, Stansen W, *et al.* No effect of dose adjustments on long-term reduction in FVC decline with nintedanib in patients with idiopathic pulmonary fibrosis (IPF). *Chest* 2017; 152.
17. Crestani B, Kolb M, Wallaert B, *et al.* M33 Long-term efficacy of nintedanib is maintained in patients with idiopathic pulmonary fibrosis (ipf) irrespective of dose: subgroup analysis of inpulsis-on. *Thorax* 2017; 72: A255–A255.
18. Costabel U, Inoue Y, Richeldi L, *et al.* Efficacy of nintedanib in idiopathic pulmonary fibrosis across prespecified subgroups in INPULSIS. *Am J Respir Crit Care Med* 2016; 193: 178–185.
19. Taniguchi H, Xu Z, Azuma A, *et al.* Subgroup analysis of Asian patients in the INPULSIS((R)) trials of nintedanib in idiopathic pulmonary fibrosis. *Respirology* 2016; 21: 1425–1430.
20. Kolb M. Nintedanib in patients with idiopathic pulmonary fibrosis and preserved lung volume. *Thorax* 2017; 72: 340–346.
21. Wuyts WA, Kolb M, Stowasser S, *et al.* First data on efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis and forced vital capacity of  $\leq 50$  % of predicted value. *Lung* 2016; 194: 739–743.
22. Raghu G, Wells AU, Nicholson AG, *et al.* Effect of nintedanib in subgroups of idiopathic pulmonary fibrosis by diagnostic criteria. *Am J Respir Crit Care Med* 2017; 195: 78–85.
23. Kreuter M, Costabel U, Richeldi L, *et al.* Statin therapy and outcomes in trials of nintedanib in idiopathic pulmonary fibrosis. *Respiration* 2018; 95: 317–326.
24. Corte T, Bonella F, Crestani B, *et al.* Safety, tolerability and appropriate use of nintedanib in idiopathic pulmonary fibrosis. *Respir Res* 2015; 16: 116.
25. Schmid U, Doege C, Dallinger C, *et al.* Population pharmacokinetics of nintedanib in patients with idiopathic pulmonary fibrosis. *Pulm Pharmacol Ther* 2018; 48: 136–143.
26. Schmid U, Weber B, Dallinger C, *et al.* Relationship between nintedanib exposure and adverse events in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2016; 48.
27. Marzin K, Kretschmar G, Luedtke D, *et al.* Pharmacokinetics of nintedanib in subjects with hepatic impairment. *J Clin Pharmacol*. Epub ahead of print 6 November 2017. DOI: 10.1002/jcph.1025.
28. Luedtke D, Marzin K, Jungnik A, *et al.* Effects of ketoconazole and rifampicin on the pharmacokinetics of nintedanib in healthy subjects. *Eur J Drug Metab Pharmacokinet*. Epub ahead of print 2 March 2018. DOI: 10.1007/s13318-018-0467-9.
29. Bonella F, Kreuter M, Hagemeyer L, *et al.* Insights from the German compassionate use program of nintedanib for the treatment of idiopathic pulmonary fibrosis. *Respiration* 2016; 92: 98–106.
30. Valenzuela C, Molina M, Diaz Chantar F, *et al.* Initial clinical experience with nintedanib for treatment of idiopathic pulmonary fibrosis (IPF): about 20 cases. *Eur Respir J* 2015; 46.
31. Tzouvelekis A, Karampitsakos T, Kontou M, *et al.* Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: a real-life observational study in Greece. *Pulm Pharmacol Ther* 2018; 49: 61–66.
32. Toellner H, Hughes G, Beswick W, *et al.* Early clinical experiences with nintedanib in three UK tertiary interstitial lung disease centres. *Clin Transl Med* 2017; 6: 41.
33. Harari S, Caminati A, Poletti V, *et al.* A real-life multicenter national study on nintedanib in severe idiopathic pulmonary fibrosis. *Respiration* 2018; 95: 433–440.
34. Brunnemer E, Walscher J, Tenenbaum S, *et al.* Real-world experience with nintedanib in patients with idiopathic pulmonary fibrosis. *Respiration* 2018; 95: 301–309.

35. Galli JA, Pandya A, Vega-Olivo M, *et al.* Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: tolerability and adverse drug reactions. *Respirology* 2017; 22: 1171–1178.
36. Weir NA, Poreddy M, Scully A, *et al.* Gender and BMI predict antifibrotic tolerance in IPF. *B103 ILD: Management* A4259–A4259.
37. Kistler KD, Nalysnyk L, Rotella P, *et al.* Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature. *BMC Pulm Med* 2014; 14: 139.
38. Delanote I, Wuyts WA, Yserbyt J, *et al.* Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series. *BMC Pulm Med* 2016; 16: 156.
39. Balestro E, Solidoro P, Parigi P, *et al.* Safety of nintedanib before lung transplant: an Italian case series. *Respirol Case Rep* 2018; 6: e00312.
40. Leuschner G, Stocker F, Veit T, *et al.* Outcome of lung transplantation in idiopathic pulmonary fibrosis with previous anti-fibrotic therapy. *J Heart Lung Transplant*. Epub ahead of print 5 July 2017. DOI: 10.1016/j.healun.2017.07.002.
41. Lambers C, Boehm PM, Lee S, *et al.* Effect of antifibrotics on short-term outcome after bilateral lung transplantation a multi-centre analysis. *Eur Respir J* 2018; 51. DOI: 10.1183/13993003.00503–2018.
42. Ogura T, Taniguchi H, Azuma A, *et al.* Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2015; 45: 1382–1392.
43. Vancheri C, Kreuter M, Richeldi L, *et al.* Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis. Results of the INJOURNEY trial. *Am J Respir Crit Care Med* 2018; 197: 356–363.
44. Redente EF, Aguilar MA, Black BP, *et al.* Nintedanib reduces pulmonary fibrosis in a model of rheumatoid arthritis-associated interstitial lung disease. *Am J Physiol Lung Cell Mol Physiol* 2018; 314: L998–L1009.
45. Huang J, Maier C, Zhang Y, *et al.* Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1941–1948.
46. Distler O, Brown KK, Distler JHW, *et al.* Design of a randomised, placebo-controlled clinical trial of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SENSCIS). *Clin Exp Rheumatol* 2017; 35(Suppl. 106): 75–81.
47. Flaherty KR, Brown KK, Wells AU, *et al.* Design of the PF-ILD trial: a double-blind, randomised, placebo-controlled phase III trial of nintedanib in patients with progressive fibrosing interstitial lung disease. *BMJ Open Respir Res* 2017; 4: e000212.
48. De Ruysscher D, Granton PV, Lieuwes NG, *et al.* Nintedanib reduces radiation-induced microscopic lung fibrosis but this cannot be monitored by CT imaging: a preclinical study with a high precision image-guided irradiator. *Radiother Oncol* 2017; 124: 482–487.

Visit SAGE journals online  
journals.sagepub.com/  
home/tar

 SAGE journals