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ADIS DRUG EVALUATION

Nintedanib: A Review of Its Use in Patients with Idiopathic Pulmonary Fibrosis

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Abstract Nintedanib (Ofev®) inhibits receptor tyrosine kinases implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF). This article reviews the efficacy and tolerability of oral nintedanib in the treatment of IPF, as well as summarizing its pharmacological properties. In the randomized, double-blind, multinational, 12-month INPULSIS-1 and -2 trials in patients with IPF, nintedanib significantly reduced the decline in forced vital capacity versus placebo, indicating a slowing of disease progression. The time to first acute exacerbation was significantly increased with nintedanib in INPULSIS-2, but not in INPULSIS-1, and significantly less deterioration in health-related quality of life was seen with nintedanib in INPULSIS-2, but not in INPULSIS-1. Nintedanib had an acceptable tolerability profile in patients with IPF; gastrointestinal adverse events (diarrhoea, nausea, vomiting) were reported most commonly. In conclusion, nintedanib is an important new option for the treatment of IPF.

Nintedanib in idiopathic pulmonary fibrosis: a summary
Orally administered inhibitor of the receptor tyrosine kinases VEGFR 1–3, FGFR 1–3, PDGFR-α and PDGFR-β
Significantly reduced the decline in forced vital capacity (FVC) in the INPULSIS-1 and -2 trials, indicating a slowing of disease progression
Significantly reduced the risk of progression (i.e. absolute decline in percent predicted FVC of >10 % or death) in the INPULSIS-1 and -2 trials
Significant benefit seen for acute exacerbations in the INPULSIS-2 and TOMORROW trials, but not in the INPULSIS-1 trial
Significantly less deterioration in health-related quality of life seen in INPULSIS-2, but not in INPULSIS-1
Acceptable tolerability profile
Associated with gastrointestinal adverse events (e.g. diarrhoea, nausea, vomiting)

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1 Introduction

Idiopathic pulmonary fibrosis (IPF) is characterized by a progressive loss of lung function with worsening dyspnoea and cough and impaired health-related quality of life (HR-QOL); median survival from the time of diagnosis is ≈2–3 years [1].

Although the pathogenesis of IPF is not fully understood, it is thought that repetitive lung injury (such as that associated with cigarette smoke, industrial dusts, gastro-oesophageal reflux and viral infection) leads to destruction of epithelial alveolar cells [1–4]. Subsequent dysregulation of the repair process results in the proliferation/migration of fibroblasts and their differentiation into myofibroblasts, abnormal extracellular matrix deposition and excessive collagen accumulation in the lung interstitium and alveolar space, leading to progressive fibrosis and stiffening of the lungs [2–4]. Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) mediate various processes, including fibrogenesis and angiogenesis, and are implicated in the pathogenesis of IPF [5]. Thus, the receptor tyrosine kinases VEGF receptor (VEGFR), FGF receptor (FGFR) and PDGF receptor (PDGFR) represent rational targets in IPF.

The tyrosine kinase inhibitor nintedanib (BIBF 1120; Ofev®) was recently approved in the USA [6] and the EU [7] for the treatment of IPF. This article reviews the efficacy and tolerability of nintedanib in the treatment of IPF, as well as summarizing its pharmacological properties. Nintedanib was initially developed as an anticancer agent [8]. However, discussion of the use of nintedanib (Vargatef®) in non-small-cell lung cancer of adenocarcinoma tumour histology, for which it is also approved in the EU [9], is beyond the scope of this review.

2 Pharmacodynamic Properties

Nintedanib is a small molecule, intracellular inhibitor of receptor and non-receptor tyrosine kinases [8, 10, 11]. In vitro, nintedanib inhibited the receptor tyrosine kinases VEGFR 1–3 [50 % inhibitory concentration (IC_{50}) 13–34 nmol/L], FGFR 1–3 (IC_{50} 37–108 nmol/L), PDGFR-α (IC_{50} 59 nmol/L), PDGFR-β (IC_{50} 65 nmol/L) and Flt-3 (IC_{50} 26 nmol/L) [10]. IC_{50} values for nintedanib against the non-receptor tyrosine kinases Lck, Lyn and Src were 16, 195 and 156 nmol/L, respectively [10]. Nintedanib was associated with sustained tyrosine kinase inhibition (e.g. VEGFR-2 was inhibited for ≥32 h in vitro) [10].

By competitively and reversibly inhibiting the adenosine triphosphate binding pocket of the receptor tyrosine kinases VEGFR, FGFR and PDGFR, nintedanib blocks the intracellular signalling needed for the proliferation, migration and transformation of fibroblasts [6, 10, 12]. It is not known if inhibition of Flt-3 and non-receptor tyrosine kinases contributes to the activity of nintedanib in IPF [6].

In vitro, nintedanib significantly ($p < 0.05$) inhibited the PDGF-BB- and VEGF-stimulated phosphorylation of PDGFR and VEGFR, respectively, in lung fibroblasts derived from patients with IPF [13]. Nintedanib also significantly ($p < 0.05$) inhibited the PDGF-BB-, basic FGF- and VEGF-stimulated proliferation of lung fibroblasts derived from patients with IPF or non-fibrotic controls [13], as well attenuating the PDGF- or FGF-2-induced motility of lung fibroblasts from patients with IPF or non-fibrotic controls [14]. In vitro, nintedanib significantly ($p < 0.05$) increased matrix metalloproteinase (MMP)-2 activity and protein levels in lung fibroblasts from patients with IPF or non-fibrotic controls, and significantly ($p < 0.05$) inhibited the secretion of tissue inhibitor of metalloproteinase (TIMP)-2 [13].

Nintedanib inhibited the proproliferative activity of interleukin (IL)-1β in lung fibroblasts from patients with IPF and non-fibrotic controls in vitro [15]. In addition, nintedanib significantly ($p < 0.05$) inhibited collagen secretion induced by the profibrotic cytokine transforming growth factor-β (TGF-β) in lung fibroblasts from patients with IPF in vitro, as well as significantly ($p < 0.05$) inhibiting TGF-β-induced collagen deposition in IPF fibroblasts [13]. Moreover, the TGF-β-induced differentiation of fibroblasts (derived from patients with IPF) to myofibroblasts was inhibited by nintedanib in vitro [11]. Nintedanib also counteracted the profibrotic effects of TGF-β in lung myofibroblasts isolated from patients with IPF [16]. For example, nintedanib prevented the TGF-β-induced reduction in pro-MMP-2 expression, TGF-β-induced collagen secretion and TGF-β-induced proproliferative activity [16].

Nintedanib demonstrated antifibrotic and anti-inflammatory activity in mouse models of bleomycin- and silica-induced pulmonary fibrosis [11]. Nintedanib reduced lung fibrosis and total levels of collagen in the lung, as well as reducing lymphocyte counts, neutrophil counts, IL-1β levels, IL-6 levels, TIMP-1 levels, keratinocyte chemoattractant levels and/or granuloma formation [11].

Administration of nintedanib 200 mg twice daily (supratherapeutic dosage in IPF) for 15 days to patients with advanced renal cell cancer was not associated with clinically relevant prolongation of the corrected QT interval [17].

3 Pharmacokinetic Properties

A nintedanib dose of 100 mg had an absolute bioavailability of 4.7 % in healthy volunteers [6, 7]. The maximum plasma concentration (C_{max}) was reached in ≈2–4 h following administration of nintedanib soft capsules in the fed state [6, 7]. Nintedanib exposure was increased and absorption was delayed in the fed versus the fasted state; nintedanib should be taken with food [6, 7]. Steady state was reached by day 7 in Japanese patients with IPF who received nintedanib [18].

Plasma protein binding of nintedanib was 97.8 % (primarily to albumin) [6, 7]. Following intravenous infusion, nintedanib had a steady-state volume of distribution of 1050 L [6, 7].

Nintedanib undergoes hydrolytic cleavage by esterases yielding the free acid moiety BIBF-1202 [6, 7]. BIBF-1202 then undergoes glucuronidation by uridine 5′-diphosphate glucuronosyltransferase (UGT) 1A1, UGT1A7, UGT1A8 and UGT1A10 to BIBF-1202 glucuronide. Nintedanib is also metabolized by cytochrome P450 (CYP) isozymes (mainly CYP3A4) to a minor extent [6, 7].

Nintedanib is mainly eliminated by faecal/biliary excretion, with 93.4 % of a radiolabelled dose recovered via this route [19]. Renal excretion accounted for only 0.65 % of the dose [19]. Nintedanib had an effective half-life of 9.5 h in patients with IPF [6]. The total plasma clearance of intravenous nintedanib was 1390 mL/min, with a renal clearance of 20 mL/min [6, 7].

The nintedanib dosage does not need to be adjusted on the basis of age, bodyweight or gender, or in smokers [6]. Dosage adjustment is also not required in patients with mild or moderate renal impairment; data in patients with severe renal impairment are lacking [6, 7]. Adjustment of the initial nintedanib dosage is not required in patients with mild hepatic impairment [7], although such patients should be monitored for adverse reactions and dosage adjustment or discontinuation of nintedanib should be considered as needed [6]. Administration of nintedanib to patients with moderate or severe hepatic impairment is not recommended [6, 7].

Nintedanib was a substrate (to a minor extent) for CYP3A4, but nintedanib, BIBF-1202 and BIBF-1202 glucuronide did not inhibit or induce CYP isozymes in vitro [6, 7]. Nintedanib was a substrate for P-glycoprotein (P-gp) and weakly inhibited P-gp in vitro [6, 7]. Nintedanib was not a substrate for organic anion transporter polypeptide (OATP)-1B1, OATP-1B3, OATP-2B1, organic cation transporter (OCT)-2, multidrug resistance-associated protein 2 or breast cancer resistance protein (BCRP), but was a substrate for OCT-1 [6, 7]. Nintedanib weakly inhibited OCT-1 and BCRP in vitro [6, 7].

Patients coadministered nintedanib with potent P-gp inhibitors (e.g. ketoconazole, erythromycin) should be monitored closely for adverse reactions, and coadministration of nintedanib and potent P-gp inducers [e.g. carbamazepine, phenytoin, hypericum (St. John's wort)] should be avoided [6, 7]. Local prescribing information should be consulted for further information regarding these potential drug interactions.

The exposure of pirfenidone was not affected by the coadministration of nintedanib in Japanese patients with IPF [18]. However, with coadministration of pirfenidone, the nintedanib C_{max} and area under the plasma concentration-time curve at steady state decreased to 59 and 68 %, respectively, of the values seen with nintedanib alone [18].

4 Therapeutic Efficacy

The efficacy of oral nintedanib in the treatment of IPF was examined in randomized, double-blind, placebo-controlled, multinational, 12-month trials [20, 21]. The main focus of this section is the phase III INPULSIS-1 and -2 trials [21]. However, results of the phase II, dose-finding TOMORROW trial are also briefly discussed [20].

Inclusion criteria in the TOMORROW and INPULSIS-1 and -2 trials included age ≥40 years, IPF diagnosis within the previous 5 years, forced vital capacity (FVC) of ≥50 % of predicted value, diffusion capacity of the lung for carbon monoxide (DL_{CO}) of 30–79 % of predicted value, and high-resolution computed tomography (HRCT) of the chest performed within the previous 12 months [20, 21]. Patients in TOMORROW also had an IPF diagnosis consistent with American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria and a partial arterial oxygen pressure (when breathing ambient air) of ≥55 mmHg (at altitudes ≤1500 m) or ≥50 mmHg (at altitudes >1500 m) [20].

Patients in the TOMORROW trial received nintedanib 50 mg once daily ($n = 86$), 50 mg twice daily ($n = 86$), 100 mg twice daily ($n = 86$), 150 mg twice daily ($n = 85$) or placebo ($n = 85$) [20]. Patients in the INPULSIS trials were randomized 3:2 to receive nintedanib 150 mg twice daily ($n = 309$ in INPULSIS-1 and $n = 329$ in INPULSIS-2) or placebo ($n = 204$ in INPULSIS-1 and $n = 219$ in INPULSIS-2) [21]. Among nintedanib and placebo recipients, premature discontinuation occurred in 25.2 versus 17.6 % of patients in INPULSIS-1 and in 23.7 versus 20.1 % of patients in INPULSIS-2, at least one intermittent or permanent dose reduction to 100 mg twice daily to manage adverse events as stipulated in the trial protocol occurred in 26.5 versus 4.9 % of patients in INPULSIS-1 and in 29.2 versus 2.7 % of patients in INPULSIS -2 and treatment interruption occurred in 25.6 versus 11.8 % of patients in INPULSIS-1 and in 21.9 versus 8.2 % of patients in INPULSIS-2 [21].

Concomitant therapy with prednisone (up to 15 mg/day or equivalent) was permitted if the dosage had been stable for ≥8 weeks prior to screening [20, 21], although patients receiving high-dose prednisone, acetylcysteine or azathioprine were excluded [21]. Overall, 49 % of patients in the TOMORROW trial [20] and 21 % of patients in the INPULSIS trials [21] were receiving corticosteroids at baseline.

The primary endpoint in all three trials was the annual rate of decline in FVC [20, 21]. Additional prespecified and

post hoc analyses are available as abstracts [22–30] and posters [23, 25, 31], with information also obtained from the EU summary of product characteristics (SPC) [7].

4.1 The TOMORROW Trial

In the TOMORROW trial, the adjusted annual rate of decline in FVC was 0.06 L/year with nintedanib 150 mg twice daily and 0.19 L/year with placebo [$p = 0.06$ using a closed testing procedure for multiplicity correction (primary analysis) and $p = 0.01$ using hierarchical testing (also prespecified)] [20]. No significant differences were seen between lower nintedanib dosages and placebo for the adjusted annual rate of decline in FVC (−0.17 L/year for nintedanib 50 mg once daily, −0.21 L/year for nintedanib 50 mg twice daily and −0.16 L/year for nintedanib 100 mg twice daily) [20].

From baseline to month 12, patients receiving nintedanib 100 or 150 mg twice daily versus placebo had a significantly smaller mean absolute reduction in FVC (−0.13 and −0.06 vs. −0.23 L; $p < 0.01$) or percent predicted FVC (−3.15 and −1.04 vs. −6.00 %; $p < 0.05$) [20]. In addition, significantly fewer recipients of nintedanib 150 mg twice daily versus placebo had a reduction in mean FVC of >10 % or >200 mL (23.8 vs. 44.0 %; $p = 0.004$) [20].

Adjusted mean absolute changes in resting oxygen saturation significantly favoured patients receiving nintedanib 100 or 150 mg twice daily compared with those receiving placebo (+0.06 and −0.18 vs. −1.29 %; $p < 0.05$), and an improvement in total lung capacity was seen with nintedanib 150 mg twice daily (adjusted mean absolute change of +0.12 vs. −0.24 L with placebo; $p < 0.001$) [20].

Both the incidence of acute exacerbations (2.4 vs. 15.7 per 100-patient-years) [risk ratio 0.16; 95 % CI 0.03–0.70; $p = 0.02$] and the adjusted mean change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score (−0.66 vs. +5.46 points; $p = 0.007$) significantly favoured patients receiving nintedanib 150 mg twice daily versus placebo recipients [20].

After completing 52 weeks' treatment, patients could enter a further blinded treatment phase in which those originally assigned to nintedanib continued their dosage (including 48 recipients of nintedanib 150 mg twice daily) and those originally assigned to placebo switched to nintedanib 50 mg once daily ($n = 54$) [22]. The mean total duration of exposure in nintedanib 150 mg twice daily recipients and the comparator arm was 14.2 and 16.8 months, respectively. At week 76 among nintedanib 150 mg twice daily recipients and the comparator arm, the mean absolute reduction in percent predicted FVC was 3.1 versus 6.3 %, the acute exacerbation rate was 3.2 versus 13.4 per 100-patient-years and mortality was 16.3 versus 21.8 % [22].

Based on the results of the TOMORROW trial [20], a nintedanib dosage of 150 mg twice daily was selected for use in the INPULSIS-1 and -2 trials [21].

4.2 The INPULSIS-1 and -2 Trials

Nintedanib 150 mg twice daily reduced the decline in FVC in patients with IPF in the INPULSIS-1 and -2 trials, indicating a slowing of disease progression [21]. The adjusted annual rate of decline in FVC was significantly lower with nintedanib than with placebo in INPULSIS-1 (between-group difference of 125.3 mL/year; 95 % CI 77.7–172.8; $p < 0.001$) and INPULSIS-2 (between-group difference of 93.7 mL/year; 95 % CI 44.8–142.7; $p < 0.001$), as well as in a prespecified pooled analysis of both trials (between-group difference of 109.9 mL/year; 95 % CI 75.9–144.0; $p < 0.001$) [Table 1]. Prespecified sensitivity analyses demonstrated that the results of the primary analysis were robust [21].

The adjusted absolute mean changes from baseline to week 52 in FVC (−95.1 vs. −205.0 mL in INPULSIS-1 and −95.3 vs. −205.0 mL in INPULSIS-2) and percent predicted FVC (−2.8 vs. −6.0 % in INPULSIS-1 and −3.1 vs. −6.2 % in INPULSIS-2) were significantly ($p < 0.001$) smaller in nintedanib than in placebo recipients [21]. In both trials, nintedanib recipients were significantly ($p = 0.001$) more likely than placebo recipients to be stable at week 52 (i.e. have no absolute decline in percent predicted FVC of >5 %) [52.8 vs. 38.2 % in INPULSIS-1 and 53.2 vs. 39.3 % in INPULSIS-2]. In addition, nintedanib recipients were significantly ($p < 0.001$) more likely than placebo recipients to have no absolute decline in percent predicted FVC of > 10 % in INPULSIS-1 (70.6 vs. 56.9 %), but not in INPULSIS-2 (69.6 vs. 63.9 %) [21]. In an additional analysis, nintedanib recipients were significantly ($p < 0.05$) less likely than placebo recipients to experience a relative decline in percent predicted FVC of >5 % (52.1 vs. 66.7 % in INPULSIS-1 and 50.2 vs. 62.6 % in INPULSIS-2) or >10 % (34.3 vs. 50.0 % in INPULSIS-1 and 36.8 vs. 47.5 % in INPULSIS-2) [23].

The risk of progression (i.e. absolute decline in percent predicted FVC of >10 % or death) was significantly reduced with nintedanib versus placebo by 47 % in INPULSIS-1 (24.3 vs. 40.7 %) [hazard ratio (HR) 0.53; 95 % CI 0.39–0.72; $p = 0.0001$], 33 % in INPULSIS-2 (29.8 vs. 42.0 %) [HR 0.67; 95 % CI 0.51–0.89; $p = 0.0054$] and 40 % in the pooled analysis (27.1 vs. 41.4 %) [HR 0.60; 95 % CI 0.49–0.74; $p < 0.0001$] [7].

The time to first acute exacerbation (key secondary endpoint) did not significantly differ between nintedanib and placebo recipients in INPULSIS-1, but was

Table 1 Efficacy of oral nintedanib in idiopathic pulmonary fibrosis in the INPULSIS trials

Study name	Treatment (mg)	No. of mITT pts	Adjusted annual rate of decline in FVC (mL/year)[a]	Incidence of acute exacerbation (% of pts)	Adjusted mean change from baseline in SGRQ total score[b]
INPULSIS-1 [21]	NIN 150 bid	309	114.7**	6.1[c]	+4.34
	PL	204	239.9	5.4	+4.39
INPULSIS-2 [21]	NIN 150 bid	329	113.6**	3.6[c]	+2.80*
	PL	219	207.3	9.6	+5.48
Pooled analysis of INPULSIS-1 and -2 [21]	NIN 150 bid	638	113.6**	4.9[c]	+3.53
	PL	423	223.5	7.6	+4.96

bid twice daily, *FVC* forced vital capacity, *mITT* modified intent to treat, *NIN* nintedanib, *PL* placebo, *pts* patients, *SGRQ* St. George's Respiratory Questionnaire

* $p < 0.05$, ** $p < 0.001$ vs. PL

[a] Primary endpoint, assessed in the mITT population

[b] The SGRQ total score ranges from 0 to 100 (higher scores indicate worse health-related quality of life)

[c] Hazard ratio (NIN vs. PL) for time to first acute exacerbation of 1.15 (95 % CI 0.54–2.42) in INPULSIS-1, 0.38 (95 % CI 0.19–0.77) in INPULSIS-2 and 0.64 (95 % CI 0.39–1.05) in the prespecified pooled analysis

significantly increased with nintedanib versus placebo in INPULSIS-2 (Table 1) [21]. In the prespecified pooled analysis, the time to first acute exacerbation did not significantly differ between nintedanib and placebo recipients (Table 1). However, the time to first adjudicated acute exacerbation (confirmed or suspected) was significantly increased with nintedanib versus placebo, according to the results of a prespecified sensitivity analysis of pooled data from INPULSIS-1 and -2 (HR 0.32; 95 % CI 0.16–0.65; $p = 0.001$). Adjudicated acute exacerbation events occurred in 1.9 % of nintedanib recipients and 5.6 % of placebo recipients [21].

The adjusted mean change from baseline to week 52 in the SGRQ total score (key secondary endpoint) did not significantly differ between nintedanib and placebo recipients in INPULSIS-1 (Table 1) [21]. However, the SGRQ total score increased to a significantly smaller extent (i.e. less deterioration in HR-QOL) with nintedanib than with placebo in INPULSIS-2 (Table 1). In the prespecified pooled analysis, the adjusted mean change from baseline in the SGRQ total score did not significantly differ between nintedanib and placebo recipients (Table 1) [21].

In the prespecified pooled analysis, there was no significant difference between nintedanib and placebo recipients in all-cause mortality (5.5 vs. 7.8 %) [HR 0.70; 95 % CI 0.43–1.12; $p = 0.14$], death because of respiratory causes (3.8 vs. 5.0 %) [HR 0.74; 95 % CI 0.41–1.34; $p = 0.34$] or death occurring between randomization and 28 days after the last dose of study drug (3.8 vs. 6.1 %) [HR 0.68; 95 % CI 0.39–1.19; $p = 0.16$] [21].

In a pooled analysis of the TOMORROW and INPULSIS trials, the all-cause mortality rate over 52 weeks was 5.8 % in patients receiving nintedanib 150 mg twice daily and 8.3 % in placebo recipients (HR 0.70; 95 % CI 0.46–1.08; $p = 0.0954$) and the respiratory mortality rate over 52 weeks was 3.6 and 5.7 % in the corresponding treatment groups (HR 0.62; 95 % CI 0.37–1.06; $p = 0.0779$) [31]. The on-treatment mortality rate was significantly lower in patients receiving nintedanib than in those receiving placebo (3.5 vs. 6.7 %) [HR 0.57; 95 % CI 0.34–0.97; $p = 0.0274$] [31].

4.2.1 Subgroup Analyses

The effect of nintedanib on the annual rate of decline in FVC appeared consistent across various prespecified subgroups [24]. For example, in terms of the annual rate of decline in FVC, the nintedanib treatment effect did not significantly differ between patients with a baseline percent predicted FVC of ≤70 % (difference between nintedanib and placebo of 113.5 mL/year; 95 % CI 51.3–175.7) and those with a baseline percent predicted FVC of >70 % (between-group difference of 109.0 mL/year; 95 % CI 68.2–149.9); there was no significant treatment by subgroup interaction (p-value for interaction of 0.9505) [25]. The annual rate of decline in FVC was also significantly smaller with nintedanib than with placebo in Asian patients ($n = 322$) [between-group difference of 94.1 mL/year; 95 % CI 33.7–154.6] [26].

Nintedanib appeared beneficial in patients with marginally impaired FVC at baseline, according to the results of a post hoc subgroup analysis [27]. The difference between nintedanib and placebo in the adjusted annual rate of decline in FVC was 133.1 mL/year (95 % CI 68.0–198.2) in patients with a baseline percent predicted FVC of >90 % and 102.1 mL/year (95 % CI 61.9–142.3) in patients with a baseline percent predicted FVC of ≤90 %; there was no significant treatment by subgroup

interaction (p-value for interaction of 0.53) [27]. Another post hoc subgroup analysis found that the annual rate of decline in FVC was significantly smaller with nintedanib than with placebo both in patients with a baseline forced expiratory volume in 1 s (FEV_1):FVC ratio of >0.8 (between-group difference of 126.1 mL/year; 95 % CI 81.6–170.6) and those with a baseline FEV_1:FVC ratio of ≤0.8 (between-group difference of 95.5 mL/year; 95 % CI 41.9–149.1) [28].

In terms of the annual rate of decline in FVC, the nintedanib treatment effect did not significantly differ between patients with baseline emphysema (difference between nintedanib and placebo of 102.0 mL/year; 95 % CI 43.2–160.9) and those without baseline emphysema (between-group difference of 115.4 mL/year; 95 % CI 73.8–157.1), according to the results of a post hoc subgroup analysis; there was no significant treatment by subgroup interaction (p-value for interaction of 0.5199) [29].

Another post hoc subgroup analysis demonstrated that in terms of the adjusted annual rate of decline in FVC, the nintedanib treatment effect did not significantly differ between patients with honeycombing on HRCT and/or confirmation of usual interstitial pneumonia on biopsy (difference between nintedanib and placebo of 117.0 mL/year; 95 % CI 76.3–157.8) and those without these features (between-group difference of 98.9 mL/year; 95 % CI 36.4–161.5); there was no significant treatment by subgroup interaction (p-value for interaction of 0.81) [30].

5 Tolerability

Nintedanib had an acceptable tolerability profile in patients with IPF. Nintedanib was associated with gastrointestinal (GI) adverse events in the INPULSIS-1 and -2 trials, with diarrhoea being the most commonly reported GI adverse event (Fig. 1) [21]. Over 90 % of cases of diarrhoea reported in nintedanib recipients were of mild to moderate severity. Diarrhoea in nintedanib recipients is generally manageable (see Sect. 7), with discontinuation because of diarrhoea occurring in 4.5 % of nintedanib recipients and 0 % of placebo recipients in INPULSIS-1 and in 4.3 and 0.5 % of patients in the corresponding treatment groups in INPULSIS-2 [21]. The incidence of diarrhoea increased as the nintedanib dosage increased in the TOMORROW trial [20]. Other commonly reported GI adverse events in the INPULSIS trials were nausea and vomiting (Fig. 1) [21].

Serious adverse events were reported in 31.1 % of nintedanib recipients and 27.0 % of placebo recipients in INPULSIS-1 and in 29.8 and 32.9 % of patients in the corresponding treatment groups in INPULSIS-2 [21]. Fatal adverse events were reported in 3.9 % of nintedanib recipients and 4.9 % of placebo recipients in INPULSIS-1

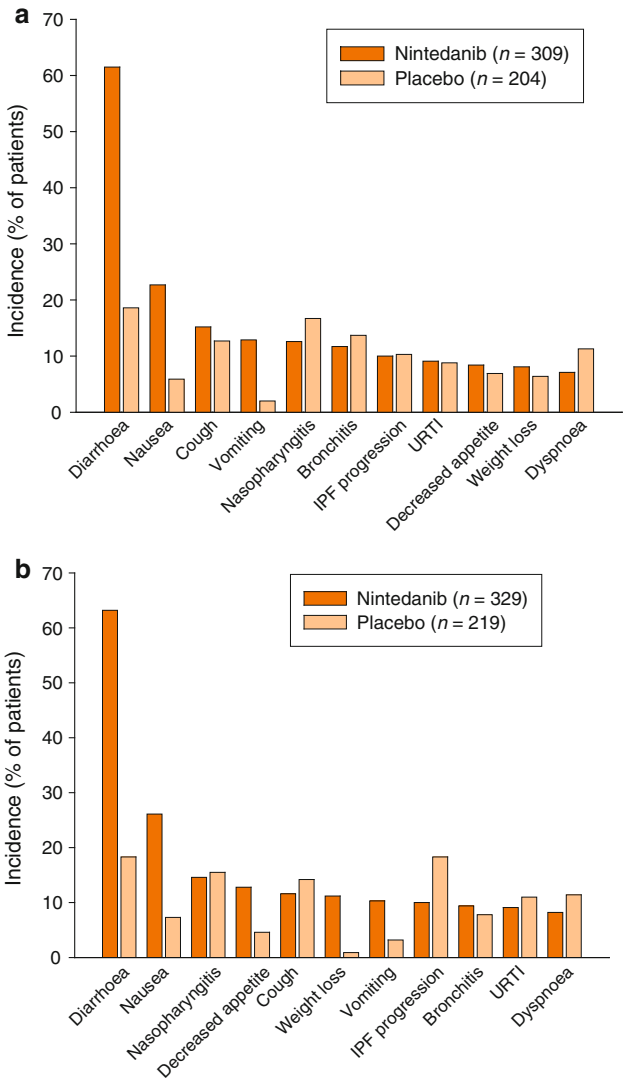

Fig. 1 Tolerability of oral nintedanib in idiopathic pulmonary fibrosis in the placebo-controlled INPULSIS trials [21]. Shown are the most commonly occurring adverse events in **a** INPULSIS-1 and **b** INPULSIS-2. *IPF* idiopathic pulmonary fibrosis, *URTI* upper respiratory tract infection

and in 7.6 and 9.6 % of patients in the corresponding treatment groups in INPULSIS-2 [21].

Alanine aminotransferase and/or aspartate aminotransferase levels increased to ≥3 × the upper limit of normal in 4.9 % of nintedanib recipients and 0.5 % of placebo recipients in INPULSIS-1 and in 5.2 and 0.9 % of patients in the corresponding treatment groups in INPULSIS-2 [21]. None of the nintedanib recipients in the INPULSIS trials met Hy's law criteria [21], and liver enzyme elevations were reversible and were not associated with clinical manifestations of liver injury [7].

In terms of specific adverse events, arterial thromboembolic adverse events [e.g. myocardial infarction (MI)] have been reported in nintedanib recipients [6]. Patients

with a history of cardiac disease (i.e. MI within 6 months or unstable angina pectoris within 1 month of randomization) were excluded from the INPULSIS trials [21]. Among nintedanib and placebo recipients, any cardiac disorder was reported in 9.7 versus 9.3 % of patients in INPULSIS-1 and in 10.3 versus 11.9 % in INPULSIS-2, serious cardiac disorders were reported in 4.5 versus 5.4 % of patients in INPULSIS-1 and 5.5 versus 5.5 % in INPULSIS-2, and fatal cardiac disorders were reported in 0.3 versus 1.0 % of patients in INPULSIS-1 and 0.6 versus 1.8 % in INPULSIS-2. Moreover, among nintedanib and placebo recipients, ischaemic heart disease was reported in 4.2 versus 4.9 % of patients in INPULSIS-1 and in 4.3 versus 3.2 % in INPULSIS-2, serious ischaemic heart disease was reported in 2.6 versus 3.4 % of patients in INPULSIS-1 and in 2.1 versus 1.4 % in INPULSIS-2, and MI was reported in 1.6 versus 0.5 % of patients in INPULSIS-1 and in 1.5 versus 0.5 % in INPULSIS-2 [21].

VEGFR inhibitors may increase the risk of bleeding [7]. Bleeding events were reported in 10 % of nintedanib recipients and 7 % of placebo recipients in the INPULSIS trials, with serious bleeding events reported in 1.4 and 1.3 % of patients in the corresponding treatment groups [7]. Nonserious epistaxis was the most commonly reported bleeding event [7].

The mechanism of action of nintedanib means that patients may have an increased risk of GI perforation [7]. However, GI perforation was reported in only 0.3 % of nintedanib recipients and 0 % of placebo recipients in clinical trials [6].

Following completion of the INPULSIS trials, all patients could receive open-label nintedanib in an extension study [32]. During the extension phase, the mean duration of exposure in patients continuing nintedanib and those initiating nintedanib was 11.8 and 11.2 months, respectively. Among patients continuing and those initiating nintedanib, at least one adverse event occurred in 88.8 versus 93.8 % of patients, at least one serious adverse event occurred in 31.9 versus 29.6 % and adverse events leading to discontinuation of the study drug occurred in 12.6 versus 18.4 %. Diarrhoea, the most commonly reported adverse event, occurred in 56.0 % of patients continuing nintedanib and 56.6 % of patients initiating nintedanib, with discontinuation because of diarrhoea occurring in 2.3 and 6.3 % of patients in the corresponding treatment groups [32].

6 Dosage and Administration

Nintedanib is approved in the USA and the EU for the treatment of IPF [6, 7]. The recommended dosage of nintedanib is 150 mg twice daily, with the doses administered $\approx$12 h apart [6, 7]. Nintedanib can cause fetal harm if administered during pregnancy; the US prescribing information states that nintedanib is rated pregnancy category D [6] and the EU SPC states that nintedanib must not be used during pregnancy [7]. Local prescribing information should be consulted for warnings and precautions related to nintedanib, as well as for information regarding dosage modifications to manage adverse reactions (e.g. diarrhoea, liver enzyme elevations).

7 Place of Nintedanib in the Management of Idiopathic Pulmonary Fibrosis

Historically, treatment options for IPF have been very limited. Indeed, guidelines from the ATS, ERS, Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) that were published in 2011 concluded that there was insufficient evidence to support the use of any specific drug in IPF [1]. However, subsequently published data led to the approval of nintedanib and pirfenidone for IPF, and these agents will most likely transform the management of this disease [33]. An update of the 2011 ATS/ERS/JRS/ALAT evidence-based guidelines for the treatment of IPF gives conditional recommendations for both nintedanib and pirfenidone; however, these therapies are not recommended to be taken together [34].

A decline in FVC in patients with IPF is consistent with disease progression, although there has been controversy as to whether a reduction in FVC decline is associated with reduced mortality [35, 36]. Importantly, a numerical trend towards improved mortality was seen across the pivotal nintedanib and pirfenidone clinical trials which also showed significant reductions in FVC decline [37].

Nintedanib significantly reduced the decline in FVC in patients with IPF in the phase III INPULSIS trials, indicating a slowing of disease progression (Sect. 4). Although infrequent, acute exacerbations of IPF are associated with high mortality [38]. Nintedanib 150 mg twice daily had a beneficial effect on acute exacerbations in the TOMORROW and INPULSIS-2 trials, but not in the INPULSIS-1 trial (Sect. 4). In a prespecified sensitivity analysis of pooled data from the INPULSIS trials, the time to first adjudicated acute exacerbation (confirmed or suspected) was significantly increased with nintedanib versus placebo. Beneficial effects on HR-QOL were seen with nintedanib versus placebo in INPULSIS-2, but not in INPULSIS-1. Mortality did not significantly differ between nintedanib and placebo recipients in the pooled analysis of the INPULSIS trials or in a pooled analysis of the TOMORROW and INPULSIS trials, although the studies were not powered for this endpoint.

It should be noted that patients in the TOMORROW and INPULSIS trials had mild to moderate physiological impairment (i.e. baseline FVC of ≥50 % of predicted value and DL_{CO} of ≥30 %) [33], and data in patients with more severe disease (i.e. FVC of <50 % of predicted value) would be of interest [39]. Studies examining the earlier use of nintedanib (i.e. for the prevention rather than slowing of disease progression) would also be of interest [39].

Nintedanib has an acceptable tolerability profile; GI adverse events occur most commonly and are generally manageable (Sect. 5). At first signs, diarrhoea should be treated with adequate hydration and antidiarrhoeal medication (e.g. loperamide) [6, 7]. Treatment interruption should be considered if diarrhoea persists, after which nintedanib may be restarted at a reduced dosage (100 mg twice daily) or the full dosage (150 mg twice daily). Nintedanib should be discontinued if severe diarrhoea persists despite symptomatic treatment. Supportive measures (e.g. antiemetic therapy) should be used in patients with nausea and vomiting. Dose reduction or treatment interruption may also be needed; nintedanib should be discontinued if severe nausea or vomiting does not resolve [6, 7].

Liver function should be monitored prior to and during treatment with nintedanib; dosage modification or treatment interruption may be needed in nintedanib recipients who experience liver enzyme elevations [6, 7]. Nintedanib should be used with caution in patients who have previously undergone abdominal surgery [6, 7], with the EU SPC recommending that nintedanib be initiated ≥4 weeks after abdominal surgery [7]. Treatment with nintedanib should be discontinued in patients who develop GI perforation [6, 7].

Nintedanib should also be used with caution in patients at higher cardiovascular risk, including those with known coronary artery disease, and interruption of nintedanib treatment should be considered in patients who develop signs or symptoms of acute myocardial ischaemia [6, 7]. Nintedanib should only be used in patients with a known risk of bleeding (e.g. those with a predisposition to bleeding or those receiving full-dose anticoagulant treatment) if the anticipated benefit outweighs the potential risk [6, 7].

Pirfenidone is also available in the USA [40] and the EU [41] for the treatment of IPF; pirfenidone should be administered three times daily with food (total dosage of 2430 mg/day). Although the precise mechanism of action of pirfenidone is unknown, it has shown antifibrotic, anti-inflammatory and antioxidant activity in vitro and in animal models [5]. Pirfenidone reduced the decline in FVC in patients with IPF in three phase III trials (CAPACITY study 004 [42], ASCEND [43] and a Japanese trial [44]), but not in a fourth phase III trial (CAPACITY study 006 [42]). Pirfenidone also reduced all-cause and IPF-related mortality in a pooled analysis [43] of the CAPACITY and ASCEND trials, with the results of CAPACITY censored at day 365. However, convergence of the treatment arms may have occurred beyond week 52 and an analysis including data for the full follow-up period would be of interest [36]. A survival analysis of the CAPACITY and ASCEND trials reported in the US prescribing information found no significant difference between pirfenidone and placebo in all-cause mortality (HR 0.75; 95 % CI 0.51–1.11); this analysis assessed mortality over the study duration and available follow-up period [40]. Pirfenidone had a manageable tolerability profile, with the most commonly occurring adverse events including GI adverse events (e.g. nausea) and dermatological adverse events (e.g. rash, photosensitivity reactions) [45].

It is not possible to establish the relative efficacy of nintedanib versus pirfenidone given the absence of head-to-head trials, and there are currently no validated predictive biomarkers to guide their use in IPF [8, 33]. For the time being, the choice of treatment will most likely be based on patient and physician preference and differences in the tolerability profiles of the drugs [33]. Studies examining the efficacy of combination therapy with nintedanib and pirfenidone would be interest, given that IPF involves multiple fibrotic pathways and there is potential for synergism between these two drugs [33, 39, 46].

In conclusion, nintedanib is an important new option for the treatment of IPF.

Data selection sources: Relevant medical literature (including published and unpublished data) on nintedanib was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 27 May 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Nintedanib, BIBF-1120, Ofev, idiopathic pulmonary fibrosis, IPF, cryptogenic fibrosing alveolitis, usual interstitial pneumonia.
Study selection: Studies in patients with idiopathic pulmonary fibrosis who received nintedanib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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