Effects of nintedanib in patients with IPF: subgroup analysis by Charlson Comorbidity Index (CCI)

Elisabeth Bendstrup,[1] Francesco Bonella,[2] Elena Bargagli,[3] Fabian Caro,[4] Marilyn K Glassberg,[5] Birgit Schinzel,[6] Leticia Orsatti,[6] Ian Glaspole[7]

[1]Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark; [2]Interstitial and Rare Lung Disease Unit, Ruhrlandklinik, University Hospital, Duisburg-Essen University, Essen, Germany; [3]Section of Respiratory Diseases and Lung Transplantation, Department of Clinical Medicine and Neurosciences, Siena University Hospital, Siena, Italy; [4]Hospital María Ferrer, Buenos Aires, Argentina; [5]Miller School of Medicine, University of Miami, Miami, FL, USA; [6]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [7]Department of Allergy, Immunology and Respiratory Medicine, Alfred Health, and Department of Medicine, Monash University, Melbourne, Australia

Introduction

- Patients with idiopathic pulmonary fibrosis (IPF) frequently have comorbidities that may complicate the course of their disease, impair quality of life and reduce survival.[1]
- Nintedanib is an approved treatment for IPF that slows loss of lung function, with a side-effect profile characterised mainly by gastrointestinal events.[2-5]

Aim

- To assess the effects of nintedanib in patients with IPF in subgroups based on comorbidity burden.

Methods

- Data were pooled from five clinical trials in which patients were randomised to receive nintedanib or placebo: the Phase II TOMORROW trial (52 weeks),[2] the two Phase III INPULSIS trials (52 weeks),[3] the INMARK trial (12 weeks)[4] and a Phase IIIb trial (approximately 6 months).[5]
- Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI), which scores 19 comorbidities and age to provide a total score between 0 and 37.[6]
- In subgroups of patients by CCI score at baseline (≤ versus > the median), we analysed the following:
  - Annual rate of decline in FVC (mL/year)
  - Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score[7]
  - Time to first investigator-reported acute exacerbation
  - Time to death
- Exploratory interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib versus placebo between subgroups. No adjustment for multiplicity was made.
- Adverse events are presented descriptively.

Results

Patients

- Data were analysed from 1690 patients. At baseline, the maximum CCI score was 9 and the median was 3; 21.3% had a CCI score >3.

Baseline characteristics in subgroups by CCI score

CCI ≤3 at baseline (n=1330)		CCI >3 at baseline (n=360)
77.1	Male (%)	80.0
65.4 (7.5)	Age (yr)	74.7 (5.9)
59.9	White (%)	71.9
1.4 (1.3)	Years since diagnosis of IPF	1.5 (1.3)
71.9	Former or current smoker (%)	72.2
2868 (831)	FVC (mL)	2764 (755)
82.8 (18.6)	FVC % predicted	84.9 (18.3)
51.2 (16.3)	DLco % predicted	50.4 (16.0)
37.0 (19.5)	SGRQ total score	38.9 (18.6)

Mean (SD) or % of patients.

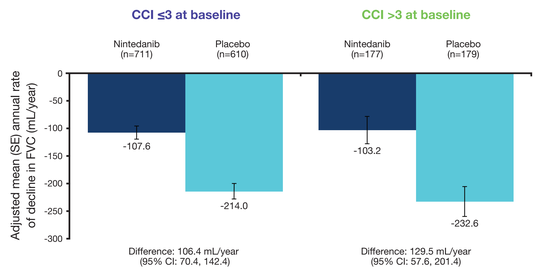
Exposure

- Mean (SD) exposure to nintedanib and placebo was 9.2 (4.0) and 8.3 (4.3) months in patients with CCI score ≤3 at baseline and 8.2 (4.3) and 7.7 (4.4) months in patients with CCI score >3 at baseline, respectively.

Annual rate of decline in FVC (mL/year)

- The treatment effect of nintedanib versus placebo on the rate of decline in FVC (mL/year) was consistent between the subgroups by CCI score at baseline (Figure 1).

Figure 1. *Annual rate of decline in FVC (mL/year) in subgroups by CCI score at baseline*

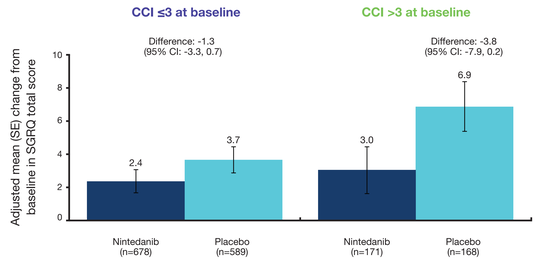


Treatment-by-time-by-subgroup interaction p=0.57.

SGRQ total score

- Over 52 weeks, SGRQ total score increased (worsened) to a greater extent in patients with CCI score >3 than ≤3 at baseline, particularly in the placebo group (Figure 2). The treatment effect of nintedanib on the change from baseline in SGRQ total score was numerically more pronounced in patients with CCI score >3 than ≤3, but no heterogeneity was detected in the treatment effect between the subgroups (p=0.26 for interaction).

Figure 2. *Change in SGRQ total score at week 52 in subgroups by CCI score at baseline*



The SGRQ total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life.[7]
Treatment-by-subgroup interaction p=0.26.

Acute exacerbations and deaths

- No heterogeneity was detected in the treatment effect of nintedanib in patients with CCI score ≤3 and >3 at baseline on time to first acute exacerbation or time to death (Table).

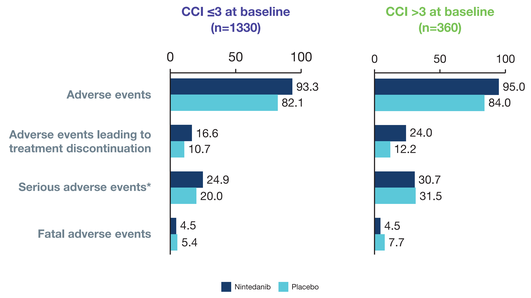
Table. *Time to first acute exacerbation and death in subgroups by CCI score at baseline*

	CCI ≤3 at baseline		CCI >3 at baseline	
	Nintedanib (n=716)	Placebo (n=614)	Nintedanib (n=179)	Placebo (n=181)
Acute exacerbation of IPF, n (%)	26 (3.6)	31 (5.0)	9 (5.0)	15 (8.3)
Hazard ratio (95% CI)	0.60 (0.35, 1.01)		0.49 (0.21, 1.11)	
p-value for treatment-by-subgroup interaction	0.75			
Death, n (%)	34 (4.7)	33 (5.4)	9 (5.0)	13 (7.2)
Hazard ratio (95% CI)	0.69 (0.42, 1.12)		0.58 (0.25, 1.35)	
p-value for treatment-by-subgroup interaction	0.68			

Adverse events

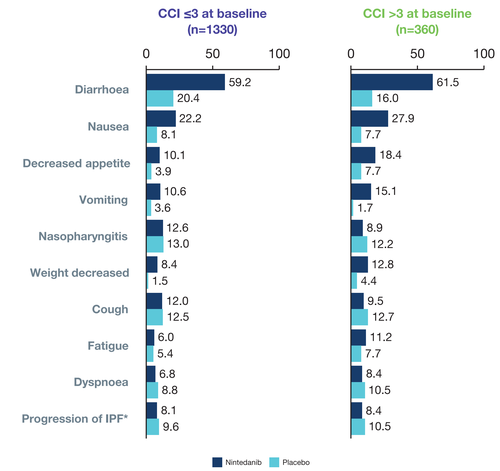
- The adverse event profile of nintedanib was similar in both subgroups (Figures 3 and 4).
- The proportion of patients who discontinued treatment due to adverse events was greater in those with CCI score >3 versus ≤3, driven mainly by gastrointestinal events (Figures 3 and 4).
- Serious adverse events were reported more frequently in subjects with CCI score >3 versus ≤3 in both the nintedanib and placebo groups.

Figure 3. *Adverse events (reported irrespective of causality) in subgroups by CCI score at baseline*



Data are % of patients with ≥1 such adverse event. *Events that resulted in death, were life-threatening, resulted in hospitalisation or prolonged hospitalisation, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were deemed serious for any other reason.

Figure 4. *Most frequent adverse events (reported irrespective of causality) in subgroups by CCI score at baseline*



Data are % of patients with ≥1 such adverse event reported in >10% of patients in either subgroup, coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). *Corresponded to MedDRA term 'IPF', which included disease worsening and acute exacerbations of IPF.

Conclusions

- **The benefit of nintedanib in reducing the rate of decline in FVC was similar between patients with CCI score ≤3 and >3 at baseline.**
- **The rate of treatment discontinuation was higher in patients with a higher comorbidity burden. Proactive management of adverse events is important to help patients with IPF to stay on antifibrotic therapy.**

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Acknowledgements and Disclosures

These trials were funded by Boehringer Ingelheim International GmbH (BI). The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).
The authors did not receive payment for the development of this poster. Editorial support and formatting assistance was provided by Melanie Stephens and Wendy Morris of FleishmanHillard Fishburn, London, UK, which was contracted and funded by BI. BI was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations.

Elisabeth Bendstrup has received grants and personal fees as a speaker/advisory board member from Boehringer Ingelheim, Roche, AstraZeneca, GlaxoSmithKline. Ian Glaspole has received fees as a speaker/advisory board member from Boehringer Ingelheim, Roche, Menarini, Ad Alta, Pulmotect.

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Poster developed for the European Respiratory Society International Congress, 7–9 September 2020.