Long-term effect of nintedanib treatment of idiopathic pulmonary fibrosis in 11 countries of Europe and Asia

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Introduction

Nintedanib (NIN), which was introduced to IPF treatment in 2014, is known to slow down IPF progression; however, data on long term effect of NIN on overall survival (OS) in large IPF cohorts are scarce. We aimed to investigate nintedanib therapy outcome in a large multicentric real-world cohort of IPF patients with various initial stages of the disease.

Methods

Our study included 869 IPF patients treated with NIN and 691 controls with no antifibrotic treatment (NAF) enrolled for the EMPIRE registry in years 2015–2020. We compared OS in both groups with further stratification to mild, moderate, and advanced disease at baseline (FVC predicted >80%, 50–80%, and <50%). The baseline was defined either as NIN therapy initiation (NIN group) or enrolment (NAF group).

Results

The NIN patients had higher BMI, more frequently UIP pattern on HRCT, longer duration of symptoms, and lower FVC, were significantly younger and more frequently never-smokers. We observed better outcomes in the NIN group compared to the NAF group, both in terms of OS (median OS 66.1 vs. 34.7 months, adjusted HR 0.40, P<0.001) and FVC decline (adjusted annual rates -0.053 vs -0.122 l/yr, P=0.001) (Table 1, Figure 1).

Although OS rates were significantly higher in patients with higher baseline FVC predicted (Table 2), a consistent favourable NIN outcome was observed in all three groups: median OS not reached vs 62.2 mo in the FVC >80%, 62.6 vs 23.5 mo in the FVC 50–80%, and 37.2 vs 12.0 mo in the FVC <50% group (Figure 2). This was also confirmed by adjusted HR for mortality (Table 3).

Conclusions

Nintedanib treatment in IPF patients can substantially prolong life expectancy in real world. This effect was evident in all cohorts of patients despite the NAF group having had better initial characteristics. We are aware of the limitations of our real-world study compared to randomized clinical trials; on the other hand, the number of the patients enrolled, and the length of follow-up can support the persuasiveness of the conclusions.

Figure 1. Overall survival of NIN and NAF patients

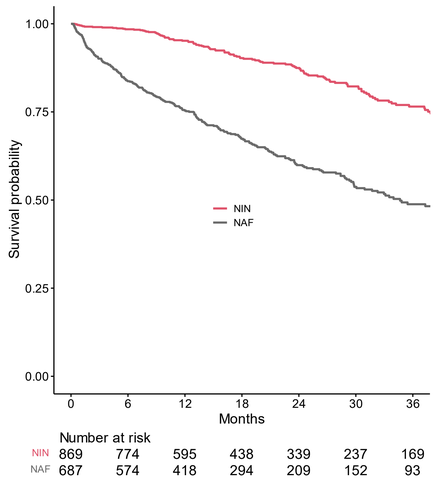

Figure 2. Overall survival of NIN and NAF patients stratified according to their baseline FVC predicted

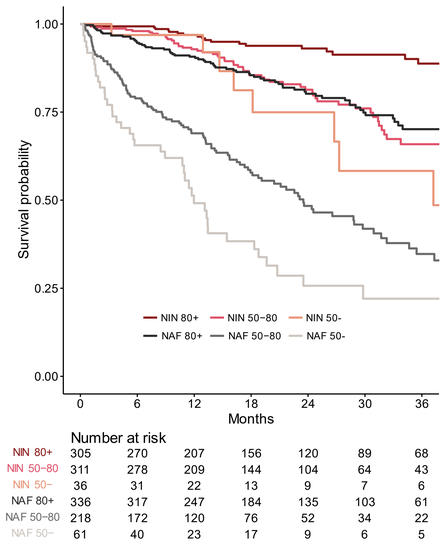

Table 1. Therapy outcomes in NIN and NAF patients (95% CI in parentheses)

	NIN	NAF	P
Median survival (months)	66.1	34.7	<0.001
1-year survival probability	0.952 (0.936; 0.967)	0.754 (0.721; 0.787)	
2-year survival probability	0.875 (0.848; 0.903)	0.599 (0.558; 0.643)	
3-year survival probability	0.765 (0.723; 0.809)	0.488 (0.404; 0.541)	
HR for mortality[1]	0.3 (0.24–0.37)		<0.001
HR for mortality[1] – adjusted[2]	0.4 (0.3–0.53)		<0.001
FVC annual rate of change (l/yr)	-0.051 (-0.073; -0.029)	-0.109 (-0.142; -0.076)	p = 0.004
FVC annual rate of change – adjusted (l/yr)	-0.053 (-0.078; -0.028)	-0.122 (-0.157; -0.088)	p = 0.001

[1] the NAF group is used as a reference group for HR calculation
[2] adjusted for age, sex, height, NYHA, FVC and DLCO at baseline

Table 2. Therapy outcomes in NIN patients with different FVC predicted (%) at baseline (95% CI in parentheses)

	FVC (%) 80+	FVC (%) 50–80	FVC (%) 50-	P
Median survival (months)	not reached	62.6	37.2	<0.001
1-year survival probability	0.969 (0.948; 0.990)	0.929 (0.898; 0.960)	0.969 (0.910; 1.000)	
2-year survival probability	0.931 (0.896; 0.966)	0.814 (0.760; 0.871)	0.750 (0.577; 0.974)	
3-year survival probability	0.888 (0.836; 0.943)	0.659 (0.577; 0.752)	0.583 (0.377; 0.902)	
HR for mortality – FVC (%) 50–80[1]		3.035 (1.868; 4.930)		p < 0.001
HR for mortality – FVC (%) 50–80[1] – adjusted[2]		2.186 (1.242; 3.847)		p = 0.007
HR for mortality – FVC (%) 50-[1]		4.074 (1.817; 9.134)		p < 0.001
HR for mortality – FVC (%) 50-[1] – adjusted[2]		2.370 (0.881; 6.373)		p = 0.087
FVC annual rate of change (l/yr)	-0.061 (-0.095; -0.028)	-0.029 (-0.064; 0.005)	-0.016 (-0.134; 0.103)	p = 0.38
FVC annual rate of change – adjusted (l/yr)	-0.056 (-0.090; -0.023)	-0.022 (-0.056; 0.011)	-0.028 (-0.151; 0.095)	p = 0.374

[1] the FVC (%) 80+ group is used as a reference group for HR calculation
[2] adjusted for age, sex, height, NYHA and DLCO at baseline

Table 3. Difference of hazard ratios associated with mortality in NIN and NAF patients with different FVC predicted (%) at baseline (adjusted for age, sex, height, NYHA and DLCO at baseline; 95% CI in parentheses)

	HR[1] for mortality (95% CI)	P[2]	P[3]
FVC (%) 80+	0.344 (0.208; 0.570)	< 0.001	
FVC (%) 50–80	0.438 (0.306; 0.628)	< 0.001	0.735
FVC (%) 50-	0.377 (0.153; 0.929)	0.034	

[1] the NAF group is used as a reference group for HR calculation
[2] difference nintedanib vs. no antifibrotics
[3] differential effect of nintedanib between FVC (%) subgroups

Acknowledgements

The study was supported by Boehringer Ingelheim; the EMPIRE registry is supported by F. Hoffman-La Roche and Boehringer Ingelheim. The funders had no role in the design, analysis or interpretation of the results in this study. The funders were given the opportunity to review the manuscript for medical and scientific accuracy as it relates to substances, as well as intellectual property considerations.

The study was approved by Ethics Committee of Thomayer Hospital and Institute for Clinical and Experimental Medicine, Prague, Czech Republic, and local ethics committees in individual countries and sites involved in the registry.

Disclosures

MV received fees from Boehringer Ingelheim and Roche for consultancy, advisory boards and presentations, and an independent grant from Roche; MSte received fees for advisory boards from Boehringer Ingelheim, Roche and Teva; NM received fees for advisory boards and presentations from Boehringer Ingelheim and Roche; KL received payments for lectures, advisory boards, research and congress participation from Boehringer Ingelheim and Roche; JTT was an advisory board member and received fees for lectures from Boehringer Ingelheim and Roche; MStu received research grants from Boehringer Ingelheim and Roche; DJ was an advisory board member and received fees from Boehringer Ingelheim and Roche; NS was an advisory board member for Boehringer Ingelheim; VM, MH, SL, OM, and JG declare no conflicts of interest.

Presented at the ERS International Congress 2022, 4–6 September 2022, Barcelona, Spain