Healthy survivor bias in patients with idiopathic pulmonary fibrosis in clinical registries

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Introduction

Antifibrotic treatment prolongs survival of patients with idiopathic pulmonary fibrosis (IPF). However, imperfect follow-up of patients in real-world registries may obscure the benefit due to differences in patient groups. We explored whether patients with an eventually long follow-up, who were either treated with pirfenidone (PIR) or did not receive antifibrotics (other treatment, OT), had different input characteristics than patients whose follow-up was not long enough (death, treatment termination, loss to follow-up). Aim of the analysis was to investigate a hypothesis that the pirfenidone therapy supports longer survival of patients with less favourable health conditions and clinical characteristics, while only the patients with more favourable prognosis remain under longer follow-up if they do not receive antifibrotic therapy.

Methods

The study included patients from the EMPIRE registry enrolled between 2015 and 2018. Index date (baseline) was defined as either PIR therapy initiation (PIR group), or enrolment for the registry (OT group). Baseline FVC (%) and DLCO (%) were analysed in patients, who were followed up for up to 24 months (mo). End of follow-up was defined as loss to follow-up, death, or pirfenidone therapy termination (in the PIR group only)

Results

There were 769 patients in the PIR group and 633 in the OT group at baseline; baseline FVC (%) 73.7 vs 83.2, DLCO (%) 46.3 vs 51.0. In the PIR group, 345 and 126 pts remained under follow-up after 12 and 24 mo; in the OT group, 208 and 62 pts after 12 and 24 mo. Patients from the OT group remaining under follow-up after 12 and 24 mo had the most favourable baseline characteristics – baseline FVC (%) 90.2 (remaining after 12 mo) and 92.7 (24 mo) and DLCO (%) 56.3 (12 mo) and 59.0 (24 mo). The shift was less apparent in the PIR group – baseline FVC (%) 73.8 (12 m) and 72.6 (24 m) and DLCO (%) 48.0 (12 m) and 51.2 (24 m) (Table 1).

In the PIR group, patients who either discontinued or remained under follow-up after 6 and 12 mo from baseline had similar baseline FVC and DLCO values. On the other hand, patients in the OT group who discontinued in their follow-up after 6 or 12 mo had significantly lower initial FVC values than those who remained under follow-up (Figure 1).

Conclusions

There was a different drop-out of patients in the PIR and OT group, with a higher drop-out rate of patients with less favourable baseline FVC (%) and DLCO (%) in patients without antifibrotic therapy. Interpretation of real-world data that describe lung functions must therefore be always cautious, particularly in a longer time frame, taking into consideration the real number of patients remaining under follow-up.

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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.

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Table 1. Baseline lung function parameters of patients, who remained under follow-up at various time points (association of early drop-out of patients with mean values of baseline values of lung parameters)

Endpoint	Follow-up	Pirfenidone		Other treatment	
		Patients under f-up	Mean value (SD)	Patients under f-up	Mean value (SD)
FVC predicted (%)	0 months	769	73.7 (15.8)	633	83.2 (24.2)
	6 months	567	73.9 (15.7)	403	86.5 (22.9)
	12 months	345	73.8 (15.9)	208	90.2 (22.9)
	18 months	202	72.8 (14.4)	124	89.6 (23.9)
	24 months	126	72.6 (12.7)	62	92.7 (25.3)
DLCO at baseline (%)	0 months	769	46.3 (13.8)	633	51.0 (21.8)
	6 months	567	46.3 (13.3)	403	53.0 (21.4)
	12 months	345	48.0 (13.0)	208	56.3 (20.5)
	18 months	202	48.7 (13.1)	124	57.2 (19.9)
	24 months	126	51.2 (12.7)	62	59.0 (20.0)

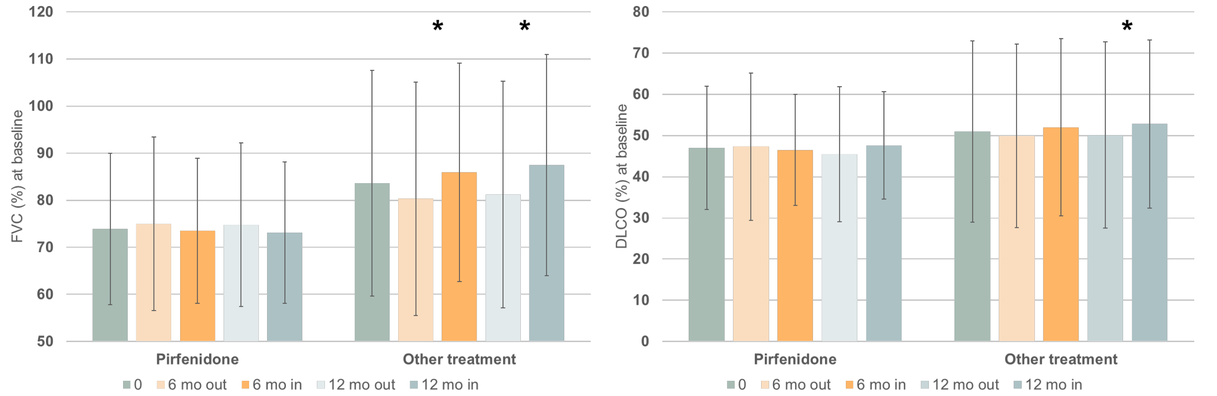

Figure 1. Comparison of baseline values of FVC predicted (left) and DLCO predicted (right) of patients who discontinued ("out") or remained ("in") under follow-up after 6 and 12 months from baseline. Statistically significant difference between two respective groups is indicated by asterisk.