Risk factors for disease progression in idiopathic pulmonary fibrosis

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ABSTRACT

In this retrospective study of a randomised trial of simtuzumab in idiopathic pulmonary fibrosis (IPF), prodromal decline in forced vital capacity (FVC) was significantly associated with increased risk of mortality, respiratory and all-cause hospitalisations, and categorical disease progression. Predictive modelling of progression-free survival event risk was used to assess the effect of population enrichment for patients at risk of rapid progression of IPF; C-index values were 0.64 (death), 0.69 (disease progression), and 0.72 (adjudicated respiratory hospitalisation) and 0.76 (all-cause hospitalisation). Predictive modelling may be a useful tool for improving efficiency of clinical trials with categorical end points.

INTRODUCTION

Assessment of new therapies for idiopathic pulmonary fibrosis (IPF) requires long clinical trials with large populations due to marked heterogeneity of IPF progression. Improved prediction of IPF progression could streamline trial design, allowing for enrichment of vulnerable patients at risk for rapid disease progression.[1–3]

This post hoc analysis of data from a large phase II trial of the lysyl oxidase-like 2 (LOXL2) inhibitor simtuzumab (RAINIER)—which terminated for lack of efficacy[4]—assessed the relationship between variables, including change in forced vital capacity in weeks 1–14 (ΔFVC 0–14) and either categorical risk of disease progression or subsequent change in forced vital capacity (ΔFVC) over 12 months. Based on these results, a predictive model for progression-free survival (PFS) events was developed to approximate the influence of enrichment for risk on the RAINIER population.

MATERIALS AND METHODS

Details of the RAINIER study of simtuzumab in IPF (NCT01769196) conducted from March 2011 until January 2016, and terminated due to lack of efficacy, were previously reported[4] and summarised in online supplementary file 1. This analysis included simtuzumab-treated and placebo-treated patients. Progression of IPF was defined as ≥10% relative decline in FVC% predicted from baseline with ≥5% absolute change, and PFS as time to progression or death.

Multivariate analysis of ΔFVC from weeks 14–66 was developed using age, body mass index, smoking status, geographical region, duration of IPF diagnosis, FVC, residual volume, diffusing capacity of the lung for carbon monoxide (DLCO)% predicted, 6 min walk distance (6MWD), St George's Respiratory Questionnaire (SGRQ), serum LOXL2 level and quantitative high-resolution CT (HRCT) fibrosis score. Additional variables included change in longitudinal variables (FVC, DLCO% predicted, SGRQ, and 6MWD) from weeks 0–14. Multivariate survival analysis of death, categorical disease progression, and respiratory and all-cause hospitalisation was developed with the baseline variables and ΔFVC 0–14. Model development and performance details are provided in online supplementary file 1. The prodromal period included week 14 postbaseline measurements and provided ≥52 weeks of subsequent follow-up for the majority of patients.

RESULTS

At 14 weeks, 501/544 RAINIER patients remained on study. Online supplementary table 1 summarises patient baseline and clinical characteristics. The majority of patients were male, former smokers, aged 68.1±7.3 years and from North America.

Early rapid decline in lung function (FVC 0–14 of ≥100 mL; 210 patients) was associated with increased mortality risk (HR 1.31, 95% CI 1.05 to 1.64, p=0.017), adjudicated respiratory hospitalisation (HR 1.22, 95% CI 1.08 to 1.38, p=0.001) and categorical disease progression (HR 1.95, 95% CI 1.75 to 2.17, p<0.0001). Over a 52-week period spanning study weeks 14 and beyond, FVC at week 14 and change in FVC and SGRQ for the prodromal period of weeks 0–14 (ΔFVC 0–14) were negatively associated with ΔFVC modelled as a continuous variable (online supplementary table 2).

Key results for modelling the outcomes of categorical disease progression, death, all-cause hospitalisation and adjudicated respiratory hospitalisation are provided in table 1. Larger decline in ΔFVC 0–14 was associated with increased risk of categorical events; baseline FVC was not a significant predictor of risk of first all-cause hospitalisation.

Early rapid decline in lung function was associated with slower subsequent decline in FVC (R=−20.50 mL, p<0.001); ΔFVC beyond week 14 was negatively associated with ΔFVC 0–14 (estimate=−0.205, p<0.001) (table 1).

Applying the estimated parameters from the

Table 1 Models for categorical disease progression, death, first all-cause hospitalisation and adjudicated respiratory hospitalisation

Outcome	Stepwise selected baseline predictors	HR	95% CI for HR	C-index	95% CI for C-index
Categorical disease progression	Baseline FVC (required)*	0.98	(0.96 to 1.00)	0.69	(0.64 to 0.73)
	ΔFVC, weeks 0–14*†	0.51	(0.46 to 0.57)		
	Baseline FEV_1/FVC	1.03	(1.01 to 1.06)		
	Baseline HRCT score	1.02	(0.01 to 1.03)		
Death	Baseline FVC (required)*	0.97	(0.90 to 1.04)	0.64	(0.54 to 0.73)
	ΔFVC, weeks 0–14*†	0.76	(0.61 to 0.95)		
	Baseline DLCO% predicted	0.95	(0.91 to 1.00)		
	Baseline FEV_1/FVC	1.11	(1.04 to 1.18)		
	Log (LOXL2)	2.96	(1.26 to 6.94)		
	Log (IPF duration of diagnosis)	0.63	(0.42 to 0.95)		
All-cause hospitalisation	Baseline FVC (required)*	1.01	(0.98 to 1.04)	0.76	(0.73 to 0.79)
	BMI	0.95	(0.91 to 0.99)		
	Baseline DLCO% predicted	0.97	(0.95 to 0.99)		
	Baseline FEV_1/FVC	1.03	(1.00 to 1.07)		
	Baseline SGRQ score	1.02	(1.01 to 1.02)		
	Baseline HRCT score	1.02	(1.01 to 1.04)		
Adjudicated respiratory hospitalisation	Baseline FVC (required)*	1.00	(0.96 to 1.03)	0.72	(0.67 to 0.77)
	ΔFVC, weeks 0–14*†	0.82	(0.73 to 0.93)		
	Baseline DLCO% predicted	0.95	(0.93 to 0.97)		
	Baseline FEV_1/FVC	1.06	(1.02 to 1.09)		
	Baseline SGRQ score	1.02	(1.01 to 1.03)		

*Variable analysed in 100 mL increments.
†ΔFVC analysed in 100 mL increments, with HR of <1. In the Abstract and Results sections, ΔFVC was analysed in 100 mL decrements, with HR >1.
BMI, body mass index; DLCO, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in one second/forced expiratory volume; ΔFVC, change in forced vital capacity; FVC, forced vital capacity; HRCT, high-resolution CT; IPF, idiopathic pulmonary fibrosis; LOXL2, lysyl oxidase-like 2; SGRQ, St George's Respiratory Questionnaire.

PFS model (online supplementary file 1) to patients enrolled in RAINIER, we obtained an average probability of a PFS event at 1 year of 47.8%; 517 patients meeting RAINIER eligibility criteria are needed to reach 247 events, a threshold selected based on power calculations of RAINIER.[4] Based on this model, 93.2% of RAINIER-eligible patients have a >10% probability of experiencing a PFS event on placebo; for 17.6% of RAINIER-eligible patients, the probability of a PFS event is >80% (table 2). With increased enrichment, the number of patients required to achieve the target event rate decreases; however, screen failure rate increases (table 2). Comparing the observed PFS event rate in RAINIER to model predictions, incremental enrichment from a 60% probability threshold to an 80% probability threshold increased the observed proportion of patients with PFS events by 4.7%; however, the number of patients required at screening increased by 81%.

DISCUSSION

In this retrospective analysis, patients with IPF with accelerated decline over a period of 14 weeks are at increased risk of categorical adverse events (10% decline in FVC, all-cause and respiratory hospitalisations or death) over the subsequent 52 weeks, relative to patients with a slower rate of decline (table 1). In future trials using composite end points of categorical events, rate of decline over this short prodromal period could be used to enrich or stratify a study population with patients at increased risk of events indicative of disease progression. Table 1 suggests baseline HRCT score may further enrich prediction. However, if linear decline in FVC as a continuous variable is the primary end point, the prodromal rate of decline over 14 weeks is not apparently useful for stratification or enrichment. Here, more rapid decline in FVC is associated with increased risk of categorical adverse outcomes (but not linear decline), consistent with analysis of the pirfenidone registration trials, despite significant differences in inclusion criteria between those trials and RAINIER.[5–7]

Table 2 Model of number of patients meeting the inclusion criteria required to meet target event rate decreases

Strategy	Proportion of patients with predictive probability of experiencing a PFS event at year 1 on placebo in RAINIER (%)	Observed proportion of patients with PFS events at year 1 in the risk group in RAINIER (%)	Number of patients eligible for RAINIER required at screening to identify one patient in the risk group, n	Number of patients in risk group needed to identify 1 PFS event in that risk group, n	Total number of RAINIER-eligible patients needed to reach target event rate (247 events in risk group), n
RAINIER overall	47.8	47.1	–	–	517
Model-predicted probability threshold, percentile					
>10%	93.2	49.3	1.07	2.03	538
>20%	80.4	55.3	1.24	1.81	556
>30%	67.7	61.0	1.48	1.64	599
>40%	53.7	66.4	1.86	1.51	693
>50%	42.2	73.6	2.37	1.36	796
>60%	33.6	83.0	2.98	1.20	886
>70%	25.5	88.1	3.92	1.14	1100
>80%	17.6	87.7	5.68	1.14	1601

PFS, progression-free survival.

Predictive modelling-based enrichment of RAINIER-eligible patients for rapid progression decreases the number of patients required to observe a target number of PFS events but increases screen failure rate. High screen failure rates may increase enrolment duration and number of sites required, making excessive enrichment counterproductive for overall trial efficiency. Enrichment for high risk of progression could also better represent patients with severe IPF who may be excluded from clinical trials. Further work is needed to define optimal inclusion criteria for IPF clinical trials. Study limitations include the following: this was a retrospective analysis, patients with mild lung function impairment were excluded, and placebo-treated and simtuzumab-treated patients were combined.

Rapid prodromal decline in FVC appears less useful in predictive modelling of subsequent declinc in FVC as a continuous variable in patients with IPF. Predictive models based on clinical trial data incorporating recent decline in FVC may improve trial design using categorical efficacy end points.

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