



REVIEW

Challenges in idiopathic pulmonary fibrosis trials: the point on end-points

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ABSTRACT: Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias and is associated with both a variable clinical course and a poor prognosis. Investigators involved in clinical trials and clinicians reviewing the IPF literature are confronted with daunting challenges in selecting reliable outcome measures, interpreting the clinical and statistical importance of these findings, and applying this knowledge to the clinical care of their patients. In order to evaluate the efficacy of new treatment regimens, a number of studies have been performed, employing a range of clinical and surrogate end-points. In most studies, the primary end-point consists of a single outcome measure. A desirable single clinical end-point for IPF should be reliable, valid, responsive to changes in disease status, clinically meaningful, predictive of clinical outcome and responsive to treatment effect of a given intervention. Proper consideration and effective choice of outcome measures used in IPF studies will help establish effective and achievable drug development programmes and will enable clinicians and investigators to make informed critical decisions in recommending a treatment regimen to their IPF patients.

KEYWORDS: End-points, forced vital capacity, idiopathic pulmonary fibrosis, idiopathic pulmonary fibrosis trials, 6-min walk test

Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening interstitial lung disease (ILD). It has a significant impact on the quality of life of patients, and the prognosis is worse than most other ILDs [1–3].

In IPF, lung parenchyma architecture is irreversibly disrupted with resulting functional impairment [2]. No cases of spontaneous regression have been observed; presumably because there is no way the fibrotic change can be reversed. However, within this framework, there is a high degree of inter-individual variability with respect to disease extent, disease progression and survival time [2, 4]. One study has shown that the clinical course of patients with mild-to-moderate IPF is characterised by: 1) minimal physiological deterioration as measured by forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DL_{CO}) and alveolar–arterial oxygen tension difference ($P_{A-a}O_2$); 2) frequent hospitalisations for respiratory disorders; and 3) an acute, rapid and fatal deterioration of lung disease in almost half of the patients who die from an IPF-related cause [5]. The marked variability in the extent and rate of disease

progression from one individual to the next means that early and accurate diagnosis and early referral may give the best chance of optimal therapy, as response rates may be higher when treatment is initiated before the development of irreversible fibrosis [1, 2]. As the diagnosis of definite IPF is frequently made without surgical lung biopsy, it is relevant to ask whether the method of diagnosis could influence treatment outcomes, *i.e.* whether it could act as bias for any end-point. It has been demonstrated in a well-defined cohort of IPF patients that neither disease severity, as assessed by baseline FVC % predicted, nor rate of disease progression, as assessed by change in FVC % predicted, were significantly different in patients who had a surgical lung biopsy compared with those who did not. Moreover, the treatment effect for pirfenidone was similar in patients with and without a surgical lung biopsy [6].

PRIMARY END-POINTS

Reliable, objective parameters to assess disease progression and treatment response are currently poorly defined and not fully validated. Thresholds for change in several lung function parameters

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Received:

Feb 14 2011

Accepted after revision:

April 04 2011

PROVENANCE

Publication of this peer-reviewed article was supported by InterMune Inc., Brisbane, CA, USA (article sponsor, *European Respiratory Review* issue 121).

European Respiratory Review
Print ISSN 0905-9180
Online ISSN 1600-0617

(total lung capacity, FVC, single-breath DL_{CO} , arterial oxygen pressure, PA_{a,O_2} and oxygen saturation) have been identified as representative of a favourable or improved response to therapy in patients with IPF [2]. However, there are insufficient data to establish whether these are the most reliable and valid measurements of therapeutic efficacy [7]. Attempts to identify clinical and surrogate end-points for IPF clinical trials have either failed or merely provided positive signals, generating hypotheses requiring further investigation [7–10]. In the past 20 yrs many clinical trials have been conducted to evaluate the efficacy and safety of different and innovative drugs in the treatment of IPF. Table 1 demonstrates the heterogeneity of primary end-points used in these trials [8, 9, 11–18]. Studies have generally measured lung function as this is the most valid end-point. However, the challenges involved in choosing the most appropriate outcome have not been discussed in these papers.

Regulatory guidance from the US Food and Drug Administration (FDA) has identified several key parameters with regard to end-points [19]. The FDA assessment acknowledges that interpreting change in lung function in IPF is challenging, but proposes that a categorical reduction in FVC of $\geq 10\%$ could be regarded as clinically meaningful based on available evidence. Mortality is identified as the ideal and most compelling primary end-point in clinical trials, particularly as there are no well-established or validated surrogates for mortality in IPF. However, the importance of other clinically meaningful end-points is highlighted, including: survival; survival plus disease progression (composite end-point); preservation of lung function; dyspnoea; functional status; and quality of life. It is important to note that mortality findings should be supportive of other clinical end-points [19].

IPF CLINICAL END-POINTS: DESIRABLE CHARACTERISTICS

A desirable single clinical end-point for IPF should be reliable, valid, responsive to changes in disease status, clinically

meaningful, predictive of clinical outcome and responsive to treatment effect of a given intervention.

Reliability

A reliable clinical end-point is one that offers stability of measurement. The distance walked at the 6-min walk test (6MWT) is a practical, simple assessment of self-paced exercise capacity [20]. The test is very reliable in patients with IPF, showing only small variation when repeated in the same subject over a short period of time (coefficient of variation 4.2%) [21]. The 6MWT is well established as a surrogate end-point in clinical studies of pulmonary arterial hypertension (PAH) [22]. Recently, the reliability of the 6MWT in IPF was assessed using data from the largest clinical trial to date (INSPIRE (effect of interferon γ -1b on survival in patients with idiopathic pulmonary fibrosis); $n=822$). Comparison of the 6MWT on two separate days (mean interval 24 days) demonstrated high reliability (intraclass correlation coefficient 0.82; $p<0.001$) [23].

Validity and responsiveness to changes in disease status

A good end-point should correlate well with other measures of disease status (validity) and should be responsive to changes in disease status. FVC is widely used and accepted as a clinically meaningful measure of IPF disease status [2]. Recent data show that when FVC and 6MWT are assessed for validity and responsiveness using other functional parameters (DL_{CO} , the St George's Respiratory Questionnaire score and the University of California, San Diego, Shortness of Breath Questionnaire score), the correlations are statistically significant ($p<0.001$), if rather weak (figs 1 and 2) [23, 24].

Ability to show clinically meaningful difference

One of the key challenges that the investigator faces when selecting primary outcome measures, is determining the significance of any observed differences (statistical significance *versus* clinical relevance) and communicating the same to clinicians who will be applying the trial results. Minimal clinically important difference (MCID) is defined as the smallest difference in an outcome measure that patients would perceive to be important and that would lead a clinician to consider a change in a patient's status [25]. Estimated MCID for FVC is approximately three to five units and for 6MWT is 23–45 m [23, 24].

Ability to predict clinical outcome

A valid end-point should correlate reasonably well to clinical outcome (survival). A number of end-points have been found to be predictors of mortality in published IPF studies, including: FVC [7, 26–29]; DL_{CO} (% pred) [7, 26, 29]; alveolar–arterial gradient [7, 27]; dyspnoea [27]; 6MWT desaturation ($<88\%$) [30]; 6MWT distance [23, 31, 32], high-resolution computed tomography (HRCT) fibrosis score [33]; HRCT pattern (typical/atypical) [34]; and respiratory hospitalisation [1]. Of these, FVC and 6MWT can be considered as the best predictors of mortality at baseline in IPF. Published literature has identified a categorical reduction of $\geq 10\%$ in FVC as both reliable and predictive of mortality, and is associated with a greater than two-fold increase in the risk of death [7, 27, 28]. It has also been noted that a change in 6MWT (walked distance in m) is highly predictive of mortality;

TABLE 1 Primary end-points of idiopathic pulmonary fibrosis clinical trials performed in the last 20 yrs

NOBLE <i>et al.</i> [11]	FVC				
TANIGUCHI <i>et al.</i> [12]	VC				
DANIELS <i>et al.</i> [13]					PFS [#]
KING <i>et al.</i> [14]					Survival
RAGHU <i>et al.</i> [15]	FVC	DL_{CO}	Pa_{a,O_2}		
KING <i>et al.</i> [16]				6MWT	
KUBO <i>et al.</i> [17]					Survival
DEMEDTS <i>et al.</i> [18]	VC	DL_{CO}			
AZUMA <i>et al.</i> [8]			Pa_{a,O_2} [†]	6MWT [†]	
RAGHU <i>et al.</i> [9]					PFS ⁺

FVC: forced vital capacity; VC: vital capacity; DL_{CO} : diffusing capacity of the lung for carbon monoxide; Pa_{a,O_2} : arterial oxygen tension; 6MWT: 6-min walk test; PFS: progression-free survival. [#]: time to disease progression defined as decline in FVC (%) from baseline predicted FVC or death; [†]: lowest arterial oxygen saturation measured by pulse oximetry during 6MWT; ⁺: defined as $\geq 10\%$ decline from baseline of predicted VC or an increase ≥ 5 mmHg in the alveolar–arterial oxygen tension difference at rest.

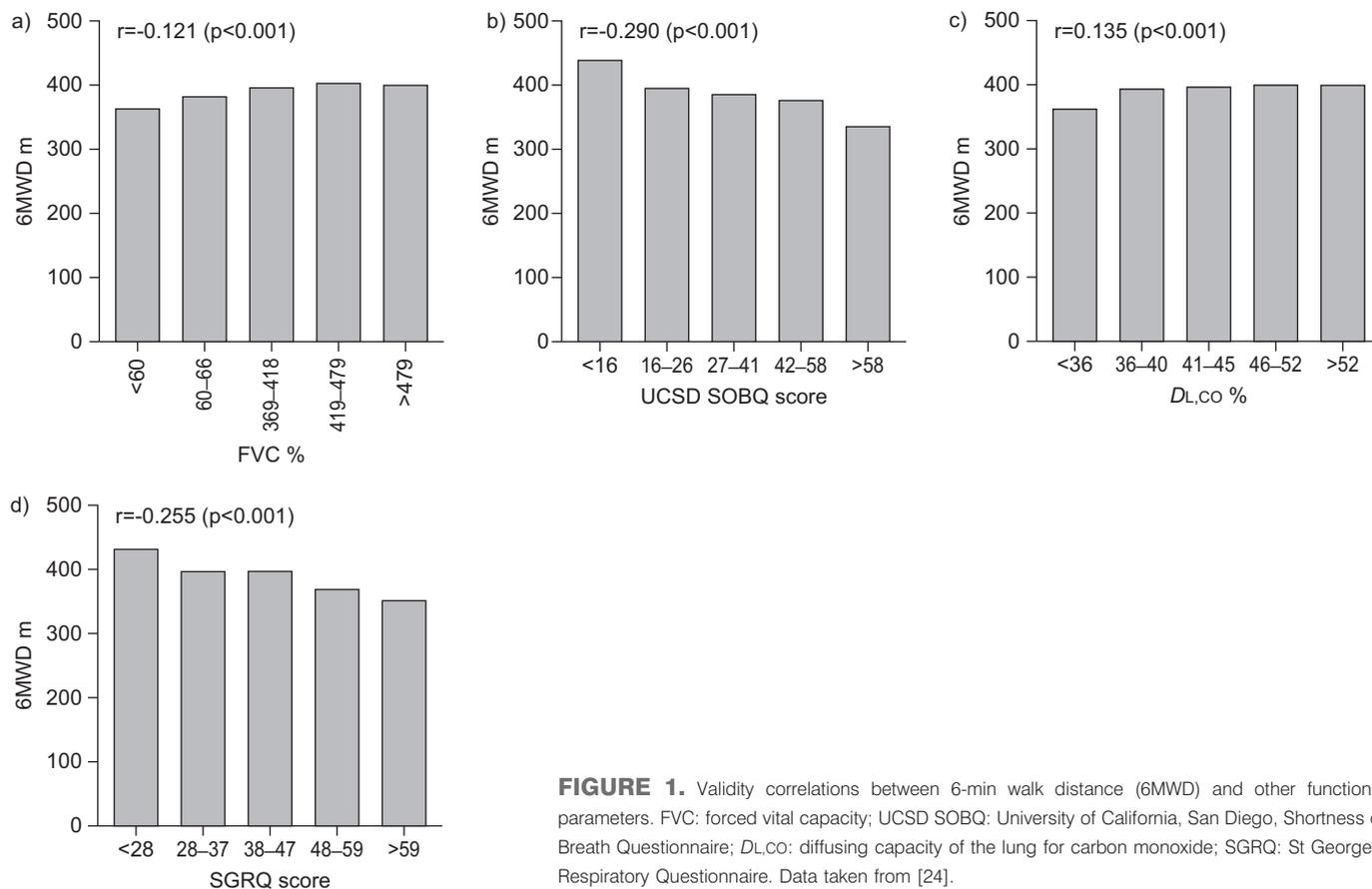


FIGURE 1. Validity correlations between 6-min walk distance (6MWD) and other functional parameters. FVC: forced vital capacity; UCSD SOBQ: University of California, San Diego, Shortness of Breath Questionnaire; DL_{CO}: diffusing capacity of the lung for carbon monoxide; SGRQ: St George's Respiratory Questionnaire. Data taken from [24].

a 24-week decrement of >50 m was associated with a four-fold increase in the risk of death over the subsequent 12 months ($p<0.001$) [23].

The validation of a simple, reproducible measure of outcome in a mortality scoring system is an important but challenging task. A mortality risk scoring model for patients with IPF was recently provided by DU BOIS *et al.* [35]. The proposed abbreviated clinical model comprises four readily available clinical measures of disease status (age, FVC at baseline, 24-week change in FVC and 24-week history of respiratory hospitalisation) that reliably predict 1-yr mortality in patients with IPF. This simplified scoring system may be a valuable tool for determining mortality risk of IPF patients in clinical practice, facilitating clinical decision making in the management of patients with IPF [35].

Sensitivity to treatment effect

VALEYRE *et al.* [36] have assessed the longitudinal change in FVC and 6MWT in pooled pirfenidone 2,403 mg·day⁻¹ (n=345) and placebo (n=347) groups from the CAPACITY trials. FVC and 6MWT distance were measured at baseline and at 12-week intervals until week 72. The pattern of change over time in FVC and 6MWT in the two groups was found to be very similar (fig. 3). The treatment effect for both outcome measures was evident at week 12, reached a peak at week 36 and persisted through week 72. However, the correlation at week 72 across these two measurements in individual patients was weak

($r^2=0.10$ for both groups), suggesting that these outcomes measure different functional domains of the IPF disease process [36].

COMPOSITE END-POINTS

Composite end-points take two or more outcome measures and combine them into a single outcome measure [37]. Composite end-points have been used to increase the overall event rate and thereby reduce the number of patients needed for a clinical trial. A well-designed and validated composite end-point can provide a reliable means of testing new treatments using a trial of relatively short duration [38]. A composite end-point may also address the issue of multiplicity (no adjustment to type 1 error required), may help to assess the "net effect" of treatment, and can be a useful support for the choice of a primary end-point [37, 38]. A composite end-point should meet the following criteria: each component is clinically meaningful and biologically plausible; each component is sensitive to treatment; the expected treatment effect on each component is similar; and each component can be analysed and reported individually [39]. A composite end-point that includes measures of outcome clearly related to the mortality risk seems to be one of the more reliable end-points for IPF clinical studies. Thus, progression-free survival, the end-point usually employed for lung cancer (a disease whose biology is in some respects similar to that of IPF) [40–42], could potentially be suggested as an optimal composite end-point for IPF.

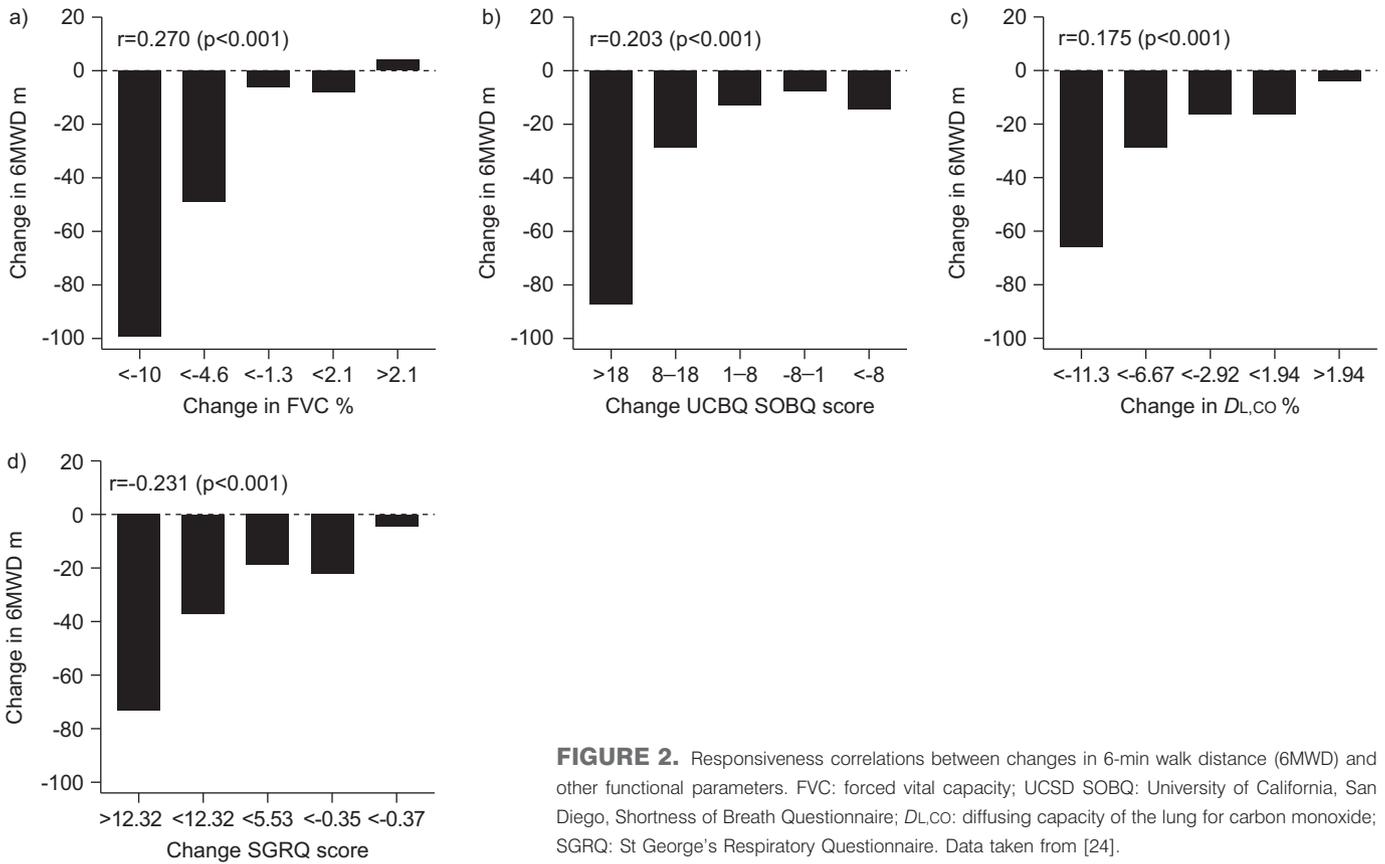


FIGURE 2. Responsiveness correlations between changes in 6-min walk distance (6MWD) and other functional parameters. FVC: forced vital capacity; UCSD SOBQ: University of California, San Diego, Shortness of Breath Questionnaire; DL,co: diffusing capacity of the lung for carbon monoxide; SGRQ: St George's Respiratory Questionnaire. Data taken from [24].

CONCLUSION

The clinical course of IPF is variable and its natural history poses many challenges for clinical research. Investigators involved in the planning of IPF clinical studies face considerable challenges in selecting outcome measures that will allow statistical assessment of clinically meaningful effects or outcomes. A number of clinical and surrogate end-points have been proposed and evaluated in studies. Changes in FVC and

6MWT have been found to be reliable, valid and responsive clinical outcome measures in patients with IPF. Mortality, the ideal and most compelling primary end-point, can be useful but is challenging to study requiring large cohorts of patients and long-lasting studies. Since there is increasing evidence indicating that the fundamental hallmarks of cancer biology are comparable to those of IPF, the primary end-point of progression-free survival, which is usually employed for lung

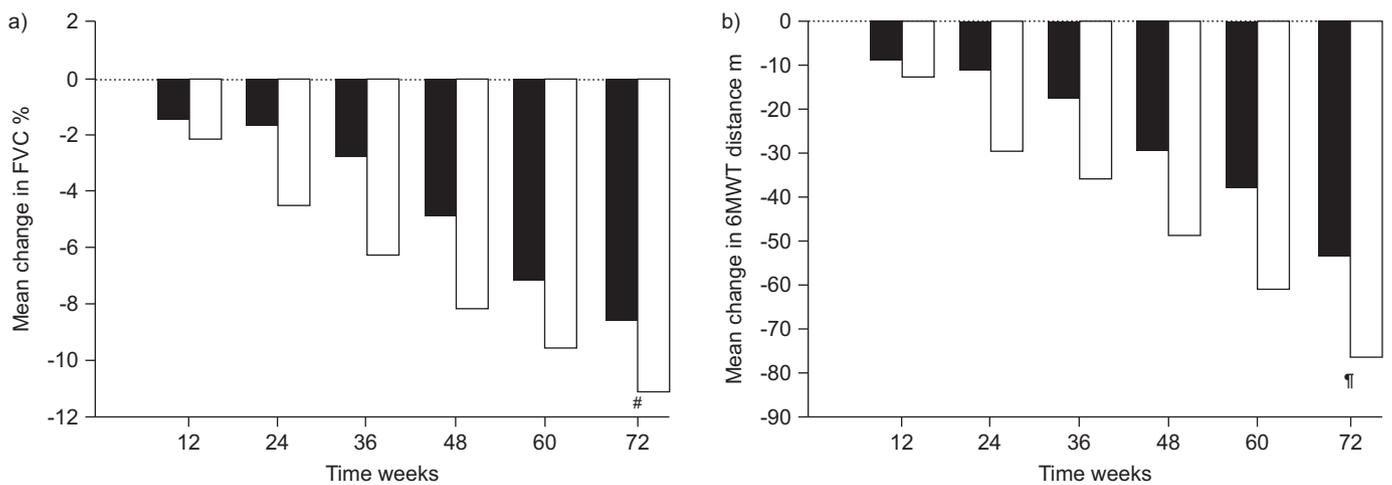


FIGURE 3. The pattern of change over time (72 weeks) in a) forced vital capacity (FVC) and b) 6-min walk test (6MWT) in patients receiving pirfenidone (□: n=345) or placebo (■: n=347). #: p=0.005; †: p=0.001. Adapted from [36].

cancer, could be potentially suggested as an end-point for IPF. The predictive value of easily measured and reliable clinical and physiological variables could improve the care of patients with IPF. However, more studies are needed to improve treatment of IPF with current and new compounds, alone or in combination.

STATEMENT OF INTEREST

C. Albera has acted as a speaker and a consultant for InterMune Inc. and has received fees of less than €5,000 in the past year.

ACKNOWLEDGEMENTS

This article is based on the proceedings of a satellite symposium held at the 2010 ERS Annual Congress (Barcelona, Spain), which was sponsored by InterMune Inc. The author was assisted in the preparation of the text by professional medical writers at IntraMed International (Milan, Italy). The medical writing support was funded by InterMune Inc.

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