CLINICAL INVESTIGATION

Clinical trials of idiopathic pulmonary fibrosis: choosing the (right) primary end point

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Idiopathic pulmonary fibrosis (IPF), the most common and lethal of all idiopathic interstitial pneumonias, is a disease that is both rare and orphan. However, in the last decade more than 3000 patients have been enrolled in high-quality clinical trials of IPF, an impressive achievement for a rare condition. The most challenging obstacle in clinical trials of orphan drugs is the recruitment of an adequate number of patients to obtain sufficient evidence of efficacy and safety, but similarly critical is the choice of the appropriate primary end points. In disorders with a poor prognosis – such as IPF - survival is the most logical outcome to measure the efficacy of a given drug. However, such trial design is feasible only in diseases that are fairly common and have a short survival. When a mortality study is impractical, an alternative approach is the use of predictors of survival. There is general agreement that the ideal primary end point should be reliable, reproducible, clinically meaningful, predictive of outcome, responsive to treatment effect, equally applicable to all patients and easy to measure, but none of the outcomes utilized over the last decade of clinical trials of IPF meets all these criteria. In this article we carefully analyze pros and cons of the outcomes most commonly used in pharmacological studies of IPF, and suggest that the choice of the appropriate primary end point should balance scientific, statistical and clinical rigor as well as clinical trial feasibility.

Keywords: clinical trials • forced vital capacity • idiopathic pulmonary fibrosis • outcomes • primary end points • survival

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease of unknown etiology characterized anatomically by scarring of the lungs, physiologically by progressive lung function deterioration and clinically by shortness of breath, resulting in early death [1]. However, within this framework, various clinical phenotypes exist with respect to disease extent, functional decline and survival [2]. Despite a number of high-quality clinical trials evaluating the efficacy of potential therapeutic agents, IPF still lacks an adequate treatment. In fact, there are no licensed medical therapies in the USA and the only care options endorsed by the most recent consensus guidelines are lung transplantation and enrolment in a clinical trial [1].

The past decade has seen a number of well-designed clinical trials in IPF being undertaken and completed. While these studies have provided valuable insights into the natural history of IPF, the outcomes have mostly been disappointing with only few encouraging exceptions (e.g., pirfenidone and nintedanib) [3–5]. In addition, they have also raised a number of questions and fuelled the debate on how future IPF studies should be designed [2.6]. The main problems in conceiving effective clinical trials in IPF relate to the complex nature of the pathogenetic process, the highly variable and unpredictable disease course, the possibility of inadequate drug

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deposition in the targeted area and, most importantly, the uncertainty regarding the most appropriate and clinically meaningful end points [7]. In fact, while all of the efficacy and safety end points in a clinical trial provide key information, whether a trial is positive or negative is determined by the effect of the intervention on the predefined primary end point.

There is general agreement that an optimal outcome measure should be reliable, reproducible, responsive to changes in disease status, clinically meaningful, predictive of clinical outcome, responsive to treatment effect, equally applicable to all IPF phenotypes as well as easy to measure. However, none of the outcomes utilized over the last decade of clinical trials of IPF meets all these criteria (Table 1).

Two recent perspective articles have triggered debate on how best to judge efficacy in Phase III clinical trials of IPF and, most notably, whether all-cause mortality should be used as a primary end point [8,9]. These two perspective articles have laid the foundation for this review article.

Primary end points utilized so far Forced vital capacity

A randomized, double-blind, placebo-controlled, Phase II trial evaluated the safety and efficacy of subcutaneous etanercept (25 mg twice weekly) in 88 patients with clinically progressive IPF [10]. After 48 weeks of treatment, no significant differences in any of the efficacy end points (changes in the percentage of predicted forced vital capacity [FVC] or diffusion capacity of the lung for carbon monoxide [DL_{CO}], and in the alveolar-arterial oxygen gradient at rest from baseline) were observed between the groups.

The CAPACITY studies (CAPACITY 1 – PIPF 006 and CAPACITY 2 – PIPF 004), two almost identical randomized, double-blind, placebo-controlled, multinational Phase III studies, evaluated the efficacy of oral pirfenidone over 72 weeks [4]. In study 004, mean FVC change at week 72 (the primary outcome) was -8.0% in the pirfenidone 2403 mg/day group and -12.4% in the placebo group (p = 0.001). Conversely, in the 006 study, the change in FVC at week 72 did not differ significantly between the active and placebo arms (p = 0.501).

The TOMORROW trial (to improve pulmonary fibrosis with BIBF 1120), a 12-month, randomized, double-blind, placebo-controlled Phase II study, evaluated the safety and efficacy of BIBF 1120 (nintedanib), a tyrosine kinase inhibitor that suppresses pro-angiogenic intracellular signaling by targeting the proliferative growth factor receptors on platelets (PDGFR), vascular endothelium (VEGFR) and fibroblasts (FGFR) [5]. BIBF 1120 at a dose of 150 mg twice daily showed a trend toward a reduction in the decline in FVC – the primary outcome. Specifically, in the group receiving 150 mg of BIBF 1120 twice a day, FVC declined by 0.06 l per year, as compared with 0.19 l per year in the placebo group; almost a 70% reduction in the rate of loss.

The PANTHER-IPF was designed to compare a triple combination therapy (N-acetylcysteine [NAC], prednisone and azathioprine) with NAC monotherapy or placebo in patients with IPF [11]. The primary outcome was the change in longitudinal FVC measurements over a 60-week period. The triple-therapy arm of this study was stopped after a prespecified efficacy and safety interim analysis, planned at approximately 50% of data collection. Results showed that the combination therapy, as compared with placebo, was associated with an increase in all-cause mortality, all-cause hospitalizations and treatment-related severe adverse events. Of note, the NAC and placebo arms of the PANTHER-IPF were continued. Thus, the question of whether NAC monotherapy is efficacious in IPF will be answered in the near future.

The MUSIC trial, a prospective, randomized, doubleblind, multicenter, parallel-group, placebo-controlled, Phase II study evaluated the efficacy and safety of macitentan in IPF patients [12]. Of the 178 randomized patients, 119 were allocated to macitentan and 59 to placebo. The study did not meet its primary end point (change from baseline up to month 12 in FVC).

Vital capacity

The IFIGENIA study, a double-blind, randomized, placebo-controlled multicentre study, assessed the efficacy over 1 year of a high oral dose of NAC (600 mg three-times daily) added to standard therapy (a combination of prednisone and azathioprine) compared with prednisone and azathioprine alone (the 'placebo' arm). The so-called triple therapy appeared to slow the decline of both vital capacity (VC) and DL_{CO} (the primary end points) [13]. However, the efficacy of the combination therapy has not been confirmed in a subsequent placebo-controlled randomized trial, PANTHER-IPF [11].

Change in VC was also the primary end point of a multicenter, double-blind, placebo-controlled Phase III study in which 275 Japanese patients with IPF were randomly assigned in a 2:1:2 ratio to high-dose (1800 mg/ day) or low-dose (1200 mg/day) pirfenidone or placebo over a 52-week period [3]. The study met its primary outcome (e.g., the rate of decline of VC was higher in the placebo arm [-0.16 l] compared with both the highdose [-0.09 l; p = 0.042] and low-dose pirfenidone arms [0.08 l; p = 0.039]).

Survival

The INSPIRE study was a large, randomized controlled trial evaluating the effect of IFN γ -1 β in patients with mild-to-moderate IPF (n = 826). This study, which was

Table 1. Primary end points utilized in recent clinical trials of idiopathic pulmonary fibrosis.								
Trial (year)	FVC	VC	DL_{co}	P(A-a)O ₂	Survival	6MWT	Disease progression	Ref.
Raghu G <i>et al</i> .† (2004)							\checkmark	[26]
Azuma A <i>et al</i> . (2005)				✓		✓		[20]
Demedts M et al. (2005)		\checkmark	\checkmark					[13]
Kubo H <i>et al</i> . (2005)					✓			[15]
King TE Jr <i>et al</i> . (2008)						\checkmark		[21]
Raghu G <i>et al.</i> (2008)	\checkmark		\checkmark	\checkmark				[10]
King TE Jr <i>et al</i> . (2009)					✓			[14]
Daniels CE <i>et al.</i> [‡] (2010)							✓	[25]
STEP-IPF (2010)						\checkmark		[22]
Taniguchi H <i>et al</i> . (2010)		\checkmark						[5]
King TE Jr <i>et al.</i> [§] (2011)							✓	[24]
Noble PW <i>et al</i> . (2011)	\checkmark							[6]
Richeldi L <i>et al</i> . (2011)	\checkmark							[5]
Noth I <i>et al.</i> ¹ (2012)							✓	[16]
PANTHER-IPF (2012)	\checkmark							[11]
Raghu G <i>et al</i> . (2013)	\checkmark							[10]
Raghu G <i>et al.</i> # (2013)							\checkmark	[23]
 ¹Decrease in the predicted FVC ≥10% or increase in the P(A–a)O₂ at rest of ≥5 mmHg or death. ¹10% decline from baseline in FVC or death. ¹Decrease from baseline in FVC ≥10% and DL_{co} ≥15% or an acute exacerbation of idiopathic pulmonary fibrosis or death. ¹Time to death, hospitalization or a decline in FVC ≥10%. [*]Death, respiratory hospitalization or decline in lung function. 6MWT: 6-min walk test; DL_{co}: Diffusion capacity of the lung for carbon monoxide; FVC: Forced vital capacity; P(A-a)O₂: Alveolar–arterial oxygen gradient; VC: Vital capacity. 								

stopped after a predefined interim analysis that provided conclusive evidence of lack of efficacy, represents to date the only high-quality study with overall survival as the primary outcome [14].

Kubo and coworkers evaluated the effect of anticoagulant therapy on survival of patients with IPF in an open-label study, in which 56 Japanese patients were randomly assigned to receive prednisolone alone or prednisolone plus anticoagulants [15]. The authors observed a significant difference between the survival curves of the anticoagulant and nonanticoagulant groups but this positive effect has not been confirmed in a subsequent larger high-quality, randomized, placebo-controlled trial [16].

6-min walk test

The distance walked at the 6-min walk test (6MWT) is a practical measure of self-paced exercise capacity. The 6MWT has been used to stage disease severity, assess efficacy of treatment and predict mortality in a number of conditions, including congestive heart failure, chronic obstructive pulmonary disease and pulmonary arterial hypertension [17–19]. The reliability of this test in IPF has recently been demonstrated using data from one of the largest clinical trials performed thus far in this disease [14].

In a multicenter, randomized, double-blind, placebocontrolled Phase II trial, 107 Japanese patients were randomly assigned to receive either an escalating dosage of pirfenidone or placebo [20]. The primary end point (change in the lowest blood oxygen saturation [spO₂] during a 6-min exercise test) was not met.

In a double-blind, placebo-controlled Phase III study (BUILD-1), 158 IPF patients were randomly assigned to receive bosentan, a dual endothelin (ET) receptor antagonist (ET_A and ET_B), or placebo. Bosentan did not meet its primary end point (change in 6-m walk distance by month 12) [21].

In a double-blind, placebo-controlled, Phase III study (STEP-IPF), 180 patients with advanced IPF (defined as a DL_{CO} <35% of the predicted value) were randomized to sildenafil (20-mg three-times daily) or placebo for 12 weeks. The difference in the primary outcome

was not significant, with nine out of 89 patients (10%) in the sildenafil group and six out of 91 (7%) in the placebo group having an improvement of ≥ 20 m in the 6-m walk distance (p = 0.39) [22].

Composite outcome measures

Composite end points consist of two or more individual outcomes combined together. Progression-free survival – commonly defined as a combination of decline in FVC or death – is the combined outcome measure used most frequently in clinical trials of IPF.

The ARTEMIS-IPF was a randomized, double-blind, placebo-controlled, Phase III study evaluating effectiveness of ambrisentan, an A-selective ET receptor antagonist, in reducing disease progression in IPF (defined as death, respiratory hospitalization or decline in lung function). The study was terminated earlier – after enrolment of 492 patients (75% of intended enrolment) – following an interim analysis indicating a low likelihood of efficacy for the composite primary end point [23].

The ACE-IPF trial evaluated the hypothesis that therapeutic doses of warfarin would reduce rates of mortality, hospitalizations and declines in FVC in patients with IPF over a period of 48 weeks [16]. The primary outcome measure was a composite outcome of time to death, hospitalization or a 10% or greater absolute decline in FVC. The study was stopped after 145 of the planned 256 subjects were enroled due to an increased mortality among subjects randomized to warfarin.

The BUILD-3, a prospective, randomized, doubleblind, placebo-controlled study, evaluated the efficacy of bosentan in patients with IPF (n = 616) of less than 3 years duration, diagnosed histologically, and with <5% of honeycombing on chest high-resolution computed tomography (HRCT) [24]. The trial did not meet its primary end point (e.g., IPF worsening defined by a decrease from baseline in FVC ≥10% and DL_{CO} ≥15% or an acute exacerbation of IPF at month 12 or death).

In a Phase II, randomized, double-blind, placebocontrolled study, 119 patients with mild or moderate IPF were randomly assigned to receive imatinib – a tyrosine kinase inhibitor (600 mg orally once daily; n = 59) or placebo (n = 60) for 96 weeks [25]. Imatinib did not differ from placebo for time to disease progression (10% decline in % predicted FVC from baseline or time to death).

In a large randomized, double-blind, placebocontrolled Phase III trial, 330 IPF patients were randomly assigned in a 1:1 ratio to receive subcutaneous IFN- γ -1b 200 µg three-times weekly or placebo [26]. Over a median of 58 weeks, IFN- γ -1b therapy did not significantly affect the primary end point of progressionfree survival; for example, time to disease progression (defined by either of the following changes: a decrease of at least 10% in the predicted FVC or an increase of at least 5 mmHb in the P(A–a)O₂ at rest) or death.

Another example of a composite outcome measure is the composite physiological index, a measure derived to capture the effect of emphysema on IPF by fitting pulmonary function tests against disease extent on HRCT. This index is simple to calculate (based on % predicted DL_{CO} , FVC and forced expiratory volume in 1 s (FEV₁), and has been shown to reflect the extent of disease more accurately than single physiological indices as well as being a powerful predictor of mortality [27]. However, composite physiological index has never been used as a primary end point in Phase III clinical trials of IPF.

Potential end points Patient-reported outcome

Patient-reported outcomes (PROs) are "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [28]. Two IPF-specific PROs (designed to assess health-related quality of life) have been developed, ATAQ-IPF (A tool to assess quality of life in IPF) and SGRQi (St George's respiratory questionnaire IPF-specific version), but they have not been validated longitudinally [29,30]. PROs developed for other diseases have been used as secondary end points in Phase III clinical trials of IPF [21,22].

Acute exacerbations

Acute exacerbations of IPF are episodes of unexplained respiratory deterioration (worsening dyspnea, increased cough and worsening of gas exchange parameters) accompanied by the appearance of new parenchymal infiltrates on chest radiograph or HRCT [31]. Though uncommon, these events are clinically relevant and often associated with an early death. However, documentation of acute exacerbations of IPF in clinical trials often requires centralized adjudication, a complex process that can lead to measurement error and lack of sensitivity due to missing data.

All-cause hospitalizations, respiratory hospitalizations & IPF-related hospitalizations

Respiratory, all-cause and IPF-related hospitalizations are clinically significant events associated with high inhospital mortality and limited survival beyond discharge [32]. Limitations of hospitalization end points include a variety of non-disease-related factors that can influence whether hospitalization occurs, such as access to health care, social support, regional practice patterns as well as the challenge of discerning the reason for hospitalization when a subject is admitted to outside hospitals [8]. Finally, patients with advanced disease may well require hospitalization due to processes that are unrelated to the biology of progressive fibrosis [9].

Discussion

A treatment trial designed to definitively determine whether a therapy is beneficial in IPF requires enormous efforts, and the choice of the primary efficacy end point is one of the most critical steps in its development. Intuitively, the efficacy of a given treatment for IPF - a disease for which the archetypal pathophysiology is a fibrotic process that reduces the size of the lung – should be measured in terms of lung size [33]. As such, FVC – a widely accepted reflection of disease progression in patients with IPF - has commonly been used as a primary end point in most therapeutical trials. Indeed, FVC is reliable (values are stable when repeated at different time points) and responsive (as measured by the correlations between change in FVC and changes in other clinically relevant parameters). Importantly, categorical decrements of FVC are powerful predictors of mortality. Specifically, a decline in % predicted FVC ≥10% at 24 weeks is associated with a nearly fivefold increase in the risk of mortality over the subsequent year [34-38]. In addition, more recent data have shown that a change as small as 5% might also have significant prognostic implications, suggesting that changes in % predicted FVC that were previously regarded as evidence of functionally stable disease are medically relevant and worthy of further clinical evaluation [39]. As with all physiological end points, the main obstacle is that patients do not decline at the same rate, and group mean in lung function inevitably includes various amounts of change. For example, in the Scleroderma Lung Study [40,41], the mean absolute difference in adjusted 12-month FVC (predicted) between the cyclophosphamide and placebo arms was 2.53% (p < 0.03). This rather small value would certainly be regarded as within the limits of measurement error if this difference was the amount of change seen in one patient over time. However, this was a group mean difference comprising a wide spectrum of changes, including no change at all, and this might have underestimated the change for those individuals who lost large amounts of their FVC [42]. The results of this clinical trial also highlighted the issue of whether statistically significant differences are also clinically significant, particularly when the potential benefits of a given drug are weighed against its adverse effects. In this regard, end points that directly measure how a patient feels (e.g., symptoms), functions (i.e., a patient's ability to perform activities in daily life), or survives (i.e., mortality) - in other words, directly relevant to patients' priorities - would clearly be more informative. Serial FVC trends do not predict survival in patients with IPF and concurrent emphysema,

which tends to preserve lung volumes [43,44]. Moreover, it remains unclear whether treatment-induced changes in FVC reliably predict changes in survival. Diffusing capacity for carbon monoxide suffers from the same limitations.

The 6MWT is used extensively as a measure of exercise tolerance in patients with various cardiac and pulmonary diseases. From a clinical stand point, 6MWT has the advantages of practicality and safety; no special equipment or advanced training is required, and unlike maximal cardiopulmonary exercise testing, it can be carried out by all but the most severely impaired patients [45,46]. Recently, data analysis from a large clinical trial in IPF has shown that a 24-week reduction of >50 m in walked distance is associated with a fourfold increase in the risk of death over the subsequent 12 months [46]. However, the 6MWT is not without limitations. In fact, the test does not provide insight into the mechanisms of exercise limitation (e.g., its results can be affected by a variety of factors unrelated to cardiopulmonary status, including age, sex, height and weight) [47]. The implementation of a composite end point could be an alternative. For example, change in FVC and distance walked during a 6-min test, are both robust predictors of mortality [34,39,46] and are sufficiently diverse in their ability to capture distinct pathophysiological domains of disease progression to be combined. Other parameters may potentially also be included in a composite index (e.g., DL_{CO}, quality of life, hospitalizations) [7]. While composite end points have several advantages (e.g., reduction of the required sample size and study duration through increase in the overall event rate), results based on composite end points may be misleading when 'driven' by the most frequent, but perhaps least important, of its constituents [48]. At present, there are no universally accepted composite end point in IPF. Other suggested end points, such as patient-reported outcomes need to be validated longitudinally, while allcause hospitalizations may be potentially confounded by non-pulmonary factors, variable hospital practices or reasons for hospital admissions.

The clinical course of a typical patient with IPF is characterized by progressive physiologic deterioration, worsening dyspnea and frequent hospitalizations [32]. However, considerable inter- and intra-individual variability exists and this makes it difficult to formulate an accurate prognosis [2]. Because of this effect, future studies should use more robust population enrichment strategies ('cohort enrichment') so that patients are selected with criteria that can predict disease progression during the study period, thereby increasing the likelihood of recording any positive drug effects with lower patient numbers [49]. This is a crucial point as several distinct disease subsets are likely to exist within IPF and phenotypic variability may contribute to nonuniform responses to treatment. In fact, without adequate patient stratification, even the positive effect of a given drug in a specific patient subgroup would inevitably be diluted or disappear because of its inefficacy in patients with different phenotypic characteristics. Recently, du Bois and coworkers developed a simplified risk scoring system based on four readily ascertainable parameters (age, FVC at baseline, 24-week change in FVC and 24-week history of respiratory hospitalization) that reliably predicts 1-year mortality in patients with IPF [35]. If validated, this risk scoring system may aid in the identification of appropriate candidates for enrolment in clinical trials and facilitate accurate stratification, both of which may contribute to more efficient and properly powered clinical trials. However, it is unclear whether this prediction model, which was developed based on data from patients with mild-tomoderate functional impairment, applies to the entire population of IPF patients.

The many negative clinical trials of new therapy for IPF have prompted debate on several issues of trial design - most notably whether all-cause mortality should be used as a primary end point [8,9,50]. What has become increasingly clear is that the number of patients and the length of trial needed to show a reasonable reduction in mortality remain prohibitive. In this regard, data from placebo arms of recently concluded clinical trials of IPF have shown that all-cause mortality rate is relatively low in patients with mildto-moderate disease that have represented – with very few exceptions - the standard study population [4]. As such, patients with 'early' IPF would need to be retained in the study and followed for a number of years. The longer the study, the greater the likelihood of dropouts, which could jeopardize the integrity of any well-designed study. In addition, it has been estimated that for a 25% reduction in mortality to be statistically significant in a placebo-controlled IPF trial, the enrolment of 2600 patients, 5 years of follow-up and US\$250 million would be required [51]. Indeed, only one mortality study has been undertaken in IPF to date and the study was negative [12]. Based on realistic estimates for efficacy on survival [4], such studies in IPF appears both unaffordable and non-executable within a reasonable time frame [52]. Mortality might be best suited for studies tailored to individuals with advanced disease, but this approach is not without drawbacks. In fact, such a population of patients is not representative of IPF as a whole and patients with advanced disease behave quite differently to those with mild-to-moderate disease, often dving of pulmonary vascular complications rather than progressive fibrosis. For instance, the effect of sildenafil on gas transfer and arterial oxygenation observed in a recent 12-week duration randomized-controlled trial of patients with advanced IPF (DL_{CO} <35% predicted) likely reflected a pulmonary vascular rather than an antifibrotic beneficial effect [22]. Therefore, disease behavior at end stage cannot be used as a template for the design of clinical trials of patients with less advanced IPF [9,53].

IPF is a dreadful disease that lacks adequate therapy. Drug development in this condition has proved challenging – with exceedingly high clinical trial failure rates; similarly, the selection of an optimal primary end point in pharmaceutical studies has proved problematic. In this setting, with the goal of delivering safe and effective therapies to our patients, we would suggest a balanced approach to end point selection.

Future perspective

The clinical course of patients with mild-to-moderate IPF - those commonly enroled in pharmacological studies - is characterized by minimal clinical and physiologic deterioration. Therefore, owing to the nature of the disease process (e.g., lung fibrosis generally progresses over many months or years), it is difficult to demonstrate large changes in functional indices such as lung function tests. In this scenario, slowing progression or stabilization of disease is probably the best that can be seen in a clinical trial (and we believe it should be viewed as a positive response to therapy). For these same reasons a mortality study in IPF appears impractical. On the other hand, in patients with advanced disease, in which antifibrotic drugs are less likely to exert any beneficial effect, improving quality of life (i.e., managing and limiting dyspnea, cough and fatigue thus enabling patients to be as physically and socially active as possible) represents, in our opinion, a realistic clinically meaningful goal in IPF clinical trials.

At present there are no robust data on the value of biomarkers in the prediction of disease outcome or stratification of patients in treatment groups. It is to be hoped that biomarkers as well as genomic signature differentiation and validation may, in the future, enable study enrichment with those patients at highest risk of progression and mortality. This will also make a mortality study in IPF finally feasible.

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Clinical trials of idiopathic pulmonary fibrosis: primary end points Review: Clinical Trial Methodology

Executive summary

- Idiopathic pulmonary fibrosis (IPF), the most common of all idiopathic interstitial pneumonias, is a progressive disease with tremendous heterogeneity and unpredictable rates of progression. IPF carries a dismal prognosis with a median survival of only 2-3 years after diagnosis.
- There are no licensed medical therapies in the USA and the only care options that are endorsed by the most recent consensus guidelines are lung transplantation and enrolment in a clinical trial.
- A treatment trial designed to definitively determine whether a therapy is beneficial in IPF requires enormous efforts. The choice of the primary efficacy end point, one of the most critical steps in clinical trial development, has recently been a matter of intense debate.
- In a disorder with a poor prognosis such as IPF survival is the most logical outcome to measure the efficacy of a given drug. However, in IPF such a trial design appears at present impractical. An alternative approach is the use of predictors of survival.
- The archetypal pathophysiology of IPF is a fibrotic process that reduces the size of the lung. As such, decline in forced vital capacity a widely accepted reflection of disease progression in IPF has commonly been used as a primary end point in most therapeutical trials.
- The ideal primary end point should be reliable, reproducible, clinically meaningful, predictive of outcome and easy to measure. Yet, none of the outcomes utilized so far in clinical trials of IPF meets all these criteria.
- Drug development in IPF has proven challenging with exceedingly high clinical trial failure rates. With the goal of delivering safe and effective therapies to our patients, we strongly believe the choice of the appropriate primary end point should balance scientific, statistical and clinical rigor as well as clinical trial feasibility.

References

- Raghu G, Collard HR, Egan JJ et al. An official ATS/ERS/JRS/ALAT statement. Idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 183, 788–824 (2011).
- 2 Martinez FJ, Safrin S, Weycker *Det al.* Clinical course of patients with idiopathic pulmonary fibrosis. *Ann. Intern. Med.* 142(12), 963–967 (2005).
- 3 Taniguchi H, Ebina M, Kondoh Y *et al.* Pirfenidone in idiopathic pulmonary fibrosis. *Eur. Respir. J.* 35, 821–829 (2010).
- 4 Noble PW, Albera C, Bradford WZ et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 377, 1760–1769 (2011).
- 5 Richeldi L, Costabel U, Selman M *et al.* Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N. Engl. J. Med.* 365, 1079–1087 (2011).
- 6 Olson AL, Swigris JJ, Brown KK. Clinical trials and tribulations – lessons from pulmonary fibrosis. QJM 105, 1043–1047 (2012).
- 7 Nathan SD, du Bois RM. Idiopathic pulmonary fibrosis trials: recommendations for the jury. *Eur. Respir. J.* 38, 1002–1004 (2011).
- 8 Raghu G, Collard HR, Anstrom KJ et al. Idiopathic pulmonary fibrosis: clinically meaningful primary end points in Phase III clinical trials. Am. J. Respir. Crit. Care Med. 185, 1044–1048 (2012).

- du Bois RM, Nathan SD, Richeldi L, Schwarz MI, Noble PW. Idiopathic Pulmonary Fibrosis: lung function is a clinically meaningful end point for Phase III Trials. *Am. J. Respir. Crit. Care Med.* 186, 712–715 (2012).
- 10 Raghu G, Brown KK, Costabel U *et al.* Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebocontrolled trial. *Am. J. Respir. Crit. Care Med.* 178, 948–955 (2008).
- 11 The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and *N*-acetylcysteine for pulmonary fibrosis. *N. Engl. J. Med.* 366, 1968–1977 (2012).
- 12 Raghu G, Million-Rousseau R, Morganti A et al. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomized-controlled MUSIC trial. Eur. Respir. J. doi: 10.1183/09031936.00104612 (2013) (Epub ahead of print).
- 13 Demedts M, Behr J, Buhl R *et al.* High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N. Engl. J. Med.* 353, 2229–2242 (2005).
- King TE Jr. Albera C, Bradford WZ *et al.* Effect of interferon γ-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 374(9685), 222–228 (2009).
- 15 Kubo H, Nakayama K, Yanai M et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. *Chest* 128, 1475–1482 (2005).

- 16 Noth I, Anstrom KJ, Calvert SB *et al.* A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 186, 88–95 (2012).
- 17 Shah MR, Hasselblad V, Gheorghiade M et al. Prognostic usefulness of the six-minute walk in patients with advanced congestive heart failure secondary to ischemic or nonischemic cardiomyopathy. Am. J. Cardiol. 88, 987–993 (2001).
- 18 Enfield K, Gammon S, Floyd J et al. Sixminute walk distance in patients with severe end-stage COPD: association with survival after inpatient pulmonary rehabilitation. J. Cardiopulm. Rehabil. Prev. 30, 195–202 (2010).
- 19 Miyamoto S, Nagaya N, Satoh T *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. *Am. J. Respir. Crit. Care Med.* 161, 487–492 (2000).
- 20 Azuma A, Nukiwa T, Tsuboi E *et al.* Doubleblind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 171, 1040–1047 (2005).
- 21 King TE Jr, Behr J, Brown KK *et al.* BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 177, 75–81 (2008).

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- 22 Zisman DA, Schwarz MI, Anstrom KJ et al.; Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N. Engl. J. Med. 363, 620-628 (2010).
- 23 Raghu G, Behr J, Brown KK et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann. Intern. Med. 158, 641-649 (2013).
- 24 King TE Jr, Brown KK, Raghu G et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 184, 92-99 (2011).
- 25 Daniels CE, Lasky JA, Limper AH et al. Imatinib treatment for IPF: randomised placebo-controlled trial results. Am. J. Respir. Crit. Care Med. 181, 604-610 (2010).
- 26 Raghu G, Brown KK, Bradford WZ et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N. Engl. J. Med. 350, 125-133 (2004).
- 27 Wells AU, Desai SR, Rubens MB et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am. J. Respir. Crit. Care Med. 167, 962-969 (2003).
- 28 US Department of Health and Human Services; US FDA. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Rockville, MD, USA (2009).
- 29 Swigris JJ, Wilson SR, Green KE, Sprunger DB, Brown KK, Wamboldt FS. Development of the ATAQ-IPF: a tool to assess quality of life in IPF. Health Qual. Life. Outcomes 8, 77 (2010).
- 30 Yorke J, Jones PW, Swigris JJ. Development and validity testing of an IPF-specific version of the St. George's Respiratory Questionnaire. Thorax 65, 921-926 (2010).
- Collard HR, Moore BB, Flaherty KR et al. 31 Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 176, 636-643 (2007)
- 32 Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 183, 431-440 (2011).

- Spagnolo P, Luppi F, Maher TM, Wuyts WA, 33 Grutters JC. Primary end points in Phase III clinical trials in idiopathic pulmonary fibrosis: one step at a time. Am. J. Respir. Crit. Care Med. 187, 1271-1272 (2013).
- du Bois RM, Weycker D, Albera C et al. 34 Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am. J. Respir. Crit. Care Med. 184, 1382-1389 (2011).
- du Bois RM, Weycker D, Albera C et al. 35 Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 184, 459-466 (2011).
- Collard HR, King TE Jr, Bartelson BB et al. 36 Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 168, 538-542 (2003).
- Latsi PI, du Bois RM, Nicholson AG et al. 37 Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am. J. Respir. Crit. Care Med. 168, 531-537 (2003).
- Flaherty KR, Mumford JA, Murray S et al. 38 Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am. J. Respir. Crit. Care Med. 168, 543-548 (2003).
- Zappala CJ, Latsi PI, Nicholson AG et al. 39 Marginal decline in FVC is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur. Respir. J. 35, 830-836 (2009).
- 40 Tashkin DP, Elashoff R, Clements PJ et al. Cyclophosphamide versus placebo in scleroderma lung disease. N. Engl. J. Med. 354, 2655–2566 (2006).
- 41 Tashkin DP, Elashoff R, Clements PJ et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am. J. Respir. Crit. Care Med. 176, 1026-1034 (2007).
- Fischer A, du Bois RM. Interstitial lung 42 disease in connective tissue disorders. Lancet 380, 689-698 (2012).
- 43 Wells AU, King AD, Rubens MB et al. Lone cryptogenic fibrosing alveolitis: a functionalmorphological correlation based on extent of disease on thin-section computed

tomography. Am. J. Respir. Crit. Care Med. 155, 1367-1375 (1997).

- 44 Schmidt SL, Nambiar AM, Tayob N et al. Pulmonary function measures predict mortality differently in idiopathic pulmonary fibrosis versus combined pulmonary fibrosis and emphysema. Eur. Respir. J. 38, 176-183 (2011).
- 45 American Thoracic Society. ATS Statement. Guidelines for the six-minute walk test. Am. J. Respir. Crit. Care Med. 166, 111-117 (2002).
- du Bois RM, Weycker D, Albera C et al. Six-46 minute walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am. J. Respir. Crit. Care Med. 183, 1231-1237 (2011).
- Heresi GA, Dweik RA. Strengths and 47 limitations of the six-minute-walk test: a model biomarker study in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 183, 1122-1124 (2011).
- Kaul S, Diamond GA. Trial and error: how to 48 avoid commonly encountered limitations of published clinical trials. J. Am. Coll. Cardiol. 55, 415-427 (2010).
- 49 Khanna D, Brown KK, Clements PJ et al. Systemic sclerosis-associated interstitial lung disease-proposed recommendations for future randomized clinical trials. Clin. Exp. Rheumatol. 28, S55-S62 (2010).
- 50 Wells AU, Behr J, Costabel U, Cottin V, Poletti V, Richeldi L. European IPF Consensus Group. Hot of the breath: mortality as a primary end-point in IPF treatment trial: the best is the enemy of the good. Thorax 67, 938-940 (2012).
- Bradford WZ, Cohen AH, Leff JA. Selection 51 of clinically meaningful primary end points in Phase III clinical trials in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 187, 1269-1270 (2013).
- Behr J. Mortality, a bar too high for 52 idiopathic pulmonary fibrosis clinical trials. Am. J. Respir. Crit. Care Med. 187, 1270 (2013).
- Lettieri CJ, Nathan SD, Barnett SD, 53 Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 129, 746-752 (2006).