Clinical trials in idiopathic pulmonary fibrosis: a framework for moving forward

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A framework for designing clinical trials in pulmonary fibrosis http://ow.ly/p9tFe

In the current issue of the *European Respiratory Journal*, RAGHU *et al.* [1] report the results of the Macitentan USe in Idiopathic Pulmonary Fibrosis Clinical (MUSIC) trial, a randomised placebo-controlled phase 2 clinical trial of macitentan, an oral endothelin antagonist, for biopsy-proven idiopathic pulmonary fibrosis (IPF). With its multicentre enrolment, appropriate allocation concealment, low withdrawal rate and intention-to-treat analysis, this clinical trial exemplifies the state-of-the-art in clinical trial design and conduct in the field of IPF. The authors should indeed be congratulated for accomplishing the difficult task of enrolling and successfully completing a clinical trial in IPF.

The MUSIC trial investigators found that macitentan was not effective for the treatment of IPF, with no meaningful differences in forced vital capacity (FVC), the study's primary end-point, or diffusing capacity of the lung for carbon monoxide at 1 year between allocation arms. The authors also detected a nonsignificant 56% relative increase in the rate of a combined end-point of lung function decline or acute respiratory decompensation of IPF among those allocated to macitentan compared to placebo, a finding driven by an acute respiratory decompensation in seven out of 119 participants in the macitentan arm compared to one out of 59 participants in the placebo arm.

The negative results of the MUSIC trial come as little surprise in light of previous reports that two other endothelin antagonist, ambrisentan [2] and bosentan [3–5], are similarly ineffective for IPF. A series of negative trials in IPF combined with the observation that the most promising therapies do not appear to improve lung function, reduce dyspnoea or prolong life [6, 7] has led to disappointment and frustration throughout the IPF community. Without a cure on the horizon, we should critically re-examine the assumptions underlying our current approach to the study of IPF so that we can design better trials that test better therapies.

Assumption 1: we should only study IPF patients with mild-to-moderate disease

Most IPF clinical trials have restricted enrolment to patients with mild-to-moderate disease (typically FVC >50% predicted). This practice seems to have arisen for multiple reasons: a (later disproven) subgroup analysis of the GIPF-001 trial suggesting that interferon-γ was effective in those with less severe disease [8]; the perception that marginally effective drugs will not be able to slow progression in advanced disease; and the concern that severely affected individuals may not be alive to have their FVC measured at the end of the trial. While the latter concern is reasonable (*vide infra*), there are no convincing data to suggest that any therapy will be more effective in those with mild disease. In fact, if our goals are to prevent both clinical events (such as respiratory hospitalisation and death) and the progression of disease, we should avoid enrolling patients with mild lung disease in clinical trials, since these patients are unlikely to die or

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experience progression during the 12–18-month time-frame of most IPF clinical trials. Instead, we should preferentially enrol those with more advanced disease who are at risk for disease progression or death.

Assumption 2: non-pharmacological management does not matter

The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines for the management of IPF are an improvement over previous guidelines [9], but provide little direction about "best practice" approaches to caring for patients with IPF. For example, the guidelines lack detailed and standardised recommendations for supplemental oxygen use (such as oxygen saturation targets during activity and sleep, and minimal definitions of supplemental oxygen compliance), approaches to the management of acute exacerbations (including minimal evaluation and standardised corticosteroid dosing and tapering), and whether patients should be routinely diagnosed and managed at academic interstitial lung disease centres (where diagnosis and management appears to be better than in the community setting) [10, 11]. Variability in practice patterns within a clinical trial can introduce noise into the observed effect of the intervention under study, thereby limiting our ability to identify effective therapies. There has been a stark absence of studies comparing the effectiveness of different management strategies in IPF. Multicentre collaborative efforts are needed to generate new evidence to guide clinical practice and standardise management approaches across centres.

Assumption 3: FVC will capture the clinical efficacy of a novel therapy for IPF

The selection of appropriate end-points for phase 3 clinical trials in IPF is the subject of an ongoing and heated debate focused on whether FVC is a clinically meaningful outcome or an unproven surrogate end-point [12–14]. A key criterion for a surrogate end-point is that treatment-induced changes in the surrogate end-point explain treatment-induced clinically meaningful outcomes [15, 16]. Since no therapy has yet been shown to effect clinically meaningful outcomes in IPF, this criterion remains untested for FVC. This seems to be a high bar for an end-point. For example, in the field of pulmonary arterial hypertension (PAH), a recent elegant study used pooled data from 10 clinical trials and found that the 6-min walk distance (6MWD), a widely accepted end-point in virtually all clinical trials in PAH, failed to meet this criterion [17]. Changes in the 6MWD only explained 22% of the treatment effect on clinical outcomes. It would be prudent to await the results of at least a single IPF clinical trial showing a beneficial effect of a therapy on important clinical outcomes before concluding that FVC would fare better in IPF than the 6MWD has fared in PAH.

Even if FVC were to meet the criteria of a surrogate end-point, it remains a problematic primary end-point. FVC will be missing for those who die, undergo lung transplantation or drop out of a study, requiring imputation of FVC in order to perform intention-to-treat analyses. Spirometry is also difficult to perform for those with advanced disease, and test performance could vary across study sites leading to measurement error. There are even a few reasons to believe that FVC may not be in the causal pathway for all clinical events. For example, a drug that prevents alveolar epithelial cell injury, but permits collagen synthesis and progression of fibrosis could prevent acute exacerbations while FVC continues to decline. Similarly, a drug that slows collagen deposition may not prevent acute exacerbations, leading to attenuation in the rate of FVC decline but failing to prevent death due to acute exacerbations.

Despite some of the problems with FVC as an end-point, we would all respond with great enthusiasm if a drug were found to positively influence FVC in the context of meaningful improvements in dyspnoea and clinical outcomes. That is to say that the fundamental problem is not that FVC fails to reflect disease severity, but rather the inherent difficulty of capturing all of the clinical efficacy of a therapy in one measure of lung compliance prone to informative missingness and error.

A more fundamental problem is that FVC is often the primary end-point for phase 2 trials, which have typically been designed as small phase 3 trials in disguise, enrolling hundreds of participants in order to detect small differences in the rate of decline in FVC between groups. What is lacking is a suitable measure of the activity (rather than severity) of IPF. Reliable measurements of alveolar epithelial cell injury, extracellular matrix remodelling and fibroblast proliferation are actively being investigated and may soon be able to serve as biomarkers of disease activity, permitting the study of the immediate biological (rather than delayed physiological) effects of a novel therapy in only a handful of IPF patients. Such proof-of-principle trials could allow us to quickly discard ineffective therapies, reserving only the most encouraging agents for phase 3 trials.

Assumption 4: the study of human lung diseases does not require humans

While exciting discoveries have improved our understanding of the biology of lung fibrosis [18–20], most studies have relied upon animal models, an approach that has not yet led to a proven therapy for IPF.

Indeed, recent work suggests that animal models of lung disease may not be fully translatable to humans [21]. The message is that we should be studying humans if we wish to understand human lung pathobiology. Scientists have long avoided this approach since it is typically not possible to control variability among humans in the usual ''laboratory'' sense. However, we are now able to control measured variability in humans by marrying the robust sciences of epidemiology and biology. Such studies are difficult to perform, requiring large sample sizes to permit control of confounding and examination of effect modification, appropriate sampling methods, and careful measurement of potential confounders and risk factors. Well-performed translational studies can only enhance our understanding of risk factors and mechanisms in human lung disease development, ultimately leading to not only effective therapies, but also novel approaches to the prevention of IPF [22].

A string of ''negative trials'' does not mean that we have failed. We simply need a new approach. With a common vision spanning the basic–translational–clinical spectrum, IPF investigators, advocacy groups, and funding and regulatory agencies must work together in order to achieve one singular goal: the elimination of IPF. We should accept no lesser success.

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