External validity of randomised controlled trials in idiopathic pulmonary fibrosis

To the Editors:

I would like to comment on the editorial by JOHNSON and RAGHU [1], which was published in the November issue of the *European Respiratory Journal*. In a very clear way, the authors overviewed the use of outcome measures in clinical trials of idiopathic pulmonary fibrosis (IPF).

I would like to propose some concerns, which could affect the external validity of randomised controlled trials in IPF [2, 3]. The first concern is about the diagnostic accuracy of the disease. IPF is a rare disease and no single accurate test for the diagnosis of IPF exists. Studies of the accuracy of diagnosing IPF are performed mostly in tertiary referral centres, and, even in these studies, an important interobserver variability exists. In most of these studies, prior knowledge of the presence of a form of interstitial lung disease existed, which may evoke an observer bias and, therefore, influence the results on the diagnostic accuracy [3].

The incidence of IPF in a general pulmonary practice is low. Diagnostic accuracy (*i.e.* sensitivity and specificity) also depends on the prevalence of the disease. A lower prevalence of the disease results in a higher number of false-positive and false-negative diagnoses [3]. In recent published trials, participating centres were selected from tertiary care centres or secondary care centres with particular interests in the management of IPF.

If a treatment for idiopathic pulmonary fibrosis is found, the chance that this treatment will be given to patients without idiopathic pulmonary fibrosis is high in a pulmonary care practice with a very low incidence of idiopathic pulmonary fibrosis. Or to summarise these concerns using a question: will it be possible to generalise these trials in a general pulmonary care practice [2]?

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DOI: 10.1183/09031936.06.00151305

From the authors:

We appreciate the important concern raised by M. Thomeer and agree that following a standardised diagnostic criteria is important for both the investigator as well as the clinician taking care of the patients in the community. While the general pulmonologist may not be as ''accurate'' in diagnosing idiopathic pulmonary fibrosis (IPF) as expert clinicians involved in the diagnosis and management of IPF and other subgroups of idiopathic interstitial pneumonias (IIP) in tertiary centres enrolling patients in clinical trials, the clinical knowledge of IPF has evolved significantly with new data and clarifications during the last few years. Recent international consensus statements by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have increased the awareness of the different entities of IIP and IPF [1, 2]. Thus, the current generation of general pulmonologists, as well as experienced pulmonologists, involved in active care of patients with pulmonary diseases are becoming quite familiar with the diagnostic criteria for these entities. In fact, all of the recent and ongoing clinical trials have utilised well-defined criteria based on set guidelines to enrol the most appropriate patients. The striking similarity of the baseline demographics in the patient populations enrolled in two recent separate multicentre clinical trials in the USA, Canada and Europe illustrates this very well [3, 4].

Indeed, results from a trial apply to the population from which the trial sample is drawn. It should be noted that the patients enrolled in recent IPF clinical trials do come from the community, the majority of whom are referred by general pulmonologists to centres conducting clinical trials in IPF. If the diagnosis criteria utilised by general pulmonologists (and, therefore, the ''IPF population in the community'') is drastically different from that utilised for the IPF sample enrolled in the clinical trials, we would agree that the results from the trial may not be relevant to the IPF patients cared for by general pulmonologists. This would be an appropriate concern if patients were simply enrolled in trials without well-defined eligibility criteria. Enrolling patients with well-defined inclusion and exclusion criteria is the only means of assuring the appropriate study population pertinent to the clinical trial. It must also be noted that in the largest IPF clinical trial reported to date, general pulmonologists in clinical practice, without a previous track record as ''IPF/interstitial lung disease experts'', directly enrolled the IPF patients to the trial. The patients, from several centres in the USA, Canada and Europe, were enrolled by clinicians who followed the study protocols in their own clinics (*i.e.* not necessarily in the tertiary and secondary centres) quite well [3]. The ongoing International study of Survival outcomes in idiopathic Pulmonary fibrosis with InteRfEon gamma trial has enrolled 800 patients from several sites in the USA, Europe and

Canada, and has also included patients seen and followed at community clinics/''centres'' by general pulmonologists in clinical practice (academic and community based). Thus, patients have been recruited and are being recruited from the community, and the results of the clinical trials do represent the patient population as defined in the studies, regardless of patients being enrolled by pulmonologists at tertiary, secondary or community-based sites.

We do agree that the use of diverse diagnostic criteria (or criteria that inconsistently make diagnoses) can pose difficulties both for establishing whether a treatment regimen is safe and efficacious in clinical trials, as well as for the applicability of the results to the broader IPF population. The joint ATS/ERS international consensus statement recommended a multidisciplinary approach to IPF diagnosis [1]. The ATS/ERS consensus statement also cautioned that in the absence of a surgical lung biopsy, the diagnosis of IPF/usual interstitial pneumonia was uncertain in patients not fulfilling the major and minor clinical criteria. Recently, FLAHERTY *et al.* [5] confirmed that a multidisciplinary approach increases the likelihood of a confident diagnosis. Since this study involved only senior and experienced experts in interstitial lung diseases (ILDs), it is unknown if such an approach taken by general pulmonologists, pathologists and radiologists in the community would yield similar or different results. If the intra- and interobserver variability in diagnosing IPF using the same criteria are significantly different and highly variable among experienced experts in IPF/ILD and the general clinicians (pulmonologists, pathologists and radiologists) in the community, the expressed concern by M. Thomeer will then be of a different magnitude and need to be addressed with continued and better education based on evidence.

Regardless, it must be recognised that the diagnosis of IPF is challenging in both the clinical trial setting as well as in clinical practice. Ensuring that accurate diagnoses are made using a common standard will help mitigate serious impediments to generalising clinical trial results for the patients cared for by the general pulmonary care practitioner. Future independent clinical trials should enrol patients in early, mid and advanced stages of well-defined study populations with IPF, and should have the adequate sample size in each of these subgroups to assess appropriate outcome measures as reviewed in our editorial [6]. Such studies will then yield results applicable to a broader spectrum of patients with IPF as confronted in day-to-day clinical practice.

In essence, the results of a well-designed clinical trial are indeed applicable to prudent general pulmonary care practitioners who need to make good clinical decisions for their patients. This will require careful and insightful interpretation of the results of clinical studies. With continued education and increased awareness, the general pulmonologist's ability to relate the results of well-designed clinical trials to their patients in whom they can diagnose idiopathic pulmonary fibrosis accurately (and as defined in the study population) will be enhanced. It is hoped that the future joint statements by the American Thoracic Society, the European Respiratory Society and other national and international chest/thoracic/respiratory societies will be able to provide new and evidence-based guidelines for accurate diagnosis and better management of idiopathic pulmonary fibrosis. Such evidence-based joint statements/guidelines will bridge the apparent gap in the understanding of this challenging disorder among experienced experts and general pulmonologists, and prompt appropriate diagnostic and therapeutic interventions to improve the outcome of patients confronted with idiopathic pulmonary fibrosis.

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DOI: 10.1183/09031936.06.00023406