Pirfenidone in idiopathic pulmonary fibrosis

To the Editors:

We read with interest the article of TANIGUCHI *et al.* [1] entitled “Pirfenidone in idiopathic pulmonary fibrosis”. These authors have spearheaded the investigation of this novel antifibrotic agent for idiopathic pulmonary fibrosis, and their efforts are commendable. In an editorial that accompanied their manuscript, COLLARD [2] pointed out a number of shortcomings of the study that raise concerns about the robustness of the results. We agree with COLLARD [2] (and the authors’ comments in the Discussion section) that these limitations (and others not mentioned) detract from the validity of the study’s results, the clinical significance of which continue to be questioned by the research community, and underscore the need for further investigation of pirfenidone.

We would like to use the article of TANIGUCHI *et al.* [1] to highlight some points regarding longitudinal studies in general, with particular emphasis on the use of statistical analyses and reporting of results. First, we believe the research community has advanced beyond the point where the use of mixed-effects (also called linear-mixed, random-effects, random-coefficient or hierarchical) models is a novelty; indeed, the capability to analyse data with these models has been available in almost every statistical package for several years. The merits of mixed-effects models include the following: 1) all available data can be used (imputation is not necessary, thus avoiding case-wise deletion due to missing data); 2) the model structure is extremely flexible, and, in contrast to ANCOVA, allows for time-varying covariates; and 3) it relaxes some of the assumptions about missing data inherent in analyses that do not use all of the data. These beneficial aspects permit these models to yield information regarding how groups change over time, how interventions effect that change and how patient characteristics might modify treatment effects [3]. Instead of using mixed-effects models to analyse data for their primary end-point, TANIGUCHI *et al.* [1] used ANCOVA, with imputation of missing data by last observation carried forward (LOCF), methods that fall short of what should, we believe, be the minimum standard for analysing longitudinal data.

In addition to using mixed-effects models to analyse longitudinal data, we urge investigators to move forward from the blanket use of LOCF for imputation of missing data; it may be appropriate to use LOCF in certain studies, but it may not. There are certain methods that authors can use to better convince readers that LOCF is right for their studies (a brief discussion follows), and sensitivity analyses are always indicated when LOCF is used.

TANIGUCHI *et al.* [1] used a mixed model approach as a sensitivity analysis, instead of using it as the method for the primary analysis, but they failed to mention the covariates or the covariance structure used in their approach. Further, they state that the sensitivity analysis “showed significant or marginally significant treatment effects and supported the

LOCF,” but they do not reveal these results. Reporting these results, which could easily be made available in the online supplementary material, would further convince readers that the use of LOCF was reasonable.

Additional information not reported by TANIGUCHI *et al.* [1] that would help readers better understand the data includes full reporting of the numbers of subjects with missing data, which could be accomplished *via* a plot for each treatment arm stratified by last assessment (fig. 1). In figure 1, although LOCF would seem appropriate for group 1, it would not be for groups 2 or 3, because the outcome is on an upward trajectory for group 2 and a downward trajectory for group 3. Thus, for groups 2 and 3, LOCF artificially deflates or inflates outcome values for time-points after the last study visit.

TANIGUCHI *et al.* [1] write “We were under the impression that LOCF would not tip the balance in favour of either of the treatment groups, if there were no substantial differences in the rate of drop-outs.” However, drop-out rate only tells part of the story. A figure that includes plots for each arm stratified by reason for drop-out/missing data (*e.g.* lack of efficacy/disease progression, side-effects of treatment and other) would shed light on whether the trajectories prior to drop-out are similar for patients with different reasons for drop-out, and whether or not missing data are missing completely at random. This has implications regarding what methods should be used for imputing missing values. Whatever the case, readers need to know that authors are inadvertently making the arm with greater drop-out look better with their method for dealing with missing data.

In their study, TANIGUCHI *et al.* [1] were confronted with hurdles commonly faced by researchers who run longitudinal studies; these include drop-out and missing data.

FIGURE 1. Mean value of outcome of interest for subjects whose last study visit occurred at 16 (group 1), 8 (group 2) or 4 weeks (group 3). BL: baseline.

Mixed-effects models provide a powerful and versatile statistical method for analysing longitudinal data and should be used wherever possible. Efforts by authors, including a full disclosure of the number of missing data and the reason for missingness (accomplished with plots for each arm stratified on the reason why data are missing), will help readers to better interpret, understand and apply results.

J. Swigris* and D. Fairclough#

*National Jewish Health, and #University of Colorado Health Outcomes Program, Denver, CO, USA.

Correspondence: J. Swigris, Autoimmune Lung Center and Interstitial Lung Disease Program, National Jewish Health, Denver, CO, USA. E-mail: swigrisj@njc.org

Statement of Interest: A statement of interest for J. Swigris can be found at www.erj.ersjournals.com/misc/statements.dtl

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From the authors:

First of all, we thank the editors of *European Respiratory Journal* (ERJ), for giving us the opportunity to respond to the correspondence by J. Swigris and D. Fairclough. We also thank J. Swigris and D. Fairclough that they read our paper [1] with interest and sent a correspondence letter to the editors of the ERJ. We were deeply encouraged to know that our paper had been received with interest.

As J. Swigris and D. Fairclough point out, as has COLLARD [2] in the past, analyses of clinical trial data, especially those of longitudinal data, can be affected by the methods by which missing data are handled. It is true that there is no perfect method for handling missing values, and we are always annoyed with challenging issues in selecting the method. We would like to agree with the suggestion in the letter that a mixed model approach should be used for the analyses of longitudinal data. We also understand that last observation carried forward (LOCF) is not necessarily the best method, and is rather a problematic one, since the assumption that observation at the time of drop-out will remain at the same level to the last observational time, needed in the estimation without bias for LOCF, is very stringent and may underestimate the true variability of missing data and inflate the type 1 error [3].

The primary reason we adopted the LOCF method in this study is that we adopted the same method in the previous study. Other reasons are as follows: LOCF is widely accepted and its principle or procedure is relatively simple, and since the analysis is done using the last observed measurement of each patient, we might interpret the results of LOCF analysis in many cases, considering the direction of bias if any. We planned to adopt the LOCF method in the primary analysis; however, for assurance, we also planned available case analysis (or observed value analysis) based on repeated measures of changes in vital capacity (VC), as described in the Discussion section of our manuscript. Due to the limited space of the paper, we only presented the conclusion: “Mixed model approach using repeated measures of changes in VC without LOCF imputation as a sensitivity analysis also showed significant or marginally significant treatment effects and supported the LOCF analysis.”

Here, we will present the results of mixed model based analysis. Incidentally, all the analyses were performed in full analysis set, and significance level was set at 0.1 both-sided. In the mixed model, we used the change in VC as response, and specified treatment, time (visit) and treatment by visit interaction as fixed effects, and patient as random effect. Covariance structure used was first-order autoregressive (AR(1)). Results are shown in tables 1, 2 and 3. Table 2 shows that effects of high and low-dose pirfenidone were significantly superior to one of placebo

TABLE 1 Mixed model analysis of changes in vital capacity from baseline: test of fixed effects		
Source	F-value	p-value#
Group	2.78	0.0623
Time (visit)	7.05	<0.0001
Group × time	0.98	0.4939
#: both-sided p-value.		

TABLE 2 Mixed model analysis of changes in vital capacity from baseline: overall adjusted means of vital capacity changes in treatment groups and comparisons of the means			
Group	Estimate	SE	
High dose	-0.04561	0.01653	
Low dose	-0.03542	0.02277	
Placebo	-0.09141	0.01641	
	Difference	SE	p-value#
High versus low dose	-0.01020	0.02813	0.7170
High dose versus placebo	0.04580	0.02329	0.0494
Low dose versus placebo	0.05600	0.02807	0.0461
#: both-sided p-values.			

This article has supplementary material available from www.erj.ersjournals.com