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

REFERENCES

1 Taniguchi H, Ebina M, Kondoh Y, *et al.* Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010; 35: 821–829.
2 Collard HR. Idiopathic pulmonary fibrosis and pirfenidone. *Eur Respir J* 2010; 35: 728–729.
3 Fairclough D. Design and Analysis of Quality of Life Studies in Clinical Trials. 2nd Edn. New York, CRC Press, 2010.

DOI: 10.1183/09031936.00071710

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 maunscript. 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

TABLE 3 Mixed model analysis of changes in vital capacity from baseline: adjusted means of vital capacity changes at the last visit in treatment groups and comparisons of the means

Group	Estimate	SE	
High dose	-0.09289	0.02248	
Low dose	-0.06855	0.03003	
Placebo	-0.14349	0.02179	
	Difference	**SE**	**p-value#**
High *versus* low dose	-0.02434	0.03752	0.5166
High dose *versus* placebo	0.05060	0.03131	0.1062
Low dose *versus* placebo	0.07494	0.03710	0.0435

#: both-sided p-values.

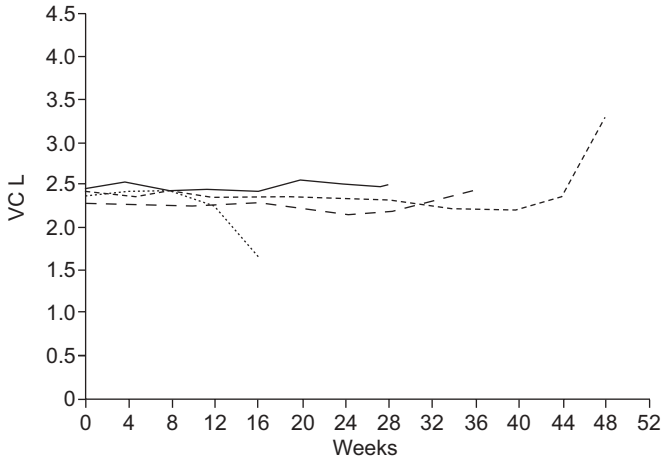

FIGURE 1. Mean values of vital capacity (VC) for drop-out patients by the last visit. ·····: ⩽16 weeks; ——: >16 to ⩽28 weeks; – – – –: >28 to ⩽40 weeks; - - - -: >40 weeks.

(p-values were 0.0494 and 0.0461 for the comparisons between high-dose and placebo, and low-dose and placebo groups, respectively). Table 3 also shows the marginally and significant effects of high- and low-dose pirfenidone (p-values were 0.1062 and 0.0435 for the comparisons between high-dose and placebo, and low-dose and placebo groups, respectively). Mixed model approach using the raw VC data as response, also shows similar results obtained with the changes in VC (see tables E1 A, B and C in the online supplementary material). In addition, we tried to analyse the repeated measures of VC using covariance structure other than AR(1), such as compound variance components or heterogeneous first-order autoregressive (ARH(1)) and obtained similar results.

Then, we examined the affections of trajectories prior to drop-out by reasons of discontinuing the study and the last visit, which was requested by J. Swigris and D. Fairclough. At first, table 2 in our paper [1] was modified to include the last visit (or the time of drop-out) of patients. The number of patients in each cell classified by reasons of discontinuing the study, treatment drug and the last visit is shown in table E2 in the online supplementary material. The transitional plots of the means of VC by the reasons of discontinuing the study and the last visit are shown in figure E1 (in the online supplementary material) and figure 1, respectively.

It was found from the transitional plots by the reasons, *i.e.* figure E1, that there was no clear upward or downward trajectory in each of the strata. For reference, the transitional plots of the means of VC by treatment group and the reasons of discontinuing the study are shown in figures A–F and tables A–F in the appendix to the online supplement. There seems to be no specific trend in trajectory of each treatment group. Transitional profiles seem different for drop-out patients with last visit ⩽16 and >40 weeks. Namely, the mean of the former patients decreased at week 16, and mean of the latter patients increased at week 48. But, careful examination suggested the decrease and the increase in the means of VC in these patients depended on of the number of VC observations. Indeed, the number of the observations decreased at week 16 and week 48 for patients with last visit ⩽16 and >40 weeks, respectively (table 4). As a result, this was thought to be one of the reasons of little difference between the results from LOCF and mixed model based analyses.

We will be happy if the results of the examination described in this article assist in showing the efficacy of pirfenidone in any way. Quite a few patients dropped out over the course of this study; in such studies, the handling of missing data plays important role. We thank again the *ERJ* editors and J. Swigris and D. Fairclough for rousing attention to the issues on missing data.

T. Nukiwa*, M. Ebina* and M. Takeuchi#
*Dept of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, and #Dept of Clinical Medicine

TABLE 4 The number of vital capacity observations at each visit for drop-out patients with last visit ⩽16 and >40 weeks

Last visit weeks	0	4	8	12	16	20	24	28	32	36	40	44	48
⩽16	24	23	19	12	3								
>40	18	17	18	18	18	18	18	17	17	17	17	7	1

(Biostatistics and Pharmaceutical Medicine), School of Pharmacy, Kitasato University, Tokyo, Japan.

Correspondence: T. Nukiwa, Dept of Respiratory Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: toshinkw@idac.tohoku.ac.jp

Statement of Interest: None declared.

REFERENCES

1 Taniguchi H, Ebina M, Kondoh Y, *et al*. Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010; 35: 821–829.
2 Collard HR. Idiopathic pulmonary fibrosis and pirfenidone. *Eur Respir J* 2010; 35: 728–729.
3 Analysis of Incomplete Data. *In*: Dmitrienko A, Molenberghs G, Chuang-Stein C. Analysis of Clinical Trials Using SAS: A Practical Guide. Cary, SAS Institute Inc., 2005. pp. 269–354.

DOI: 10.1183/09031936.00086910