Pirfenidone in rheumatoid arthritis-associated interstitial lung disease

In the TRAIL1 study[1] the annual rate of decline in forced vital capacity (FVC) in the pirfenidone group was slower than in the placebo group (66 mL *vs* 146 mL, figure 2), especially in usual interstitial pneumonia fibrosis (43 mL *vs* 169 mL, figure 3). However, the linear outcomes in figures 2 and 3 seem inconsistent with the progressions observed in the supplementary figures 4–7 for absolute percent predicted FVC (FVC%) and absolute FVC volume in Solomon et al,[1] which show an FVC effect in favour of pirfenidone at week 13 (approximately 2%, 60 mL), but in favour of placebo at week 52 (approximately 1·5%, 200 ml). Supplementary figures 6 and 7 show that these patterns are valid for the non-usual interstitial pneumonia groups, while the FVC% graphs and the FVC volume graphs of the usual interstitial pneumonia groups are approximately parallel.[1] Thus, the non-usual interstitial pneumonia graphs in supplementary figures 6 and 7 seem compatible with the slightly smaller decrease in the non-usual interstitial pneumonia placebo group compared with the non-usual interstitial pneumonia pirfenidone group seen in figure 3. However, the parallel usual interstitial pneumonia-related graphs in supplementary figures 6 and 7 seem discordant with the divergent usual interstitial pneumonia graphs in figure 3 and divergent slopes in supplementary table 3 in favour of the pirfenidone group.

The discrepancy between the linear model-based changes in FVC% and FVC volume (figures 2 and 3) and summarised measurements of absolute FVC% and FVC volume (supplementary figures 4–7) is not discussed in the paper.[1] It is unclear whether this inconsistency can be explained by missing values, as the titles of supplementary figures 4–7 indicate that the graphs are based on intention-to-treat values, whereas the patient number in the legends indicate that the graphs are based on observed values. The question is whether the results in figure 3 and supplementary table 3 reflect that the linear model amplifies favourable pirfenidone effects during the first 13 weeks (supplementary figures 4 and 5) forward into the remaining observation period. If so, the linear model might be inappropriate and conceal that a possible initial effect of pirfenidone gradually diminishes. There is no key to the true handling of missing data in intention-to-treat statistics,[2,3] but a sensitivity analysis to test the robustness of the change in FVC seems reasonable, as previously suggested when handling missing data in longitudinal trials,[2,3] for instance presenting the change in FVC% and FVC volume in the placebo group and the pirfenidone group as observed in all patients (n=123) and in patients completing the study (n=81).

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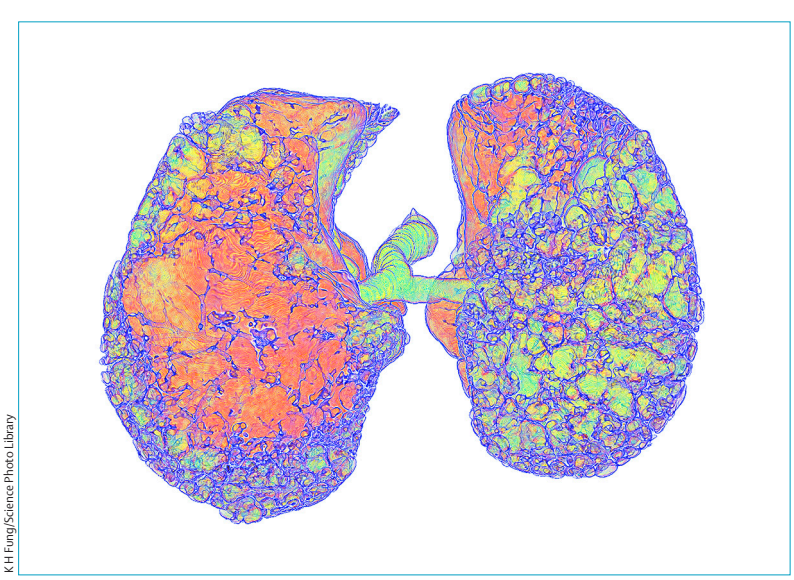

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