Arthritis & Rheumatology
DOI 10.1002/art.39930

Combined Pulmonary Fibrosis and Emphysema in Scleroderma-Related Lung Disease: Reply to Saketkoo et al.

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Received: Sep 01, 2016; Accepted: Sep 09, 2016

Saketkoo et al raise interesting questions related to findings in our recently published study of patients with systemic sclerosis-related interstitial lung disease [SSc-ILD](1). They underline the fact that forced vital capacity (FVC) did not differ between patients with combined pulmonary fibrosis and emphysema (CPFE) and those without emphysema, despite more extensive SSc-ILD in the former. However, the suggestion that this discrepancy might represent relative preservation of FVC due to emphysema was not supported by other analyses. On multivariate analysis, the presence of emphysema had no independent effect on FVC levels, once the extent of fibrosis had been taken into account. An additional unpublished analysis (prompted by the thoughtful comments of Saketkoo et al) shows no linkage between the extent of emphysema and preservation of FVC levels in the 41 patients with CPFE. For the moment, these apparent contradictions are unexplained.

We agree strongly that there is a need to examine the impact of concurrent emphysema on serial change in FVC, used as the primary end-point in recent trials in SSc-ILD (2-4). Conflicting information exists on serial changes in FVC and diffusing capacity for carbon monoxide (DLCO) in patients with idiopathic pulmonary fibrosis (IPF) and CPFE. In one cohort, the 3-year change in both variables did not differ between IPF and IPF–CPFE (5), but in another series, patients with IPF–CPFE were characterized by less decline in FVC and DLco than that observed in IPF patients without emphysema (6) In a well-defined pharmaceutical IPF cohort, patients with IPF and CPFE had significantly lower rate of decline of FVC than patients with IPF (7). In line with the suggestion by Saketkoo et al, we are close to completion of analyses evaluating whether baseline and serial changes in FVC are predictive of mortality in the subgroups of patients with and without emphysema.

We also agree that the use of spirometric values as a screening tool for SSc-ILD may be misleading (although the question of screening for ILD was not addressed in our recent manuscript). Alternative screening strategies might be a) HRCT at baseline in all SSc patients; and b) selection of SSc patients to undergo HRCT, based on the integration of clinical, physiologic and chest radiographic features. We are not aware of data that establish that either strategy is preferable.

With regard to PH-related issues, we must plead a limitation common to virtually all studies of non-invasive markers of ILD-PH. Plainly, the ideal study of this sort should include right heart catheterization (RHC) data in all cases, a deficiency underlined by Saketkoo et al.

However, sometimes "the best is the enemy of the good". To our knowledge, the DETECT study is the only published study to include systematic RHC in a large cohort of patients with reduced DLco but no formal diagnosis of PH (8). In DETECT 31% of cases had PH but the limitations of echocardiography were clear. Even in the study by Cottin et al, mentioned by Saketkoo et al, only 7/34 patients underwent RHC whereas in 28 patients the estimation of PH was based on echocardiographic data (9).

In this regard especially, the comments of Saketkoo et al merit very careful consideration. The baseline FVC/FDLco levels in our CPFE patients indicate that an elevated FVC/DLco ratio is an expected feature in CPFE. In only eight of 41 patients (19%) with CPFE was the FVC/DLco ratio <1.6 (the threshold used in the DETECT study). This observation indicates that an elevated FVC/DLco ratio cannot, in reality, be expected to provide discriminatory information on the likelihood of PH in patients with emphysema. Moreover, as this caveat held true even in patients with subclinical SSc ILD (as shown in Figure 3 in our manuscript), we submit that exactly the same reservation is likely to apply to SSc patients with isolated emphysema.

The essential question, on which Saketkoo et al focus in their closing comments, is how best to identify PH in CPFE patients, without guidance from the FVC/DLco ratio. They argue, in essence, for a policy of early right heart catheterisation. Perhaps in the end, this approach will prove to be fruitful but there is clear precedence for consideration of other non-invasive PH markers, selectively studied in ILD-PH or PH associated with chronic lung disease, including serum BNP (or pro-BNP) levels and HRCT variables (enlargement of the pulmonary artery or the ratio of the pulmonary artery diameter/aortic diameter) (10-12). Future research studies should explore whether a combination of these markers might replace the FVC/DLco ratio in CPFE or even in SSc-ILD in general.

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