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Heterogeneity in rheumatoid arthritis-associated interstitial lung disease: time for splitting?

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Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is the second leading cause of death in patients with RA, with a 5-year mortality rate of 35%.[1] The prevalence of RA-ILD varies widely (from 1% to 30%) depending on the characteristics of RA patients and on how RA is defined.[1,2] RA-ILD has a spectrum of manifestations, ranging from inflammation (acute diffuse alveolar damage, organizing pneumonia, or nonspecific interstitial pneumonia) to fibrosis, manifested most commonly as usual interstitial pneumonia (UIP). Interestingly, accumulated evidence suggests that RA-UIP distinguishes a subpopulation of RA patients in whom risk factors, prognosis, and possibly treatment response might be different from those in patients with non-UIP RA-ILD.

RA-UIP is associated with the rs35705950 polymorphism in the promoter of the *MUC5B* gene, the same (and greatest) genetic risk factor for idiopathic pulmonary fibrosis, whereas non-UIP RA-ILD is not.[3] The molecular profile associated with RA-UIP is also different from that associated with non-UIP RA-ILD, meaning different protein expression most likely due to different pathogenic pathways.[4] Similarly, articular disease activity has been associated with the incidence of non-UIP RA-ILD; however, it remains unknown whether articular disease activity is associated with RA-UIP.[5]

Studies of RA-ILD differ from one another with regard to the proportion of RA-UIP patients in comparison with that of non-UIP RA-ILD patients. This might explain, at least in part, the divergent findings across studies.

In this issue of the JBP, Rosseti-Severo et al. report on the risk factors associated with RA-ILD in a single-center study.[6] Of 134 RA patients undergoing chest HRCT and pulmonary function testing, 36% had RA-ILD, which was associated with being > 62 years of age and having moderate to high articular disease activity.[6] RA-ILD was not stratified as being either RA-UIP or non-UIP RA-ILD.[6] Interestingly, the findings of Rosseti-Severo et al.[6] are consistent with those of previous studies.[5,7] For instance, in a study by Sparks et al., females constituted more than 80% of the study population, and nonspecific interstitial pneumonia accounted for more than 80% of the RA-ILD subphenotype.[8] In the study by Rosseti-Severo et al., females constituted 89% of the study population.[6] Therefore, we can speculate that most of the patients had non-UIP RA-ILD.

It is of note that the control group in the study by Rosseti-Severo et al.[6] consisted of RA patients without ILD, meaning that the control group probably included patients with RA-associated airway disease. This might explain why risk factors such as cigarette smoking and the presence of disease antibodies were not associated with RA-ILD in their study.[6]

The accumulated evidence so far suggests that RA-UIP is significantly different from non-UIP RA-ILD. Therefore, risk factors for incident disease, as well as disease progression and response to treatment, should be investigated with that in mind. The systematic reporting of the proportion of RA-UIP patients in studies of RA-ILD is a great start. However, our minds should remain open to the fact that this splitting (subphenotyping) might not yet be telling the whole story of RA-ILD.

"*You only find what you are looking for*."
Mary Leakey

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