

Scleroderma Lung Involvement, Autoantibodies, and Outcome Prediction: The Confounding Effect of Time



Systemic sclerosis (SSc) remains a poorly understood disease and so far none of the routinely used immunosuppressive treatments has been definitively shown to benefit longterm disease outcome. Scleroderma-related cardiopulmonary involvement has been the leading cause of death in more recent decades, and pulmonary fibrosis (PF) and pulmonary hypertension (PH) account for a substantial proportion of the SSc-related deaths, as demonstrated by several large metaanalyses^{1,2,3}.

Early detection and monitoring of PF and PH may benefit outcome by permitting earlier intervention in severe or progressive cases⁴. Multiple attempts have been made to develop prediction models, both for development and for outcome, in already present SSc-related lung disease. Consistently, autoantibody specificities are among the strongest but not the only predictors of organ disease in scleroderma patients, and autoantibody characterization is a mandatory part of investigations in new SSc cases.

It is well established that while positivity for anticentromere antibodies (ACA) is associated with the limited cutaneous subset of the disease and a low risk of pulmonary or renal involvement, presence of antitopoisomerase I antibodies (ATA) conveys a substantially increased risk of PF development; moreover anti-RNA polymerase antibodies (ARA) are strongly associated with the diffuse cutaneous subset (dcSSc) and development of scleroderma renal crisis (SRC)⁵. Most cohort studies describe no particular association between ARA positivity and PH or PF development. Although this was true in an unadjusted analysis, when correcting for other variables, ARA positivity was shown to associate with an increase in the hazard of PH development in a large single-center cohort analysis⁶. In addition, compared to ACA-positive patients, those carrying ARA have been shown to develop PF more frequently^{7,8}.

Several studies have assessed and compared the value of pulmonary function tests (PFT) and high-resolution computed tomography (HRCT) for the screening and

monitoring of PF, and even though HRCT appears to be a more accurate tool^{9,10}, the associated cost and radiation burden mean that serial PFT remains the preferred method for longterm PF monitoring. An algorithm combining results from HRCT and PFT was developed by Goh, *et al* and seems to have a very good prognostic value, allowing for an easy and quick staging of lung disease and assessment of the need for immunosuppressive treatment¹¹.

In this issue of *The Journal*, the article by Hoffman-Vold, *et al* focuses on SSc-related cardiopulmonary complications in a group of patients with well-characterized autoantibody profiles and looks for specific patterns associated with ARA positivity¹². This is a prospective observational study, presenting a cohort of SSc patients with very robust associated clinical data. Lung complications have been ascertained using gold-standard tests with serial PFT and HRCT scanning used to define PF, while all PH cases were confirmed using right heart catheterization.

Similar to previous cohort studies, the authors find no association between ARA positivity and the overall risk of development of PF: nearly half of the ARA-positive patients (49%) showed no evidence of PF development over the duration of the study. Nevertheless, 18% of the ARA-positive patients did develop extensive PF, affecting more than 20% of the lung on HRCT, emphasizing the importance of PF screening in all SSc patients, irrespective of their presumed risk of this complication.

Moreover, a particularly interesting finding is that among ARA-positive patients who did develop PF, extensive fibrosis tended to develop later on in the disease course. This was unlike the ATA-positive cohort, in which the great majority of subjects who were to develop extensive PF already had it at baseline. This is in keeping with the findings of a recent observational cohort study of 294 patients from Thailand, where disease duration at first detection of PF was much shorter in ATA-positive compared to ATA-negative patients¹³. It also reflects the fact that association between

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PF development and ATA positivity has a significant interaction with disease duration, with hazard of PF doubling after 5 years of disease⁶.

There could be multiple explanations for the apparently different course of progression in PF in subjects with ATA and ARA, and different pathophysiological mechanisms for fibrotic change development are likely. For ATA-positive patients these may be autoimmune inflammation-driven, while in patients with ARA, PF progression could be perpetuated by gastroesophageal reflux, with associated microaspiration or recurrent infections, leading to alveolar epithelial injury occurring later in the disease course, which could account for the later development of extensive disease in those subjects^{14,15}.

One major confounder in the study by Hoffman-Vold, *et al* is the significant difference in disease duration at study baseline between the ARA-positive and ATA-positive patients, where those carrying ATA had on average 3 years longer disease duration than subjects carrying ARA. Given that clinically significant PF generally develops early in the disease — and multiple studies have shown that this happens to the majority of patients within the first 5 years from onset^{6,16,17} — it is not surprising that most ATA-positive patients who were going to develop significant PF had already reached this endpoint, given that mean disease duration at baseline in this group was 6.2 years, compared to 3.3 years for ARA-positive patients. This highlights the importance of accounting for disease duration in any research into outcome prediction in patients with SSc.

SSc has a very specific natural pattern of progression. As a result, the timing of peak skin disease and major organ complications, if they are to develop, could be anticipated. Thus, skin involvement in patients with dcSSc, as measured by the modified Rodnan skin score (mRSS), tends to worsen comparatively rapidly in the initial stages of the disease. The majority of patients with the diffuse subset of SSc reach their peak mRSS within the first 3 years from first non-Raynaud symptom, and skin tends to improve thereafter in about 80% of the subjects^{18,19}. Deterioration in skin disease or new development of worsening skin thickening in patients with disease duration longer than 5 years is extremely rare and often a sign of an underlying more sinister pathology.

Similar to the natural evolution of skin disease, major organ complications, with the obvious exception of PH, normally develop in the early stages of SSc and could even be a presenting feature^{5,18}. For example, incidence of SRC is highest in the first 3 years of disease, significantly lessening in later years, with only anecdotal cases of SRC developing 10 years or longer after SSc onset⁴. Clinically significant PF [defined as forced vital capacity (FVC) or DLCO < 55% or a drop in FVC or DLCO > 15% from first assessment] also tends to develop earlier on, with over two-thirds of the subjects who are to develop this endpoint reaching it in the first 5 years from disease onset⁶. On the

other hand, PH does develop later in the disease course, with an apparently constant incidence rate over time, suggesting that longer followup will be associated with a greater probability of PH development in a given subject.

As a result, any study investigating predictors of organ complications in SSc should take into account the timing of those complications and the disease duration in the study subjects. Time-to-event analysis rather than simple associations between explanatory variables and present/absent outcomes should be considered, and interaction between any of the predictor variables and time should be tested as appropriate.

In this context, the study by Hoffman-Vold, *et al* is a good illustration of many of the challenges associated with studying a rare disease with variable presentation, and a specific course of progression that can affect the studied associations if not adjusted for in the analysis. In this case, although the numbers were reasonable for a scleroderma study, they were still insufficient to allow for a comprehensive multivariable analysis. One inevitable conclusion from this article is that there is a real need for even more detailed and larger studies, assessing the effect of autoantibody specificities on the outcome of lung complications in patients with SSc. At a practical level, these findings reassert the clinical importance of ongoing monitoring of patients with SSc for potential lung complication development.

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