Editorial

Scleroderma lung involvement, autoantibodies and outcome prediction: the confounding effect of time

Svetlana I. Nihtyanova, Christopher P. Denton

Systemic sclerosis (SSc) remains a poorly understood disease and so far none of the routinely used immunosuppressive treatments has been definitively shown to benefit long-term disease outcome. Scleroderma-related cardio-pulmonary 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 meta-analyses (1-3).

Early detection and monitoring of PF and PH may benefit outcome by permitting earlier intervention in severe or progressive cases. 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 characterisation is a mandatory part of the work-up of new SSc cases.

It is well established that while positivity for anti-centromere antibodies (ACA) is associated with the limited cutaneous subset of the disease and a low risk of pulmonary or renal involvement, presence of anti-topoisomerase I antibodies (ATA) convey a substantially increased risk of PF development and anti-RNA polymerase antibodies (ARA) are strongly associated with the diffuse cutaneous subset (dcSSc) and development of scleroderma renal crisis (SRC) (4). 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-centre cohort analysis (5). In addition, compared to ACA positive patients, those carrying ARA have been shown to develop PF more frequently (6, 7).

Several studies have assessed and compared the value of pulmonary function tests (PFTs) and high-resolution computed tomography (HRCT) for the screening and monitoring of PF and even though HRCT appears to be a more accurate tool (8, 9), the associated cost and radiation burden means that serial PFTs remain the preferred method for long-term PF monitoring. An algorithm combining results from HRCT and PFTs 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 treatment (10).

In this issue, the article by Hoffman-Vold *et al.* focuses on SSc-related cardio-pulmonary complications in a group of patients with well-characterised autoantibody profiles and looks for specific patterns associated with ARA positivity. This is a prospective observational study, presenting a well-characterised cohort of SSc patients with very robust associated clinical data. Lung complications have been

ascertained using gold-standard tests with serial PFTs and HRCT scanning used to define PF, while all PH cases were confirmed using right heart catheterisation.

Similar to previous cohort studies, the authors find no association between ARA positivity and the overall risk of development of PF with nearly half of the ARA positive patients (49%) having 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, where 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 patients (11). It also reflects the fact that association between PF development and ATA positivity has a significant interaction with disease duration with hazard of PF doubling after 5 years of disease (5).

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 the fibrotic changes development are likely. For ATA positive patients these may be autoimmune inflammation-driven while in patients with ARA, PF progression could be perpetuated by gastro-oesophageal reflux with associated micro-aspiration 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 (12, 13).

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 (5, 14, 15), 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 SSc patients.

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 three years from first non-Raynaud's onset and skin tends to improve thereafter in approximately 80% of the subjects (16, 17). 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 be even a presenting feature (4, 17). 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 onset (18). Clinically significant PF (defined as FVC or DLCO of less than 55% or a drop in FVC or DLCO of more than 15% from first assessment) also tends to develop earlier on, with over 2/3 of the subjects who are to develop this endpoint, reaching it in the first 5 years from disease onset (5). On the other hand, PH does develop later in the disease course, with apparently constant incidence rate over time, suggesting that longer follow-up 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 systemic sclerosis 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 paper is that there is real need for even more detailed and larger studies, assessing the effect of autoantibody specificities on the outcome of lung complications in scleroderma patients. At a practical level, these findings reassert the clinical importance of ongoing monitoring of SSc patients for potential lung complication development.

References

1. Komócsi A, Vorobcsuk A, Faludi R, Pintér T, Lenkey Z, Költő G, et al. The impact of cardiopulmonary manifestations on the mortality of SSc: a systematic review and meta-analysis of observational studies. Rheumatology. 2012;51(6):1027-36.
2. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology. 2012;51(6):1017-26.
3. Rubio-Rivas M, Royo C, Simeon CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Seminars in arthritis and rheumatism. 2014;44(2):208-19.
4. Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in systemic sclerosis. Nature reviews Rheumatology. 2010;6(2):112-6.
5. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis & rheumatology (Hoboken, NJ). 2014;66(6):1625-35.

6. Motegi S, Toki S, Yamada K, Uchiyama A, Ishikawa O. Demographic and clinical features of systemic sclerosis patients with anti-RNA polymerase III antibodies. The Journal of dermatology. 2015;42(2):189-92.
7. Airo P, Ceribelli A, Cavazzana I, Taraborelli M, Zingarelli S, Franceschini F. Malignancies in Italian patients with systemic sclerosis positive for anti-RNA polymerase III antibodies. The Journal of rheumatology. 2011;38(7):1329-34.
8. Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N. Correlation of delta high-resolution computed tomography (HRCT) score with delta clinical variables in early systemic sclerosis (SSc) patients. Quantitative imaging in medicine and surgery. 2016;6(4):381-90.
9. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TD, Maurer B, Jordan S, et al. Brief Report: Pulmonary Function Tests: High Rate of False-Negative Results in the Early Detection and Screening of Scleroderma-Related Interstitial Lung Disease. Arthritis & rheumatology (Hoboken, NJ). 2015;67(12):3256-61.
10. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. American journal of respiratory and critical care medicine. 2008;177(11):1248-54.
11. Foocharoen C, Suwannachat P, Netwijitpan S, Mahakkanukrauh A, Suwannaroj S, Nanagara R. Clinical differences between Thai systemic sclerosis patients with positive versus negative anti-topoisomerase I. International journal of rheumatic diseases. 2016;19(3):312-20.
12. Christmann RB, Wells AU, Capelozzi VL, Silver RM. Gastroesophageal reflux incites interstitial lung disease in systemic sclerosis: clinical, radiologic, histopathologic, and treatment evidence. Seminars in arthritis and rheumatism. 2010;40(3):241-9.
13. Furnari M, Savarino V, de Bortoli N, Savarino E. Interstitial lung disease in systemic sclerosis patients may benefit more from anti-reflux therapies than from immunosuppressants. Autoimmunity reviews. 2016;15(12):1208-9.
14. Steen VD, Conte C, Owens GR, Medsger TA, Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis and rheumatism. 1994;37(9):1283-9.
15. Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis and rheumatism. 2000;43(11):2437-44.
16. Medsger TA, Jr. Natural history of systemic sclerosis and the assessment of disease activity, severity, functional status, and psychologic well-being. Rheumatic diseases clinics of North America. 2003;29(2):255-73, vi.
17. Shand L, Lunt M, Nihtyanova S, Hoseini M, Silman A, Black CM, et al. Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis: application of a latent linear trajectory model. Arthritis and rheumatism. 2007;56(7):2422-31.
18. Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. QJM : monthly journal of the Association of Physicians. 2010;103(2):109-15.