Systemic sclerosis: are anti-nuclear antibodies our guiding stars?

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PART III

Anti-topoisomerase I positive systemic sclerosis

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Prognostic properties of anti-topoisomerase antibodies in patients identified by the ACR/EULAR 2013 Systemic Sclerosis criteria

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Sir,

Auto-antibodies in Systemic Sclerosis (SSc) are important tools for disease prognostication (1). Anti-topoisomerase I antibodies (ATA) are associated with a more severe disease course, diffuse cutaneous involvement (dcSSc) and severe interstitial lung disease (ILD), while anti-centromere antibodies (ACA) are associated with a mild disease course, limited skin involvement (lcSSc) and only rare occurrence of ILD. Hence, one would assume increased mortality in the ATA+ group as compared to the ACA+ group.

Contrasting to these presumed predictive properties, Steen et al. showed that when patients are followed from their first visit to the rheumatologist rather than observed from their first symptom, there is no difference in survival between ATA+ and ACA+ patients (2). This finding might have been the consequence of the lack of sensitivity of the ACR 1980 SSc classification criteria (3) to identify early and limited cutaneous SSc. Indeed, ACA+ patients showed longer symptom duration at diagnosis (mean 7.7 years) compared to ATA+ patients (mean 3.8 years) in the manuscript of Steen et al.

The LeRoy and Medsger 2001 criteria (4) and the ACR/EULAR 2013 criteria (5) enable improved identification of limited cutaneous and early SSc patients. The Leiden Combined Care In Systemic Sclerosis Cohort (CCISS) (6) has, from its beginning, included patients according to these criteria and as such, comprises also early and mild cases not fulfilling the ACR 1980 criteria. Taking advantage of our cohort, we collected longitudinal data of 95 ATA+ and 122 ACA+ patients fulfilling the ACR/EULAR 2013 criteria and compared survival, disease progression and development of severe skin and lung involvement, using Kaplan-Meier and Cox survival analysis. Disease progression was defined as ≥1 of the following: increase in mRSS ≥5 points and ≥25%, worsening of lung involvement with ≥ 10% relative decline in forced vital capacity (FVC) and follow-up FVC <80% of predicted or with ≥ 5% to < 10% relative decline in FVC and a ≥ 15% relative decline in diffusion capacity of the lung (DLCO) with follow-up DLCO <80% of predicted, incident digital ulcers requiring prostacyclin treatment, newly diagnosed myocardial involvement, renal crisis, severe gastro-intestinal symptoms, inflammatory myositis, pulmonary arterial hypertension or mortality. According to the Medsger Disease Severity scale ≥3 (7), severe skin involvement was defined as a modified Rodnan Skin Score (mRSS) ≥30 and severe lung involvement as DLCO or FVC <50% of predicted.

At baseline, ACA+ patients were more often female (n=112/122 [91%] vs. n=68/95 [72 %], p<0.01), older (mean age 58±13 yrs. vs. 52±15 yrs., p <0.01) and numerically had a longer disease duration since their first non-Raynaud symptom (median 3.9 [IQR 1.2-9.9] yrs. vs. 2.8 [IQR 0.8-9.3] yrs., p=0.40). Severe skin involvement was seen in 3 ATA+ and none of the ACA+ patients, severe lung involvement in 23 ATA+ and

17 ACA+ patients. Forty-seven percent of ACA+ patients and 19% of ATA+ patients did not fulfil the ACR 1980 criteria. Longitudinal follow-up was available for 85 ATA+ and 107 ACA+ patients with median follow-up of 4.2 and 3.6 years, respectively. Within this period, 12 ATA+ (14%) and 7 ACA+ patients (7%) died and 44 ATA+ (52%) and 39 ACA+ patients (36%) experienced disease progression. Two ATA+ patients (3%) developed severe skin and 8 (14%) severe lung involvement. Of the ACA+ patients, none developed severe skin or lung involvement; however, 2 patients had lung function deterioration after lobectomy for lung cancer and 5 experienced deterioration without any sign of ILD (on HRCT) or pulmonary arterial hypertension (excluded after right-heart catheterization). Kaplan-Meier curves are presented in Figure 1. Notably, there were no differences in mortality (ATA+ HR 2.0 95%CI 0.7-5.2, ref ACA+) and disease progression (ATA+ HR 1.3 95%CI 0.8-2.1, ref ACA+) after correction for age at baseline, sex and time since first non-Raynaud. Differences in the development of severe skin and lung progression could not be assessed by Cox regression, as they did not occur in the ACA+ subset.

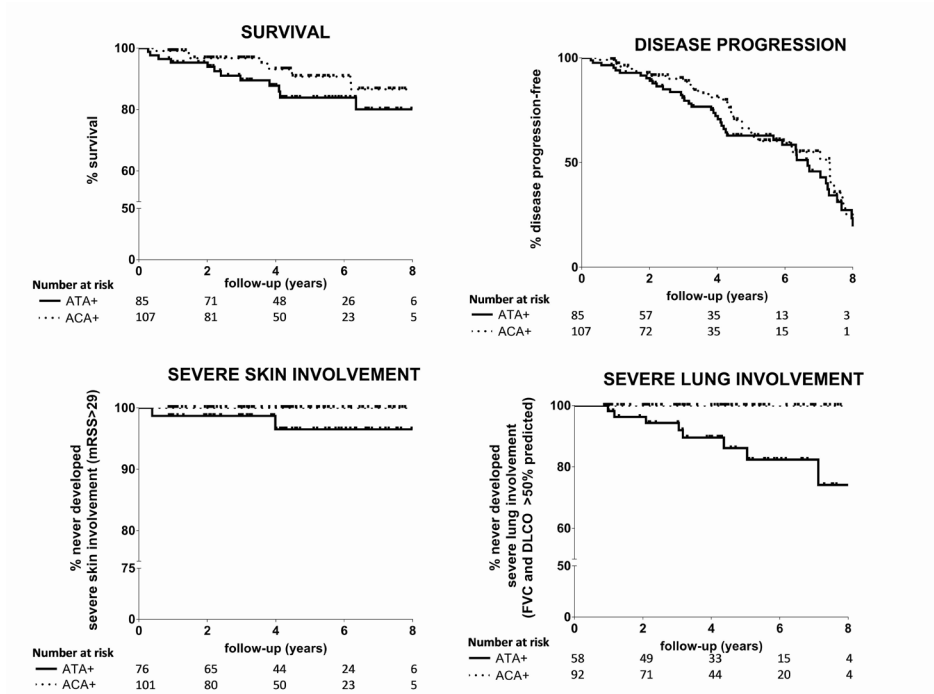

Figure 1. Comparison of survival, disease progression development of severe skin and development of severe lung involvement between ACA+ and ATA+ patients over time

Our data indicate that the introduction of the ACR/EULAR 2013 criteria has not resulted in improved prognostic properties of ACA and ATA in terms of mortality or disease progression. Still, ACA+ and ATA+ patients are phenotypically distinct. Hence, it is likely that the ACR/EULAR 2013 criteria lead to the identification of additional ATA+ patients with less severe disease. This notion is supported by the observation that mortality in the ACA+ subset is comparable to the findings reported by Steen et al. and because only 4 of the 17 ATA+ patients that were additionally identified received aggressive immunosuppression (either mycophenolate mofetil, cyclophosphamide or hematopoietic stem cell transplantation) during follow-up.

In conclusion, our findings suggest that ATA+ patients additionally identified using the ACR/EULAR 2013 criteria are not solely those identified earlier, but also include patients with a less severe disease course. Consequently, additional biomarkers are needed in SSc to guide clinical practice and patient selection for clinical trials.

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