Endothelin-1 type A receptors predict cardiac and vascular events in systemic sclerosis

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Objective: Cardiac and peripheral microvascular alterations are key features of systemic sclerosis (SSc), with outcome depending on the extent and severity of vascular lesions. Cardiac and vascular events are associated with poor outcome, being the major causes of death and morbidity in SSc. Reliable predictors of cardiac and vascular involvement are eagerly awaited. We have previously reported that angiogenic markers can predict the cardiovascular outcomes in SSc (1). In parallel, a first cross-sectional study reported an association between severe cardiovascular complications and functional antibodies against angiotensin II type 1 receptor (AT_1R) and Endothelin-1 type A receptor (ET_AR) (2). Therefore, our aim was to investigate the respective merit of all these markers in a prospective cohort.

Methods: serum anti-AT_1R and anti-ET_AR autoantibodies were measured with a sandwich ELISA together with serum levels of placenta growth factor (PlGF) and soluble vascular adhesion molecule (sVCAM) in a prospective cohort of 75 SSc patients without known cardiovascular involvement or severe comorbidities at presentation. Circulating endothelial progenitor cells (EPCs) were quantified in peripheral blood by flow cytometry after cell sorting, as previously described (1). The occurrence of at least one cardiac/vascular event was assessed during a planed 3-year follow-up by a composite index defined by the occurrence of at least one of the following event: a) one or more new ischemic digital ulcer (DU), b) pre-capillary pulmonary hypertension (PH) confirmed by right heart catheterization, c) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF)<50% d) scleroderma renal crisis (SRC), defined by a sudden and marked increase in systemic blood pressure and acute renal failure (1).

Results: The mean ± standard deviation (SD) age of SSc patients (64 women) was 55±12 year old and the mean ± SD disease duration was 9±8 years at baseline. Twenty-eight patients developed at least one cardiac/vascular event (DU in 18, PH in 5, LV dysfunction in 4 and SRC in a single patient). A strong correlation between anti-AT_1R and anti-ET_AR autoantibodies was observed ($r=0.88$, $p<0.0001$) at baseline. By univariate analysis, high baseline serum levels of anti-ET_AR were predictive of the occurrence of cardiac/vascular events ($p=0.002$), together with, as previously reported, low EPC counts ($p=0.003$) and increased levels of PlGF ($p=0.0005$) and sVCAM ($p=0.009$). No predictive value of anti-AT_1R antibodies was identified on cardiac/vascular events. Multivariate analysis confirmed high serum levels of anti-ET_AR antibodies (hazard ratio, HR: 3.71, 95% confidence interval, CI 1.44-9.52, $p=0.03$) and PlGF (HR: 5.22, 95% CI 1.96-15.87) as independent predictors of further development of cardiac/vascular events. The combination of high serum levels of anti-ET_AR antibodies and PlGF was highly predictive of cardiac and vascular events occurrence during follow-up (HR 7.27 95% CI 2.49-23.51, $P=0.0002$).

Conclusion: This study identifies for the first time anti-ET_AR antibodies as an independent predictor of cardiac and vascular events in SSc. This functional antibody, together with other angiogenic markers and in particular PlGF, may serve as biomarkers to improve cardiovascular risk stratification and therefore allow earlier therapeutic intervention.

Reference: (1) Avouac et al, Ann Rheum Dis 2012; (2) Riemekasten et al, Ann Rheum Dis 2011