



## Systemic sclerosis as prototypic disease with high levels of functional antibodies against angiotensin II type-1 and endothelin-1 type A receptor strongly predicting prognosis

G Riemekasten, A Philippe, I Lukitsch, et al.

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of affected patients may lead to early specific pharmacologic interventions.

**Comments** Duska Dragun and Gabriela Riemekasten received lecturers fees and research support from Actelion and Encysive as well as GSK.

**A11** **SYSTEMIC SCLEROSIS AS PROTOTYPIC DISEASE WITH HIGH LEVELS OF FUNCTIONAL ANTIBODIES AGAINST ANGIOTENSIN II TYPE-1 AND ENDOTHELIN-1 TYPE A RECEPTOR STRONGLY PREDICTING PROGNOSIS**

G Riemekasten, A Philippe, I Lukitsch, T Slowinski, M Näther *Charité Universitätsmedizin Berlin, Germany*

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**Background** Systemic sclerosis (SSc) features autoimmunity, vasculopathy and tissue fibrosis; the renin-angiotensin and endothelin systems have been implicated. The authors hypothesised a role for autoimmune receptor stimulation.

**Methods** The authors tested sera of 478 SSc patients (298 in the study cohort and 180 from two independent cohorts), 372 healthy subjects and 333 control-disease subjects, for antibodies against angiotensin II type 1 receptor (AT1R) and endothelin-1 type A receptor (ETAR) by solid phase assay. Organ involvement and patient survival were also investigated. Binding specificities were tested by immunoprecipitation. The biological effects of autoantibodies were tested in microvascular endothelial cells in vitro.

**Results** Anti-AT1R- and anti-ETAR-autoantibodies were detected in most SSc patients ( $p < 0.001$  compared to control diseases or healthy subjects). Autoantibodies specifically bound to respective receptors on endothelial cells. Higher levels of both autoantibodies were associated with progressive disease and in particular with vascular complications. Both autoantibodies predicted pulmonary arterial hypertension and SSc-related mortality. They exert biologic effect as they induced ERK1/2 phosphorylation and increased TGF $\beta$  gene expression in endothelial cells.

**Conclusions** Functional autoimmunity directed at AT1R and ETAR identifies SSc patients with more severe disease, pulmonary hypertension and decreased survival. AT1R- and ETAR-autoantibodies participate in disease pathogenesis and may serve as diagnostic tool for risk assessment. Identification