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First data-analysis of the prospective ETiCS-study after study-end confirms acute (microbial-induced) inflammation as a key trigger for the development of cardiac GPCR-autoantibodies

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Heart failure (HF) is the leading cause of mortality and morbidity in Western countries. In the past two decades, evidence for the clinical relevance of GPCR-autoimmunity in human HF has substantially increased. Stimulating autoantibodies targeting the second extracellular loop (ECII) of the cardiac beta1-adrenoceptor (beta1-aabs) have been claimed to be involved in the pathogenesis of HF and to increase the risk of cardiovascular death by three-fold. Still, the events triggering the formation of beta1-aabs and their impact on HF-progression are unknown.

Methods: In total 13 University Hospitals (12 German, 1 Serbian) prospectively recruited 226 patients (pts.) with a first acute myocardial infarction (FAMI), and 140 pts with acute (biopsy- or cMRI-proven) myocarditis (AMitis) into the Etiology, Titer-Course and effect on Survival of cardiac autoantibodies-study (ETiCS-study). This study aimed to investigate whether the presentation of cardiac membrane antigens (e.g., the beta1-adrenoceptor) following cardiac necrosis/inflammation triggers the formation of beta1-aabs. At baseline (BL) and three follow-ups (Fup1–3), blood was sampled to analyze the time-course of beta1-aabs. Beta1-aab titers were measured by FACS using Dyna-beads® M-270-Epoxy coated with increasing amounts of beta1-ECII-peptides (2.5–100 μg/ml), checked versus scrambled peptides (a mixture of same amino-acids). After reacting, the samples were measured by FACScan flow-cytometry; obtained data were analyzed with FlowJo (Treestar). When half-maximal binding was calculable the serum was classified beta1-aab-positive.

Results: From n=366 pts (226 FAMI/140 AMitis) recruited into the ETiCS-study 45 pts had to be excluded because of unperformed cMRI's; 46 pts stopped the study before Fup-1 (month 3). Only 180/226 FAMI- and 98/140 AMitis-pts had complete Fup1–3 (after 3, 6, and 12 months with clinical assessment, echocardiograms, and cMRI's at BL and Fup-3). In all valid ETiCS-pts (197 FAMI-/123 AMitis-pts) the titer-course of beta1-aabs was compared with the development of echo-LVEF. Relevant (high-affinity) beta1-aab-titers were detected in ~31% (37/123) of the AMitis-pts compared to only ~21% (42/197) of the FAMI-pts. In aab-positive AMitis-pts echo-LVEF did not recover and was always significantly inferior to aab-negative AMitis-pts (BL: 38 vs. 49% LVEF; Fup-3: 49 vs. 64% LVEF) whereas such a difference was not noted in FAMI-pts. In addition, aab-positive AMitis-pts had higher NT pro-BNP-, renin-, and aldosterone-levels than aab-negative AMitis-pts.

Conclusion: The first evaluation of the completed ETiCS-study clearly suggests that acute microbial-induced rather than post-infarction myocardial inflammation triggers the formation of clinically relevant beta1-aabs. AAb-positive AMitis-patients might profit from early intensification of standard HF-therapy (including early beta-blockade) and/or novel antibody-directed experimental therapies which are currently developed.