Figure 1. Arthritis score among 3 group of mice.

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Rheumatoid arthritis - prognosis, predictors and outcome

SAT0026

HIGHER LEVELS OF NATURAL ANTI-PHOSPHORYLCHOLINE ANTIBODIES ARE ASSOCIATED WITH LOWER RISK OF INCIDENT CARDIOVASCULAR EVENTS IN YOUNGER PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: The increased cardiovascular (CV) risk in rheumatoid arthritis (RA), especially in seropositive RA, is not fully explained by traditional risk factors. Immuno-inflammatory mechanisms and autoantibodies could be involved in the pathogenesis of atherosclerotic disease. Recent studies have suggested that anti-phosphorylcholine antibodies (anti-PC) of IgM subclass counteract the generation of senescent and IL-17+ T-cells, have atheroprotective effects and may play a role in formation and stabilization of atherosclerotic plaque.

Objectives: To investigate the association between IgM anti-PC antibodies with cardiovascular (CV) morbidity in patients with RA in age and sex groups and by serostatus.

Methods: The study population was derived from the BARFOT early RA cohort, recruited in 1994-1999. The outcome was CV events i.e. AMI, angina pectoris, coronary intervention, ischemic stroke and TIA tracked through the Swedish Hospital Discharge and the National Cause of Death Registries. The RA-disease measures and traditional risk factors were assessed according to the protocol. Sera collected at inclusion and the 2-year visit were analyzed with ELISA to determine levels of anti-PC IgM (Athera CVDefine kit, Athera Biotechnologies AB). The Kaplan-Meier estimates and Cox proportional-hazards regression models were applied. Analysis was stratified by median level of IgM anti-PC and performed within strata of age, sex and RA-autoantibodies.

Results: In all, 654 patients with early RA, 68% women, mean (SD) age 55(14.7) years, DAS28 5.2(1.3), 60% RF-positive and 60% ACPA-positive without prevalent CVD were included in this analysis. The level of IgM anti-PC at baseline was median (IQR) of 60.9(36.4-94.9) and at 2 years 56.0(32.3-84.2) U/ml. During follow-up of > 10 years, 141 incident CV events (21.6%) were registered. The levels of anti-PC both at inclusion and after 2 years of observation were lower in participants who experienced CV event than in those who did not, $p=0.020$ and $p=0.012$. The CV event-free survival differed between patients with levels of anti-PC above median compared with those with levels below, $p=0.003$ by log-rank test. The risk for incident CV event showed a 0.6-fold hazard (95% CI, 0.4-0.8) among patients with higher anti-PC levels as compared with those with lower levels, $p=0.003$. In the age groups, the risk for incident CV event was lower in patients aged <55 years at inclusion than in those who were older, hazard ratio (HR) 0.40 (0.17-0.94), $p=0.036$. This result persisted when adjusted for sex and all traditional risk factors, HR 0.36 (0.14-0.92), $p=0.032$. Also, the risk for incident CV events was lower in patients with higher anti-PC levels in females, HR 0.61 (0.39-0.45), and double RF- and ACPA- negative patients, 0.44 (0.21-0.90), in crude analyses. The favourable effect of anti-PC at baseline and the CV outcome was not observed in ages >55 years, males, ACPA+ and RF+ patients. There were no significant association between anti-PC level at 2 years and outcome.

Conclusion: These results suggest that higher levels of IgM anti-PC are associated with a lower risk of incident CV events over 10 years in younger patients. The favourable atheroprotective effect of IgM anti-PC may be a part of explanation of lower risk of atherosclerotic disease in younger persons, females and in those with seronegative RA.

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SAT0027

DEVELOPMENT AND VALIDATION OF A NOMOGRAM COMBINING CLINICAL AND HISTOPATHOLOGICAL SYNOVIAL FEATURES FOR PREDICTING EARLY TREATMENT RESPONSE IN NAIVE TO TREATMENT RHEUMATOID ARTHRITIS

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Background: Rheumatoid Arthritis (RA) is characterized by synovial tissue (ST) heterogeneity at disease onset in terms of inflammatory degree and microanatomical organization being related to treatment response.

Objectives: To develop a multiparametric tool for baseline treatment response prediction including disease characteristics and histopathologic features of ST biopsies, using a large single center (SYNGem Unit) naive to treatment RA cohort.

Methods: 240 naive to treatment RA who underwent US-guided ST biopsy, at the first clinical evaluation, were enrolled. Clinical and immunological characteristics were recorded for each patient. All ST FFPE specimens were stained with H&E and classified by a pathologist, blinded to clinical characteristics, using the Krenn score [1] to assess the degree of ST inflammation. All naive to treatment RA were treated according to the T2T scheme and DAS remission rate at 6-12 months was recorded. On the basis of the regression analysis, a nomogram was constructed that incorporated the significant factors predicting the "achievement of DAS-Remission at 6 months follow-up" in naive RA. The performance of the nomogram was assessed by discrimination and calibration.

Results: Univariate analysis showed that RA who achieved early (6 months) DAS-remission had, at baseline, significantly lower total Krenn score ($p<0.001$), shorter symptoms duration ($p=0.005$) and lower disease activity ($p<0.001$) than RA not achieving this clinical outcome. ROC curve analysis revealed that RA having, at baseline, a total Krenn score <4.5 [(AUC)95%CI.: 0.67(0.60-0.74), $p<0.001$] achieved more likely DAS-remission at 6 months (53.1%) than RA with total Krenn score ≥ 4.5 (28.9%, $p<0.001$). Interestingly, RA whose ST was biopsied within 3 months from joint symptoms beginning showed significantly lower ST inflammation as total Krenn score than RA whose ST was analyzed among 3-12 months ($p=0.04$) or after 12 months ($p=0.002$) since symptoms beginning. However, in terms of follicular structure presence, the microanatomical organization of the synovial inflammatory infiltrate did not differ comparing RA whose ST was biopsied within 3 months from joint symptoms beginning (44.4%) and RA whose ST was biopsied among 3-12 months (47.6%, $p=0.74$) or after 12 months (52.7%, $p=0.33$) since symptoms beginning.

Logistic regression analysis revealed that, at baseline, being VERA, not having HDA and having a total Krenn score <4.5 were synergistic factors of DAS-remission achievement at 6 months [OR:10.5(95%CI:2.28-48.01); $p<0.05$]. Based on the regression analysis, a nomogram integrating baseline clinical (disease activity and duration) and histological (total Krenn score) characteristics was developed in which the value of each of the variables was given a point score. A total score was calculated by adding each single point score and, by projecting the value of the "total points" score to the "probability" line up to 87.5%.

Conclusion: Krenn score is a reliable tool for the semi-quantitative assessment of ST inflammation on US-guided ST biopsies being contingent to baseline disease characteristics and can be integrated within a nomogram to better predict the therapeutic response in naive to treatment RA.

References:

[1] Krenn V, et al. Histopathology 2006

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