Interleukin-7 in aortic adventitia of patients with rheumatoid arthritis and coronary artery disease

Introduction Rheumatoid arthritis (RA) patients have increased cardiovascular risk (CV) due to accelerated atherosclerosis (ATS), which significantly contributes to excess mortality in RA. The increased CV risk cannot be fully explained by traditional risk factors and systemic chronic inflammation appears to play a crucial role. Interestingly, IL-7, a proinflammatory cytokine involved in RA pathogenesis, appears to play a role also in ATS but its effect on cardiovascular disease (CVD) in RA has not been studied yet.

Objectives To examine serum IL-7 levels and expression of IL-7, IL-7R, CD3 and CD20 in aortic adventitia of RA and non-RA patients with coronary artery disease (CAD) and to search for relationships between systemic IL-7 levels and expression of vascular markers, cardiovascular risk factors including metabolic and inflammatory parameters.

Methods We examined 19 RA and 20 non-RA patients undergoing coronary artery bypass graft surgery included in the Feiring Heart Biopsy Study. Serum IL-7 levels were measured by chemiluminescence (MSD). Biopsies from the adventitia of thoracic aorta from a subset of patients (12 RA and 14 non-RA) were stained for IL-7, IL-7R, CD3 and CD20 by immunohistochemistry and scored per mm² of tissue.

Results Non-RA patients had lower IL-7 serum levels than RA (3.4±3.3 vs. 6.7±3.5, p<0.05). Independently of RA diagnosis, IL-7 significantly correlated with CRP (rho=0.450, p=0.008), triglycerides (TG, rho=0.366, p=0.005), glucose (rho=0.642, p=0.001) and hypertension (p=0.036). Levels of IL-7 were associated with New York Heart Association class (rho=0.429, p=0.014) and this was stronger in non-RA patients (rho=0.577, p=0.010). No associations were found with smoking or markers of CAD severity (i.e., numbers of arteries with stenosis or previous myocardial infarcts (MI)).

The number of IL-7+ and IL-7R+ cells/mm² in adventitia were significantly higher in RA (134.2±45.5 and 144±49.9 respectively) than non-RA patients (46.9±22.8 and 54.4±20.2, p<0.005) and were associated with serum IL-7 levels (rho=0.551 and rho=0.588, p<0.01). Both IL-7+ and IL-7R+ cells were associated with a positive history of MI (rho=0.047 and p=0.005) and IL-7R+ cells with the number of previous MIs (rho=0.408, p=0.038). Only in RA patients, IL-7R+ cells showed a trend for correlation with TG (rho=0.771, p=0.072). IL-7+ and IL-7R+ cells correlated with CD3 (rho=0.688, p=0.013 and rho=0.630, p=0.028), but no correlation was found with CD20. Cholesterol and HDL levels were associated with IL-7+cells only in non-RA patients (rho=0.729, p=0.04 and rho=0.733, p=0.038).

Conclusions Among patients with CAD, those with RA had higher serum IL-7 and a greater expression of both IL-7 and IL-7R in aortic adventitia. Systemic levels of IL-7 were related to its vascular expression. Thus, the IL-7/IL-7R axis may play a role in the accelerated ATS observed in RA; further studies are needed to elucidate the precise role of IL-7 in CV risk in RA.

References

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Disclosure of interest None declared

P056 IMPORTANT ROLE OF CD11C+ DENDRITIC CELLS IN INFLAMMATORY ARTHRITIS

Introduction The main function of dendritic cells (DCs) is to present antigen to T-cells and therefore they play an important role in bridging the innate and the adaptive immune response. However, DCs can be divided in different subsets, which have intrinsic differences that lead to functional specialisation in the generation and maintenance of autoimmunity. Therefore the aim of our study was to investigate the role of CD11c+ conventional DCs and monocytes derived DCs in inflammatory arthritis.

Methods We analysed histological sections of K/BxN serum transfer arthritis as well as hTNFtg arthritis for the presence of CD11c+ cells by immunohistochemistry. We also performed synovial biopsies and analysed the cellular composition of the inflammatory infiltrate with respect to DCs. We used CD11c-diphtheria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter, allowing for specific depletion of CD11c+ cells by administration of diphtheria toxin (DT). K/BxN serum transfer arthritis was induced, and mice were given either DT or PBS or in wt and BARF3 deficient mice. In addition CD11c DTR mice were crossed into hTNFtg animals and also received either DT or PBS. The severity of arthritis was determined clinically and histologically.

Results We show that CD11c+ cells are present in significant numbers in the synovia of K/BxN and TNF driven arthritis. Both CD8+CD11c+ and CD11b+CD11c+ , can be found in synovial tissue. In K/BxN serum transfer arthritis, clinical scores showed that CD11c-DTR transgenic mice that received DT had significantly reduced paw swelling and loss of grip strength compared to PBS treated animals. Histological analysis found reduced inflammation after the depletion of CD11c+ cells in K/BxN arthritis. In addition local bone destruction and the number of osteoclasts was significantly reduced. Analysis of K/BxN arthritis in wt mice and BATF3-/-, mice, which lack CD8+CD11c+ DCs revealed no difference in arthritis severity between the two groups. In addition to K/BxN arthritis, we found that also in TNF-driven arthritis...
depletion of CD11c+ cells led to a significant reduction of synovial inflammation and a complete depletion of osteoclasts.

**Conclusions** These data show that in addition to initiating an adaptive immune response, CD11c+dendritic cells, are also involved in innate effector mechanisms of inflammatory arthritis. Especially CD11b+CD11c+ and monocyte derived inflammatory cells involved in innate effector mechanisms of inflammatory arthritis, suggesting that they could be an important therapeutic target for patients suffering from inflammatory arthritis.

**Disclosure of interest** None declared

### P057 EFFECTS OF ANTI-TNF THERAPY ON VASCULAR BIOMARKER LEVELS IN RHEUMATOID ARTHRITIS

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**Introduction** Previous studies have shown an increased risk of cardiovascular disease in rheumatoid arthritis (RA), due to RA-associated inflammation. Different vascular biomarkers, such as anti-hsp65 antibodies, asymmetric dimethylarginine (ADMA) and B-type natriuretic peptide (BNP) have been associated with atherosclerosis and RA. Anti-hsp65 antibodies were found in RA patients and these antibodies linked also to inflammation and atherosclerosis. ADMA is an endogenous competitive inhibitor of NOS and consequential can lead to increased nitrosative and oxidative stress. ADMA has been implicated with atherosclerosis, and also with rheumatoid arthritis. BNP also associated to cardiovascular diseases.

**Objectives** The aim of this study was to assess the effects of anti-TNF therapy on different vascular biomarkers, such as anti-hsp65, ADMA and BNP in patients with RA and their correlation with different laboratory and clinical markers.

**Methods** Altogether 36 RA patients were recruited and treated with either etanercept (ETN) or certolizumab pegol (CZP) in this 12 months follow-up study. Assessments were performed at baseline, at month 6 and 12. Amounts of IgG antibodies reacting with recombinant M. bovis hsp65 (Lionex, Braunschweig, Germany) were measured by ELISA. ADMA was assessed by HPLC with fluorescent detection. BNP fragments were assessed by commercially available ELISA kit (Biomedica, Vienna). In addition, disease activity (DAS28), age, disease duration, CRP, IgM rheumatoid factor (RF), anti-CCP (aCCP) and plasma lipid levels were also measured. Arterial flow-mediated vasodilation (FMD), carotid intima-media thickness (cIMT) and arterial pulse-wave velocity (PWV) were assessed by ultrasound.

**Results** There were no significant changes in the levels of anti-hsp60, ADMA and BNP due to anti-TNF therapy. However, baseline level of BNP is correlated with the levels of RF (R=0.479, p=0.004) and aCCP (R=0.591, p<0.001). Serum BNP levels at baseline and at month 6 were significantly increased in RF positive compared to RF negative patients (680.60±381.64 versus 292.94±198.27 pmol/L; p=0.007 and 668.95±346.51 versus 312.20±207.01 pmol/L; p=0.001) and also in aCCP positive compared to aCCP negative patients (670.61±633.04 versus 137.98±436.41 pmol/L; p=0.030 and 652.93±283.21 versus 456.48±423.11 pmol/L; p=0.021).

Furthermore we found the following correlations between baseline values: anti-hsp60 level correlated with ADMA (R=0.900, p=0.037), triglyceride (TG) (R=0.462,p=0.040) and PWV (R=0.564, p=0.040). Baseline level of ADMA positively correlated with body mass index (BMI) score (R=0.720, p=0.040) and also with HDL levels (high density lipoprotein) of patients (R=0.473, p=0.047).

**Conclusions** BNP levels were significantly higher in RF compared to RF- patients, which imply that BNP may associate with RF positivity. Specific biomarkers, such as ADMA, anti-hsp60 and BNP may play important role cardiovascular disease in RA.

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### P058 S100 PROTEINS EFFECTIVELY DISCRIMINATE SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS FROM HEALTHY CONTROLS, BUT ARE NOT ASSOCIATED WITH MEASURES OF DISEASE ACTIVITY

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**Introduction** The S100 proteins are important regulators of diverse calcium-dependent cellular processes including growth regulation, migration and apoptosis. Dysregulated expression of multiple members of S100 family is a common feature of cancer and several autoimmune diseases.

**Objectives** The aim of this study was to examine whether circulating levels of S100A4, S100A8/9 and S100A12 proteins could be useful as diagnostic or activity specific markers in systemic lupus erythematosus (SLE).

**Methods** S100 plasma levels were measured by ELISA in a cohort study of 44 patients with SLE, 8 patients with incomplete SLE (iSLE) and 43 healthy controls (HCs). Disease activity was assessed using SLEDAI-2 K. We examined cross sectional associations between concentrations of S100 proteins and SLE status, SLEDAI-2 K scores, and levels of conventional biomarkers.

**Results** Plasma levels of all analysed S100 proteins (S100A4, S100A8/9 and S100A12) were significantly higher in SLE patients compared to HCs (p<0.001, p<0.01, p<0.001, respectively). In iSLE patients, the levels of S100A4 and S100A12 but not S100A8/9 were significantly higher compared to HCs (p<0.001, p<0.01, p<0.001, respectively). ROC curve analysis was performed to establish the optimal threshold to discriminate SLE patients from HCs based on S100 levels. At the optimal cutoff point of 238 ng/ml, the area under curve (AUC) for S100A4 was 0.990 (95% CI: 0.977 to 1.000, p<0.001) with a sensitivity of 96% and specificity of 93.0%. The remaining two proteins also showed significant, but not as strong discriminative value [S100A8/9: AUC 0.684 (95% CI: 0.572 to 0.795, p<0.05); S100A12: AUC 0.809 (95% CI: 0.719 to 0.898, p<0.001)]. We found that only S100A12 levels were significantly associated with the SLEDAI-2K score (r=0.318, p=0.035). Both S100A8/9 and S100A12 levels were significantly higher in SLE patients with arthritis (p=0.043, p=0.015, respectively) and with haematological