AB0101

ASSOCIATION OF FETUIN-A SERUM LEVEL AND GLUCOCORTICOID INTAKE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Fetuin-A (FA) is a pluripotential glycoprotein, which plays an important role in bone turnover [1], inflammation, metabolic diseases [2] and etc. Several studies demonstrated association between FA serum level and rheumatoid arthritis (RA) severity and disease activity [3], however, there was made a suggestion that observed associations were due to glucocorticoids intake [4].

Objectives: To study the association of serum FA levels, glucocorticoids intake and RA activity.

Methods: 81 patients with RA verified by ACR/EULAR 2010 criteria were enrolled in our study. 43 patients were under glucocorticoid therapy with mean cumulative dose 7899±9029,4 mg (hereinafter M±SD) and 38 patients were not. DAS28 index was calculated to determine RA activity. FA serum concentrations were measured by ELISA. Correlations between serum FA levels and RA activity were assessed in each group. Statistic analysis was performed using software package "Statistica 10.0".

Results: The mean level of serum FA was 760,72±112,56 µg/ml. There was a negative correlation between FA serum level and DAS28 index ($r=-0,433$; $p<0,0001$) when calculated among all patients. We observed positive correlation between FA serum level and cumulative dosage of glucocorticoids ($r=0,297$; $p=0,008$). At the same time FA serum level and DAS28 index were correlated negatively in patients who were under glucocorticoid therapy ($r=-0,419$; $p<0,0001$) and were not ($r=-0,559$; $p=0,001$).

Conclusion: Serum FA level correlates with RA disease activity and glucocorticoids intake. However, the association between FA serum level and RA disease activity was independent of glucocorticoids intake in our study.

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AB0102

SPECIALIZED PRO-RESOLVING MEDIATOR RECEPTORS AS INFLAMMATORY RESOLUTION BIOMARKERS IN RHEUMATOID ARTHRITIS

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Background: The regulation of inflammation is a dynamic process involving several molecules as lipid mediators. The Specialized Pro-resolving Mediators (SPMs), such as Resolvin (RvD and RvE), Protectins, Maresins and Lipoxin A4 (LXA4), are bioactive metabolites of omega-3 and omega-6 fatty acids which drive inflammatory resolution phase and promote tissue repair. ERV, ALX/FPR2 and BLT1 are SPM receptors. Although in Rheumatoid Arthritis (RA) lipid mediators role within pathophysiology is under definition, studies on SPMs receptors role are still lacking in this disease.

Objectives: Purpose of this study is to define ERV, ALX/FPR2 and BLT1 expression in blood derived leukocytes and synovial cells and to correlate it to disease activity to define SPM receptors ad inflammatory resolution biomarkers in RA patients.

Methods: A cohort of 52 RA patients was enrolled in the study of which 40 with active disease (DAS28= 5,35 (5,18-6,40)) and 12 in sustained remission status (DAS28= 2,1 (1,83-2,42)). Each enrolled patient underwent peripheral blood (PB) drawing and 46 of them underwent US-guided synovial tissue (ST) biopsy. FACS gating strategy was used for PB and ST processing to evaluate percentage of positive cells and the mean fluorescence intensity (MFI) of ERV⁺, ALX/

FPR2⁺ and BLT1⁺ in CD45⁺CD3⁺, CD45⁺CD19⁺ for PB and ST, CD45⁺CD14⁺ and neutrophils for PB only and CD45⁺CD90⁺, CD45⁺CD64⁺CD11b⁺ macrophages (distinct in CD206⁺ and CD206⁻ subpopulations) for ST only. Each included ST was stained with haematoxylin/eosin and categorized by a pathologist, blinded to clinical characteristics, using the Krenn Score (KS) to assess ST inflammation degree. As control group, 11 undifferentiated peripheral inflammatory arthritis (UPIA) patients were enrolled in the study.

Results: Considering the whole RA cohort, DAS28 inversely correlated with BLT1⁺ positive cells on ST-derived CD45⁺ ($r=-0,48$; $p=0,048$), CD3⁺ ($r=-0,56$; $p=0,019$) and CD19⁺ ($r=-0,49$; $p=0,042$) cells, in contrast with CD90⁺ ($r=0,50$; $p=0,041$) cells. Similarly, both DAS28 and KS inversely correlated with ALX/FPR2⁺ positive cells in ST-derived CD45⁺ ($r=-0,42$, $p=0,050$ and $r=-0,41$, $p=0,046$ respectively) cells. Evaluating the MFI levels of the SPM receptors along all RA stages (naïve-to-treatment, resistant-to-treatment, sustained remission) compared with UPIA control group, interestingly ST-derived CD45⁺ cells of remission RA were depleted of ERV1 compared to naïve-to-treatment RA ($p=0,04$), despite comparable ST inflammation. Furthermore, highest ERV1 expression was found in ST-derived CD45⁺CD3⁺ and CD45⁺CD19⁺ cells in naïve-to-treatment RA compared with UPIA patients ($p=0,045$ and $p=0,012$ respectively). Moreover, the lowest BLT1 level was found in remission RA CD3⁺ cells compared with UPIA and naïve-to-treatment RA patients ($p=0,008$ and $p=0,023$ respectively).

Conclusion: SPM receptors expression seem to be tightly related to disease activity in the synovial tissue, suggesting an important involvement in the inflammatory process in RA patient.

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AB0103

THE AMBIGUOUS ROLE OF TISSUE CYTOKINES IN THE PATHOGENESIS OF RHEUMATOID ARTHRITIS

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Background: Cytokines stimulate the inflammatory response in the synovial membrane with rheumatoid arthritis (RA), initiate apoptosis of chondrocytes, activation of osteoclasts. The progression of comorbid diseases is also associated with the influence of cytokines. At the same time, anti-inflammatory cytokines are produced in various tissues. Their role in the pathogenesis of RA and its complications is ambiguous.

Adiponectin (A) and Fetuin A (FA) are classified as negative acute phase proteins. Their concentration decreases with an increase in the level of pro-inflammatory cytokines: TNF- α , IL-1 and IL-6. Molecules A and FA, regardless of various factors and from each other, have similar effects in relation to pro-inflammatory cytokines, lipid and carbohydrate metabolism.

Visfatin (V) and Nesfatin-1 (N-1) are pro-inflammatory adipokines. B is produced by cells of the mononuclear phagocytic system and connective tissue. N-1 - is produced by the cells of the intermediate and medulla oblongata and by the cells of the gastric mucosa.

Objectives: to study the correlation of B, H-1, A and FA with the severity of inflammation in RA

Methods: 60 patients with RA and 30 healthy individuals were examined. The level of cytokines was determined by an indirect enzyme-linked immunosorbent assay using commercial test systems (Bio Vendor, cat No. RD195023100, Bio Vendor Human Fetuin-A, RaiBiotech, cat No. EIA-VIS-1, RaiBiotech, cat No. EIA-NESF). All patients underwent a full examination. Diagnosed with 2010 EULAR / ACR recommendations.

Results: A decreased level of A (less than 0.8 µg/ml) was detected in 15 patients (25%), F-A (less than 653.55 µg/ml) in 16 (27%), a high level of V (more than 39 ng/ml) - in 55 (91%), N-1 (more than 37.95 ng/ml) - in 36 (60%), which is significantly more often than in healthy individuals. No significant difference in the levels of determined adipokines was found depending on the gender and body weight of patients with RA. The level of cytokines in RA is associated with high activity according to DAS 28, positivity by Anti-CCP, extraarticular manifestations of RA. The greatest correlation with extraarticular manifestations is with

cutaneous and cerebral vasculitis. The levels of FA and N-1 also correlated with more pronounced radiological changes (X-ray stage III). FA circulating inhibitor of ectopic calcification. N-1 level is positively correlated with systolic blood pressure.

Conclusion: A low level of A and FA, a high level of V and N-1 is characteristic of RA with the presence of high activity and positivity in the RF and Anti-CCP. An increased level of B is determined by more than 90% of patients, which indicates its high pro-inflammatory activity. The level of F and N-1 is also associated with the degree of damage to bone tissue (stage III, a lot of erosion). A positive correlation of level V and N-1, negative A and FA with the severity of inflammation in RA confirms the involvement of these proteins in the pathogenesis. A high level of A and V increases the risk of developing cardiovascular diseases and their complications, the effect of N-1 and FA is being studied. The effect of cytokines on osteoclasts and osteoblasts in RA is ambiguous

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AB0104

CORRELATION OF PLASMA 14-3-3 η LEVELS WITH DISEASE ACTIVITY MEASURES IN METHOTREXATE-NAÏVE RA PATIENTS TREATED WITH UPADACITINIB MONOTHERAPY IN THE SELECT-EARLY PHASE 3 STUDY

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Background: Early diagnosis and treat-to-target strategies in RA improve clinical and radiographic outcomes. 14-3-3 η is a soluble diagnostic biomarker that is involved in the pathogenesis of RA (1) including the potent activation of key signalling cascades such as the JAK-STAT pathway and whose initial expression coincides with a transition to synovitis. In undifferentiated arthralgia, 14-3-3 η independently predicts the development of RA. In confirmed RA, 14-3-3 η levels decrease with treatment response (2) and those changes are associated with clinical and radiographic outcomes, including the prediction of joint damage progression in patients who have achieved clinical remission. Upadacitinib (UPA), an oral JAK1-selective inhibitor, demonstrated significant and clinically meaningful improvements in RA vs. methotrexate (MTX) in the SELECT-EARLY phase 3 study (3).

Objectives: To determine the impact of treatment with UPA monotherapy 15mg QD on the levels of plasma 14-3-3 η and to explore its relationship with clinical measures in early MTX-naïve RA patients.

Methods: Patients from the SELECT-EARLY study were randomly selected (UPA n = 100; MTX n = 100) from the pool of patients with available plasma samples. 14-3-3 η tests were performed at Augurex according to standard operating procedures. Concentrations (ng/mL) were log-transformed for analysis. Non-parametric correlations between biomarker data and clinical end points were derived using the Spearman method. Changes in 14-3-3 η over time were compared using a Repeated Measure Mixed Linear Model. All statistical analyses were conducted in JMP 14.1 (SAS Institute).

Results: At baseline, 79% of patients were 14-3-3 η positive (≥ 0.19 ng/mL) with similar levels in both arms. Baseline levels of 14-3-3 η correlated significantly with baseline disease activity measures (CDAI $\rho = 0.164$, $p = 0.042$; DASCRP $\rho = 0.222$, $p = 0.004$; and SDAI $\rho = 0.177$, $p = 0.028$) but not with baseline mTSS ($\rho = -0.021$, $p = 0.787$); of note baseline mTSS were relatively low in this subset of early RA patients (median = 2, IQR [0 – 9.5]). Over time, 14-3-3 η levels tended to be lower in both the UPA and MTX groups. However, only treatment with UPA for 24 weeks resulted in a significant decrease in circulating 14-3-3 η ($p = 0.0002$) (Figure 1). In addition, at week 24 in the UPA arm, changes in 14-3-3 η levels correlated significantly with changes in concurrent disease activity measures (Δ CDAI $\rho = 0.264$, $p = 0.030$; Δ DASCRP $\rho = 0.267$, $p = 0.021$; and Δ SDAI $\rho = 0.267$, $p = 0.028$) but not with change in mTSS ($\rho = -0.186$, $p = 0.111$). In contrast to UPA, the relatively small changes in 14-3-3 η induced by MTX did not correlate with any clinical measures.

Figure 1

Conclusion: This study demonstrates that treatment with UPA 15mg QD monotherapy for 24 weeks significantly reduces the levels of circulating 14-3-3 η in MTX-naïve RA patients and that these changes correlate with clinical measures of disease activity. Although we were not able to detect a clear relationship between changes in 14-3-3 η and rate of structural damage progression, we would like to hypothesize that the superior clinical activity of UPA over MTX on joint damage may be related to the significant reduction in 14-3-3 η induced by UPA; this hypothesis should be tested in a larger RA cohort with a larger proportion of joint damage progressors.

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AB0105

CHECKPOINT MOLECULES AND PREGNANCY: ENHANCED SPD-L1 PREDICTS FLARE IN RA PREGNANCY AND POSTPARTUM

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Background: Rheumatoid arthritis (RA) is a female-predominant autoimmune disease that may affect women in childbearing age, making family planning an important issue for their life. There is a need for better understanding the mechanisms modulating RA in pregnancy and develop prognostic marker regarding adverse pregnancy outcome such as reduced birth weight and preterm delivery. As a crucial organ for peripheral tolerance during pregnancy, the placenta is expressing constitutively programmed cell death ligand 1 (PD-L1), major ligand of the inhibitory receptor PD-1 (Zhang et al, 2015). We hypothesize that the PD-1 pathway plays a central inhibitory role in regulating the course of the disease and pregnancy outcome in RA.

Objectives: To investigate the relationship between PD-1 pathway, disease activity during pregnancy/postpartum and pregnancy outcome in RA.

Methods: We measured soluble PD-1 and PD-L1 levels by ELISA in serum samples of 27 pregnant RA patients and 25 healthy pregnant controls at different time points during pregnancy and postpartum. As for pregnancy controls, we analyzed serum samples from 28 non-pregnant RA patients and 18 non-pregnant healthy controls. The data was analyzed in correlation with disease activity (measured by DAS28-CRP) and pregnancy outcome (defined as preterm delivery and birth weight). Statistics were calculated by Mann-Whitney U test and Wilcoxon test, correlations by Spearman rank test.

Results: In healthy pregnancy, sPD-L1 increases significantly in the 1st trimester ($p = 0.0198$) and decreases significantly postpartum ($p = 0.0029$). sPD-L1 values are higher in non-pregnant RA patients compared to non-pregnant healthy controls ($p = 0.047$) and there are no significant changes during RA pregnancy. Postpartum sPD-L1 values are significantly higher in RA patients compared to healthy controls ($p = 0.0014$), Fig. 1. Notably, regarding disease activity, we noticed a significant positive correlation between the overall sPD-L1 values in