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FRI0025 CIRCADIAN RHYTHMS OF ENDOTHELIAL NITRIC OXIDE SYNTHASE PRODUCTION IN FEMALES WITH RHEUMATOID ARTHRITIS AND ARTERIAL HYPERTENSION DEPENDING ON NOS3 T786C GENE POLYMORPHISM

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Background: One of the most common comorbidity in patients with rheumatoid arthritis (RA) is arterial hypertension (AH), with incidence ranging from 20 to 60%. Mechanisms of this comorbidity arises a lot of interest. In our previous study was established the association of *T786C NOS3* (rs2070744) gene polymorphism with AH in females with RA in the Ukrainian population [1].
Objectives: So next, we were aiming to investigate daily fluctuation of endothelial nitric oxide synthase (NOS3) in RA patients with AH depending on *NOS3 T786C* gene polymorphism.
Methods: In the study were enrolled 173 females with RA aged 43.7 ± 7.35 years (Mean ± SD) and 34 age-matched healthy women without joint diseases and autoimmune diseases (control). Serum NOS3 level was determined at 08:00 and 20:00 using Cloud-Clone Corp kits (USA). *NOS3 T-786C* polymorphism was determined by Real-Time PCR (Bio-Rad iCycler IQ5) using SNP-express kit. Study was carried out in compliance with bioethical standards and provisions of the WHO, Helsinki Declaration of the General Assembly of the World Medical Association (1989).
Results: Among enrolled patients prevailed individuals with more than 5 years disease history, II-III radiographic stage (80.9 %), and were seropositive for anti-cyclic citrullinated peptide (80.6%). There were 114 (66%) normotensive patients and 59 (34%) patients with AH (13% - I stage, 20.8% - II stage). The daily fluctuation of NOS3 serum level was established in the control group. The evening NOS3 level was higher in 1.3 times, than the morning level ($p<0.001$). In RA patients the similar fluctuations of NOS3 level was registered, but the daily NOS3 production was lower, than in control. Diurnal variation of NOS3 level depended on comorbid AH and *NOS3 T-786C* genotype. In *CC* genotype NOS3 levels at 08:00 and at 20:00 were lower in 1.2-1.3 times ($p<0.05$) than in *TT* and *TC* genotypes. In patients with RA and AH the lowest diurnal variation of NOS3 level was in *CC* genotype. The decrease of evening NOS3 production was strong associated with comorbid AH (OR 3.78; 95% CI 1.96-7.28).
Conclusion: Circadian rhythms of NOS3 production in females with RA and AH depend on *NOS3 T786C* gene polymorphism. The depression of NOS3 production in the evening can be predictor of comorbid AH in females with RA.

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FRI0026 PROTEOMICS ANALYSIS COMPARING THE MODE OF ACTION OF UPADACITINIB AND ADALIMUMAB HEAD TO HEAD IN RA IDENTIFIES NOVEL, DISCRETE EARLY IMMUNE PATHWAY MODULATION IN THE SELECT-COMPARE PHASE 3 STUDY

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Background: Upadacitinib (UPA), an oral JAK1 selective inhibitor, showed greater efficacy compared to adalimumab (ADA) in patients with active rheumatoid arthritis (RA) despite treatment with methotrexate (MTX) in the SELECT-COMPARE phase 3 study[1]. The regulatory immune networks affected by JAK1 inhibition compared with TNF-blockade have not been explored previously in a head-to-head trial.
Objectives: To infer the relative immunological pathway modulation of UPA compared with ADA in patients with RA via the evaluation of a pre-defined set of plasma proteins associated with inflammation.
Methods: Patients from the SELECT-COMPARE studies were randomly selected (PBO, n=100; UPA 15 mg QD, n=100; ADA 40 mg EOW, N = 100). The levels of 184 inflammation related proteins were analyzed using the Olink® platform; change from baseline in protein levels were expressed as Log2 Fold Change; a Repeated Measure Mixed Linear Model identified proteins differentially modulated by UPA and ADA compared to PBO, and between Responders (R defined as achieving Low Disease Activity [LDA] based on CDAI [≤ 10] at week 12) and Non Responders (NR defined as not achieving LDA at week 12) for the UPA and ADA groups. Pathway analysis were performed with Ingenuity® Pathway Analysis (Qiagen Inc.); selection criteria: mean |Log2 FC| ≥ 0.1 AND a FDR ≤ 0.05 → n = 88 out of 184 proteins; the top 10% pathways based on Z score for the ADA and UPA groups, and each visit (Week 2 and Week 8) were selected for comparison.
Results: Both UPA and ADA inhibited protein biomarkers (pBM) associated with Neutrophil / Macrophage biology. However, UPA preferentially inhibited pBM associated with T cells and ADA preferentially inhibited pBM associated with M1 or 'inflammatory' Macrophages. The pathways implicated *in silico* by these pBM changes in response to UPA and ADA tended to be similar except for T cell activity related pathways that were preferentially modulated by UPA.
In the ADA group, clinical response was mainly associated with lower levels of pBMs such as IL6, TNFRSF1A, MMP10, IL2RA, PLAUR, CCL2, TNFRSF10C, and SERPINE1, suggesting that control of these pathways may be important for response to ADA in RA.
In the UPA treated group, clinical response was mainly associated with slightly higher levels of the pBM IL17A, IL17C, CCL11, CCL20, and TIMP4.
Analysis of the reciprocal changes in the above showed that IL6, TNFRSF1A, IL2RA, NPPB, and SERPINE1 were downregulated similarly in UPA R and NR patients. By comparison, IL17A was modestly upregulated similarly in ADA R and