bisphosphonates on the one hand, with the MIC of all control groups on the other hand, revealed significant differences ($p < 0.002$).

Results: The analysis, using the paired t-test, the average MIC values in the combined group using bisphosphonates and the pooled control group, confirmed that the BMD in the zone of intervention in the bisphosphonate group was significantly higher than in the control: 0.320 ± 0.008 g / cm², respectively, versus 0.285 ± 0.019 g / cm² ($p = 0.002$). If the group was excluded from the analysis, where the defect was not filled, the tendency to differences remained: 0.320 ± 0.008 g / cm² vs. 0.308 ± 0.002 g / cm² ($p = 0.11$).

Mean BMDs of the whole segment with the use of bisphosphonates also proved to be significantly higher than in the control, both with the inclusion in the analysis of the group without replacement of the defect, and with its exception. Thus, when all control groups were included in the analysis, the mean MIC values in the group with bisphosphonates were 0.30 ± 0.01 g / cm² vs. 0.272 ± 0.12 g / cm² ($p < 0.001$). When excluding from the analysis of the group without replacement of the defect, the MIC values were respectively: 0.307 ± 0.01 g / cm² versus 0.285 ± 0.01 g / cm² ($p = 0.01$).

Conclusion: Relative to the control, an increase in BMD in the group using bisphosphonates excludes the possibility of their negative impact on the process of bone formation. The marked positive bone balance confirms the ability of bisphosphonates to maintain the remodeling mechanism at the physiological level.

References: Local application of bisphosphonates, osteoplastic materials, bio-composite material, bone implant reconstruction, bone formation.

Disclosure of Interests: None declared

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Rheumatoid arthritis - aetiology, pathogenesis and animal models

AB0082

INHIBITION OF TGF β SIGNALING USING SB-505124 BLOCKS TH17 DIFFERENTIATION AND RESTORES THE TH17/TREG BALANCE IN VIVO, BUT DOES NOT SUPPRESS EXPERIMENTAL ARTHRITIS

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Background: TGF β is an important growth factor that promotes the differentiation of T helper 17 (Th17) as well as regulatory T-cells (Treg). Due to its dual role, the potential of TGF β as therapeutic target is unclear.

Objectives: In this study we aimed to investigate the effect of inhibition of TGF β signaling with the ALK5 inhibitor SB-505124 on human Th17 differentiation *in vitro*, on cytokine production by human rheumatoid arthritis (RA) synovial explants, and study the effects of local SB-505124 treatment *in vivo* during innate immune and Th17-driven experimental arthritis models.

Methods: Magnetic sorted naïve human T cells were differentiated into Th17 cells with CD3/CD28 activation beads, IL-2, TGF β , IL-1 β , IL-23, α IFN γ and α IL-4 for 6 days. Human RA synovial biopsies were cultured for 24h w/o 5 μ M SB-505124, and supernatant was analyzed by Luminex. T cell-independent SCW arthritis and Th17-driven IL-1/mBSA arthritis were induced in C57Bl/6, and mice were treated with SB-505124 by daily intra-articular injections from day 0-4.

Results: SB-505124 potently reduced human Th17 differentiation *in vitro* by decreasing IL-17 and ROR γ t gene expression and IL-17 protein production. SB-505124 significantly suppressed IL-6 and TNF α protein production by human RA synovial explants. In addition, SB-505124 did not affect acute joint inflammation during SCW-arthritis (T-cell independent model). Interestingly, SB-505124 reduced Th17 levels in draining lymph nodes (dLN) during IL-1/mBSA arthritis while increased levels of Tregs were observed. Surprisingly, despite this skewed Th17/Treg balance, this did not result in suppression of joint inflammation and destruction in this Th17-driven arthritis model, whereas anti-IL-17 antibody treatment showed significant therapeutic effects.

Conclusion: We revealed suppressive effects of SB-505124 on human Th17 differentiation and the Th17/Treg balance in arthritic mice. However, SB-505124 did not suppress joint inflammation and destruction. This indicates that despite the importance of TGF β in Th17 differentiation, targeting TGF β signaling is not enough to suppress experimental arthritis.

Disclosure of Interests: None declared

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AB0083

STUDY OF THE ROLE OF ANGIOPOIETIN-LIKE PROTEIN TYPE 4 IN METABOLIC DISORDERS CAUSED BY INFLAMMATION IN RHEUMATOID ARTHRITIS

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Background:

Objectives: To assess the potential role of angiotensin-like protein type 4 (ANGPTL4) in metabolic disorders caused by inflammation in rheumatoid arthritis (RA).

Methods: The study included 88 patients with significant RA, 64 patients with other rheumatic diseases (RD) (36 patients with osteoarthritis (OA); 28 patients with psoriatic arthritis (PsA); 17 patients with ankylosing spondylitis (AS)) and 32 healthy individuals. Estimation of ANGPTL4 was carried out by enzyme immunoassay using the commercial test system "RayBio Human ANGPTL4 ELISA Kit" (RayBiotech, USA) in blood serum. Levels of ESR, CRP, RF, antibodies to cyclic citrullinated peptide (anti-CCP) and modified vimentin (anti-MCV) in the ELISA test were determined for all patients with RA.

Results: The level of ANGPTL4 in the blood serum of patients with RA was significantly higher than in healthy people ($p < 0.001$) and patients with other RD ($p = 0.012$ compared with OA; $p = 0.046$ with PsA; $p = 0.008$ with AS). ANGPTL4 indices in patients with RA correlated with the age of onset of RA ($r = -0.658$, $p < 0.001$), disease activity according to DAS-28 ($r = 0.449$, $p = 0.001$), level of education ($r = 0.235$, $p = 0.029$), dose of glucocorticoid hormones ($r = 0.321$, $p = 0.009$) and methotrexate ($r = -0.496$, $p = 0.05$), the presence of osteopenia ($r = 0.44$), signs of kidney damage - proteinuria ($r = 0.309$, $p = 0.037$) and hypoalbuminemia ($r = 0.386$, $p = 0.022$), as well as with CRP levels ($r = 0.488$, $p = 0.003$), ESR ($r = 0.458$, $p = 0.002$), serum vitamin D ($r = -0.417$) and urinary calcium when recalculated to creatinine ($r = 0.797$, $p = 0.032$).

Patients with RA showed a high frequency of insulin resistance (according to the HOMA-IR index) [1.27 [0.84–1.62] in patients with RA; 0.76 [0.44–1.02] in healthy individuals; $p < 0.001$) and the presence of coronary heart disease, as well as a positive correlation between disease activity (according to DAS-28) and insulin resistance (according to the HOMA-IR index) ($p = 0.033$).

Higher values of C-reactive protein ($p = 0.04$) and serum ANGPTL4 levels ($p = 0.042$, compared with patients with RA without type 2 diabetes; $p = 0.026$, compared with healthy individuals) were determined in the group of patients with RA with the presence of type 2 diabetes. ANGPTL4 acts as an inhibitor of lipoprotein lipase. His contribution to the development of dyslipidemia in RA can be demonstrated by the results we obtained when comparing groups of patients with / without signs of metabolic syndrome (MS). A positive correlation between ANGPTL4 and triglyceride levels ($r = 0.42$, $p = 0.018$) was found. An increase in the level of ANGPTL4 in blood serum of patients with RA with MS ($p = 0.027$ compared with RA without MS) can predict the development of cardiac pathology in this group of patients.

Conclusion: ANGPTL4 is directly involved in the regulation of glucose homeostasis, lipid metabolism, and insulin sensitivity. Cardiovascular diseases associated with atherosclerosis, insulin resistance and metabolic syndrome are known as the most common extraarticular manifestations of RA; the study of the role of ANGPTL4 in metabolic disorders caused by inflammation can show a new direction in the development of laboratory and therapeutic technologies in RA.

Disclosure of Interests: None declared

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AB0084

TNF RECEPTORS PROFILE CHANGES ON CYTOTOXIC T CELLS SUBSETS IN RHEUMATOID ARTHRITIS ARE ASSOCIATED WITH EFFECTIVE TREATMENT

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Background: Previous studies of co-expression profile of receptors to tumor necrosis factor alpha (TNF) in rheumatoid arthritis (RA) have revealed a number of indicators associated with diseases activity with 93% sensitivity and 90% specificity. However, the ratio of receptors to cytokines remains poorly understood. However, the question of therapy effect and its effectiveness in various alteration of cytokine receptors balance remains under investigated.

Objectives: To evaluate the dynamics of co-expression and quantitative expression of type 1 and 2 receptors for TNF in the subpopulations of CD3+CD8+ cells associated with changes in disease severity before and after effective basic therapy.

Methods: Subanalysis of patients with high disease activity level successfully treated with methotrexate and oral glucocorticoids ($n = 9$) was performed. As a control group, we used data from 43 healthy donors, comparable by sex and age distribution. Subpopulations of cytotoxic T cells were studied, which were included in the final diagnostic models for differentiating different degrees of severity of RA: naive T cells and memory T cells. The dynamics of changes in the indicators of receptors number and proportion of cells expressing the corresponding receptor were compared.

Results: For naive cytotoxic T cells, the main revealed feature was the relative stability of the number of expressed receptors (both TNFR1 and TNFR2), regardless of the therapy, while this number did not significantly differ from healthy ones for TNFR1 and was significantly lower for TNFR2 ($p < 0.05$ for all three fractions). At the same time, in terms of cell percentage, on the contrary, the therapy led to a change in total proportion of TNFR1+ cells closer to healthy donors indicators, and the proportion of TNFR2+ cells in the opposite direction.

For cytotoxic T memory cells, it was demonstrated that after successful treatment a significant increase in the number of type 1 receptors was observed, with a decrease in TNFR1+ cells proportion, while these indicators were close to the values of healthy donors. At the same time, healthy donors were characterized by a significantly higher expression of type 2 receptors in terms of cell density of receptors. It is noteworthy that with successful therapy, a slight increase in the number of TNFR2 was observed with a sharp decrease in the proportion of TNFR2+ cells ($p = 0.043$).

Conclusion: The balance of TNF receptor expression on cells actively involved in immunopathological processes affects both the density distribution of receptors on cells and co-expression in a subpopulation. Effective treatment of RA leads to equalization of the expression profile either by the percentage of cells or by the number of receptors, approaching the indicators of healthy donors, but not simultaneously.

Disclosure of Interests: None declared

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AB0085

MODULATION OF CIRCULATING SKELETAL STAMINAL CELLS IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOFACITINIB

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Background: Rheumatoid arthritis (AR) is an autoimmune systemic inflammatory disease characterized by chronic synovial inflammation resulting in bone damage and erosions, with consequently functional disability. Currently, attempts for regenerative therapies for osteo-cartilage pathologies have proved unsuccessful. Recently, a "pool" of skeletal stem cells (hSSCs: human skeletal stem cells) able to generating bone cells, has been identified in human bone (1).

Objectives: In light of these observations, we aim at characterizing skeletal stem cells in peripheral blood from RA patients candidate to Tofacitinib treatment.

Methods: In this pilot study 4 RA patients [4F; mean age 65 years; mean disease duration 19 years] candidate to Tofacitinib treatment and 4 healthy donors (HD), matched by gender and age, were enrolled. Blood samples were collected from each subject of the study, at baseline (T0) and for RA patients, after 1 month of Tofacitinib (T1), to evaluating hSSC (CD45-, CD146-, CD73+, PDPN+, CD164+) by flow cytometry. For this purpose, we performed on whole blood a negative magnetic selection for CD45 cells. Then, the eluate was labeled with antibodies anti CD146-PE, anti CD73-APC, anti CD164 - FITC and anti-Podoplanin (PDPN) PerCP/Cyanine5.5. The acquisition was performed using a FACS Calibur, which included 100,000 events per sample (Figure 1).

Results: The hSSCs percentage was significantly lower in RA patients than in HD ($p = 0.0286$). At T1, after treatment with Tofacitinib, mean hSSCs percentage significantly increased from 1.8% to 4.2% ($p = 0.016$ vs RA T0) (Figure 2A). Correlation analysis showed a significant indirect relation between the percentage of hSSC and disease activity measured by DAS28_{ESR}, SDAI and CDAI (Figure 2B).

Conclusion: The results of this study demonstrate, for the first time, circulating skeletal stem cells and their reduced expression in active RA patients. Tofacitinib treatment leads to a significant increase in hSSCs percentage. This evidence opens up new perspectives on bone repair mechanisms and on deepening of current therapeutic strategies.

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Figure 1

Figure 1. Flow cytometric strategy for hSSC analysis. Top panel represents the morphology of hSSCs (CD45-) cells. CD146- (R2) cells have been identified within of R1 region; CD73+ (R3) cells have been identified within of R2 region; CD164+ / PDPN+ (%hSSCs in UpRight (UR) quadrant) cells have been identified within of R3 region.