

THU0129 CD8+CD28- T-LYMPHOCYTES ARE ASSOCIATED WITH SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Patients with rheumatoid arthritis (RA) have an increased mortality and morbidity due to cardiovascular disease and accelerated progression of atherosclerosis. Altered populations of T-lymphocytes are associated with atherosclerosis, and chronic infection with cytomegalovirus (CMV) affects the T-cell-population.

Objectives: To study the association between subsets of T-lymphocytes, subclinical atherosclerosis assessed by intima-media thickness (IMT) and antibodies against CMV in patients with RA.

Methods: Patients with new-onset RA (n=71), aged ≤60 years at diagnosis, were consecutively included in a study of development of atherosclerosis. Ultrasound measurement of IMT of a. carotis communis was undertaken at inclusion (T0), after five years (T5) and after 11 years (T11) (n=54). At T11, flow-cytometry was undertaken to investigate subsets of T-lymphocytes (CD45+CD3+), where CD4, CD8, CD28, CD56 and CX3CR1 was studied. CX3CR1 is the ligand of fractalkine, an adhesion molecule expressed on activated endothelial cells to attract leukocytes. Serological analysis for CMV was undertaken from samples collected at T0, T5 and T11.

Results: The percentage of CD8+T-lymphocytes lacking the co-stimulatory molecule CD28 (CD8+CD28-) was significantly (standardized beta coefficient 0.39, p-value 0.01) associated with IMT at T11 in a linear regression model including T0 variables smoking, systolic blood pressure and cholesterol. No association with IMT was seen for CD4+CD28- T-lymphocytes. CX3CR1 was expressed in 71% of CD8+CD28- T-lymphocytes, compared with 8.2% of CD8+CD28+. The prevalence of immunoglobulin G seropositivity for CMV was 47/70 (67%), 42/66 (57%) and 34/56 (52%) at T0, T5 and T11 respectively. Patients with constantly positive CMV serologies (T0, T5 and T11) had a significantly higher percentage of CD8+CD28- and CD4+CD28- T-lymphocytes. Also the proportion of cells expressing CX3CR1 was in both CD4+ and CD8+ T-lymphocytes associated with constantly positive serologies for CMV.

Conclusions: Subclinical atherosclerosis in patients with RA was associated with CD8+CD28- T-lymphocytes in a regression model adjusted for traditional cardiovascular risk factors. Positive serologies for CMV were associated with an increased proportion of CD8+CD28- T-lymphocytes and T-lymphocytes expressing CX3CR1.

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THU0130 IMPROVEMENT IN MEASURES OF DEPRESSED MOOD AND ANHEDONIA IN TWO RANDOMIZED, PLACEBO-CONTROLLED PHASE III STUDIES OF SIRUKUMAB, A HUMAN ANTI-INTERLEUKIN-6 ANTIBODY, IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Interleukin-6 (IL-6) is one of the known neuroactive-cytokines involved in neuronal plasticity and stress coping and is associated with depression. Depressive symptoms are common in patients with rheumatoid arthritis (RA), a disease characterized by high peripheral IL-6. Previous analysis of a Phase II study¹ showed that sirukumab, a human monoclonal antibody that selectively binds to the IL-6 cytokine with high affinity, can help reduce depressive symptoms in RA patients.

Objectives: To further assess and validate the effects of sirukumab on relieving depressive symptoms in RA patients.

Methods: We conducted a post-hoc analysis of 2 Phase III, randomized, double-blind, placebo-controlled trials evaluating efficacy and safety of sirukumab in the treatment of RA. SIRROUND-D enrolled patients with active RA despite disease-modifying anti-rheumatic drugs and having serum C-reactive protein (CRP) ≥8mg/L at baseline. SIRROUND-T enrolled patients with active RA despite anti-TNF therapy and having serum CRP ≥8mg/L or erythrocyte sedimentation rate ≥28mm/h at baseline. Patients using antidepressants were excluded from the analysis. Patients were grouped by presence/absence of prevalent depressed mood and anhedonia (PDMA), based on the self-reported frequencies of these 2 core depressive symptoms in the SF-36, requiring one present at least "most of the time" and the other "some of the time" in the past 4 weeks. A depression score was derived based on the 2 core depressive symptoms of SF-36. Relief of depressive symptoms in patients with PDMA was evaluated by comparing changes in the depression score from baseline to week 8 between the placebo

and combined sirukumab groups directly and with adjustment for RA activity as measured by the Disease Activity Score-28 with CRP. Changes in depression score were also analyzed in RA patients who did not have an ACR50 response to sirukumab. The combined effect of anti-IL-6 treatment was estimated using meta-analysis of 2 Phase III, 1 Phase II studies of sirukumab and 1 Phase II study of the anti-IL-6 cytokine antibody siltuximab.

Results: At baseline, 19% and 22% of patients were classified as PDMA in the 2 studies, respectively. Sirukumab treatment, compared to placebo, significantly improved depressive symptoms by week 8 among PDMA patients (p=0.022 and 0.046 for the 2 studies, respectively) before adjusting for changes in RA activity. Within the sirukumab group, the reduction in depressive symptoms remained significant after adjusting for changes in RA activity (p<0.0001) and in ACR50 non-responders at week 8 (p<0.0001), while differences in improvements between the sirukumab and placebo group reduced to trends. Meta-analysis of 4 anti-IL-6 studies (1 siltuximab, 3 sirukumab) revealed that anti-IL-6 treatment helps alleviate depressive symptoms even after adjusting for changes in disease activity (Standardized Mean Difference =0.25, p=0.03).

Conclusions: Our findings are consistent with previous results from a phase II RA study. Peripheral anti-IL-6 cytokine treatment is associated with improvement in depressive symptoms in RA patients, possibly supporting a role for IL-6 dysfunction in depression.

References:

[1] Ann Rheum Dis 2015;74(Suppl2): 720.

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THU0131 PREMATURE CORONARY HEART DISEASE FREQUENCY IN RHEUMATOID ARTHRITIS WHO ARE RECEIVING BIOLOGIC AGENTS: HUR-BIO REAL LIFE RESULTS

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Background: Patients with rheumatoid arthritis (RA) are at increased risk of coronary heart disease (CHD) overall, as well as death from CHD. A direct impact of chronic inflammation on the vascular system, secondary effects of physical inactivity and some drugs used in the management of RA are shown as the reasons for the increase in this comorbidity (1).

Objectives: We aim to determine the frequency of CHD in the RA patients who receive biological agents.

Methods: Hacettepe University Biologic Registry (HUR-BIO) includes demographic and clinical data of patients treated with biological agent since 2005. By August 2016, 1235 RA patients were recorded in the database. Age, smoking status, comorbidities, current and previous treatments were analysed in 1000 patients. Disease activity was estimated by the 28-joint activity calculator (DAS28-ESR) and DAS28-CRP. Functional assessment was evaluated by the Health Assessment Questionnaire (HAQ). Premature CHD should be defined if clinical CHD or sudden death is documented in male younger than 55 years of age and in female younger than 65 years of age.

Results: Overall 1000 patients (79,8% female) were enrolled in this study. Mean age was 53,1±12,6 years old, mean disease duration was 12,3±9,3 years. CHD was detected 57 (5,7%) patients and female/male was 38/19. Premature CHD was observed in 38 (66,7%) patients. CHD patients had more frequently male, older, higher classical risk factors, higher baseline ESR level and higher functional disability (Table). HAQ score also remained high in CHD group at last visit. Classical cardiovascular risk factors, sex, seropositivity, disease activity score and HAQ score were similar in the premature and other CHD group. Coronary artery stenting, coronary artery bypass surgery and medical treatment was applied in 12 (21%), 20 (35,1%) and 25 (43,9%) CHD patients, respectively. There was no statistical difference in treatment of premature and other CHD.

Table 1. Characteristic of patients who have CHD or not

	CHD (n=57)	No CHD (n=943)	p
Female n (%)	38 (66,6)	19 (80,6)	0,011
Hypertansion n (%)	38 (66,6)	271 (28,7)	<0,001
Diabetes Mellitus n (%)	11 (19,3)	97 (10,3)	0,033
Smoking (current/past) n (%)	30 (52,6)	370 (39,2)	0,003
Age mean (SD)	64,7 (9,9)	52,4 (12,4)	<0,001
Baseline Erythrocyte sedimentation rate (SD)	45,7 (30,3)	36,1 (24,6)	0,009
Baseline HAQ mean (SD)	1,27 (0,64)	1,02 (0,62)	0,025
Last HAQ mean (SD)	0,84 (0,64)	0,66 (0,58)	0,024

CHD: Coronary heart disease, HAQ: Health Assessment Questionnaire.

Conclusions: As a results CHD were detected in 5,7 percents of RA patients who are receiving biological agents. Importantly, two third of these patients have

premature CHD. Classical risk factors are observed more frequently in CHD patients as expected but interestingly, no additional risk factors other than age were detected between premature and other CHD patients. This suggests that the primary factor triggers premature CHD is the underlying inflammatory rheumatic disease. The presence of CHD was determined by patient history which the limitation of our study. We did not assess to subclinical CHD in this study.

References:

[1] Comorbidity in rheumatoid arthritis, Carl Turesson, Swiss Medical Weekly, 2016.

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THU0132 IMMUNOGENICITY AND SAFETY OF 23-VALENT PNEUMOCOCCAL VACCINE FOR PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS FROM 2-YEAR FOLLOW UP

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Background: Comorbid infections have significant impact on morbidity and mortality, especially in autoimmune diseases. Prevention of infection is an integral part of supervision of these patients.

Objectives: To investigate immunogenicity and safety of 23-valent polysaccharide pneumococcal vaccine in patients with rheumatoid arthritis (RA) treated with diseases modifying anti rheumatic drugs (DMARDs) and biologic diseases modifying anti rheumatic drugs (bDMARDs) during the 2-year follow-up.

Methods: Out of 110 subjects (81 females (73,6%), 29 males (26,4%) aged 23–76 years) included into the study, 79 were RA patients and 31 were controls with a history of ≥ 2 episodes of lower respiratory tract infections (bronchitis, pneumonia). 52 patients with RA were on methotrexate (MTX), 14 were on leflunomide (LEF), 13 were on tumor necrosis factor alpha inhibitors (iTNF- α)+MTX. One dose (0,5 ml) of 23-valent polysaccharide pneumococcal vaccine was administered subcutaneously without discontinuation of MTX/LEF or 28–30 days prior to initiation of iTNF- α . Totally four study visits were preplanned: initial vaccination visit and 3 control visits in 1, 3 and 12 months after vaccination for 110 patients. 39 RA patients were followed up for 2 years (24 months). Routine evaluation during each visit included physical exams and laboratory tests. Levels of antibodies to pneumococcal capsular polysaccharide were measured using VacciZyme™ PCPIgG 2 kit (The Binding Site Group Ltd, Birmingham, UK). Post-immunization response coefficient was calculated for each participant as the ratio of AB levels during visits II, III, IV and V to baseline AB level at Visit I.

Results: Not a single case of clinically or radiographically confirmed pneumonia was documented during the follow up period. Pronounced positive immune reaction after administration of the vaccine under investigation was documented in RA patients during different therapies, i.e., significant post-immunization response coefficient increase. There were 61% responders among RA patients and 70% responders among the controls during one-year follow-up. Dynamics of post-immunization response coefficient in RA patients during 2-year follow up are presented in the Table. RA patients and the control group are marked more than 2-fold significant increase in the content of antibodies in 3 months after the vaccination. Despite the decline in their concentrations to 12 months, it remained at the proper level and was increased to 24 month follow-up. Good tolerability of the vaccine was documented in 65% of cases, satisfactory (injection site pain, swelling and hyperemia of the skin up to 2 cm in diameter and subfebrile fever) in 35% of cases. As these reactions had no causal relationship with current RA therapy, and fully resolved within 24 hours without additional treatment, no RA therapy modification was required. Pronounced DAS28 positive dynamics in RA patients (4,27 and 2,68 at Visit I and Visit V, respectively, $p < 0,001$) indicates the absence of any negative impact of vaccination on disease activity.

Table. Post-immunization response coefficient dynamics in RA patients during 2 year follow up. Me [25,75 percentile]. (n=39).

	Visit II (1 month)	Visit III (3 Month)	Visit IV (12 month)	Visit V (24 month)
RA patients	2,33* [1,6;3,8]	3,55* [2,32;6,23]	2,64* [2,03;6,39]	3,07* [1,56;6,18]

*p<0,05

Conclusions: Thus, all given prove the sufficient immunogenicity and safety of 23-valent pneumococcal vaccine in RA patients, getting different therapeutic regimens during the 2-year follow-up.

Disclosure of Interest: None declared

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THU0133 SERUM PENTRAXIN-3 IN THE ASSESSMENT OF CARDIOVASCULAR RISK IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is associated with the increased cardiovascular (CV) morbidity and mortality due to accelerating, progressive atherosclerosis. The chronic, systemic inflammatory process is responsible for both joint damage and increased CV risk in RA patients. Pentraxin 3 (PTX3) is an inflammatory marker, a member of long pentraxin superfamily, supposed to be involved in inflammatory process as well as in atherosclerosis.

Objectives: The goal of the study was to assess the role of PTX3 as an inflammatory marker in patients with RA and to evaluate the relationship between PTX3 and CV risk markers [carotid intima-media thickness (cIMT), QTc distance (dQTc), lipid profile].

Methods: The study group consisted of 72 consecutive RA patients, 60 (83,3%) female and 12 male (16,7%), with the mean (SD) age 53,4 (10,29) (range 21–71) and disease duration 16,8 (10,3) years (range 2–49). The activity of RA was estimated by clinical examination with the disease activity score in 28 joints (DAS28). Remission or low disease activity was observed in 35 (48,6%) patients; moderate or high disease activity (DAS28 >3,2) in 37 (51,4%) patients. Disease modifying antirheumatic drugs (DMARDs) used in the treatment included: methotrexate 61 (84,7%) patients, chloroquine or hydroxychloroquine 9 (12,5%), leflunomide 4 (5,6%), cyclosporine 1 (1,4%) patient. The majority of patients 54 (75%) were treated with biological DMARDs, currently or in the past.

Results: The mean (SD) PTX3 concentration in RA patients was 4,57 (2,83) ng/ml (range 1,43–16,07). The mean (SD) cIMT value was 0,86 (0,2) mm (range 0,43–1,77). There were 19 (26,4%) RA patients with advanced atherosclerosis (presence of atherosclerotic plaques).

The positive, significant correlations were found between PTX3 concentration and other inflammatory markers: C-reactive protein (CRP) (R=0,5), ESR (R=0,46) and white blood cell count (WBC) (R=0,41). PTX3 concentration was also correlated with clinical disease activity markers: DAS28 value (R=0,41), as well as with tender joint count (TJC) (R=0,01), swollen joint count (SJC) (R=0,009), patient's global assessment of the disease activity (R=0,02).

The mean (SD) PTX3 concentration was significantly higher in patients with moderate/high RA activity in comparison with remission/low disease activity [5,56 (3,29) vs 3,48 (1,71) ng/ml, $p=0,001$] and in patients anti-CCP positive compared with anti-CCP negative [4,57 (2,58) vs 3,02 (0,85) ng/ml, $p=0,04$].

The mean (SD) PTX3 concentration was significantly higher in patients with definite atherosclerosis (cIMT >0,9 mm) than in patients with subclinical or no atherosclerosis [5,77 (3,02) vs 3,99 (2,58) ng/ml, $p=0,04$], as well as in patients with atherosclerotic plaques in comparison with no plaques (6,18 (2,83) vs 4,02 (2,64) ng/ml, $p=0,0006$).

There was a negative correlation between PTX3 and dQTc (R= -0,33, $p=0,007$).

Conclusions: The results of the study suggest a twofold role of PTX3:

1. an inflammatory marker of the joint disease activity
2. a biomarker indicating intensity of atherosclerosis, estimated by greater cIMT value and the presence of atherosclerotic plaques. The negative correlation between PTX3 and dQTc suggests the increased risk of sudden cardiac death due to shortening of dQTc.

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THU0134 INTERSTITIAL LUNG DISEASE AND RHEUMATOID ARTHRITIS. MULTICENTER STUDY WITH TOCILIZUMAB

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Background: Interstitial Lung Disease (ILD) is a severe extraarticular manifestation of rheumatoid arthritis (RA). Anti-TNF α drugs and conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) have been involved in the development of ILD. IL6 has been implicated in the pathogenesis of ILD (Kobayashi J et al). However, a fatal case of exacerbation of ILD has been described with tocilizumab (TCZ) (Kawashiri SY et al).

Objectives: Our aim was to assess the efficacy and safety of TCZ in ILD associated with AR.

Methods: Multicenter study of RA patients with ILD treated with TCZ. ILD was diagnosed by high-resolution computed tomography (HRCT). TCZ was used at standard dose (8 mg/kg/iv/4 weeks). We have analyzed the following variables: a) 1-point change in the degree of dyspnea according to the Modified Medical Research Council (MMRC); b) Forced Vital Capacity (FVC) improvement $\geq 10\%$; and improvement $\geq 10\%$ in DLCO; c) HRCT, and d) joint assessment (DAS28 score).

Results: We studied 12 patients (9 women/3 men) with ILD related to RA.