who have developed RA so far and patients with arthralgia or at the time of RA manifestation.

Conclusion: We identified lower number of NK cells as well as NK-T and γδ-T cells in individuals at risk of developing of RA. The decrease in non-conventional T cells was observed despite the increased percentage of the classical T cells. We hypothesize that the disproportion of these lymphocyte subpopulations, described previously in established RA, observed here in at-risk individuals may reflect their predisposition for further development of RA.

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THU0084

TOFACITINIB REVERSED ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS: MECHANISTIC INSIGHTS FROM THE RAT ADJUVANT-INDUCED ARTHRITIS MODEL.

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Background: Tofacitinib, an inhibitor of JAK3 and JAK1, is approved for the treatment of rheumatoid arthritis (RA). Cardiovascular (CV) risk and events in RA patients treated with Tofacitinib is a matter of debate, but the vascular mechanisms involved are unknown.

Objectives: The aim of this study was to investigate whether Tofacitinib improves endothelial dysfunction (ED) and if so to explore the underlying mechanisms in the model of adjuvant-induced arthritis (AIA) in rats.

Methods: AIA was induced by injection of Mycobacterium butyricum in the tail of male Lewis rats. A group of rats without arthritis served as controls. At the first signs of arthritis, AIA received Tofacitinib (10mg/kg twice daily, s.c.) or 33%DMSO/PEG400 (Vehicle). Arthritis score was daily evaluated. After 21 days, preconstricted isolated aortic rings were relaxed with acetylcholine (Ach, 10-11-10-4 moles/liter) in the presence or not of inhibitor of nitric oxide (NO) synthase (L-NAME), cyclooxygenase-2 (NS398), arginase (nor-NOHA), endothelin-derived hyperpolarizing factor (EDHF) (apamin/charbdotoxin) and superoxide anions production (Tempol). Endothelium-denuded rings were used to determine the vasorelaxant response to the NO-donor sodium nitroprussate (SNP, 10-11-10-4 moles/liter). Blood pressure and heart rate were measured by invasive method. A radiographic score was attributed to hind paws.

Results: Compared to AIA-Vehicle, Tofacitinib dramatically reduced arthritis (-76%) and radiographic (-73%) scores (p<0.001), and improved Ach-induced vasorelaxation (p<0.05). Of note, Ach-induced vasorelaxation was not different between Tofacitinib-AIA and control rats. The response to SNP was not different between groups. The effect of Tofacitinib on ED was mediated by RvD5-treated mice than that in control group, although there was no significant difference.

Conclusion: The present results demonstrated that Tofacitinib reversed arthritis-induced ED, through the correction of all the acknowledged impaired endothelial pathways in the AIA model. As ED is the primum movens of atherogenesis, the use of Tofacitinib on the cardiovascular comorbidities associated to RA.

References:

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THU0085

RESOLVIN D5 MODULATES TH17/TREG CELL DIFFERENTIATION AND SUPPRESSES OSTEOCLASTOGENESIS

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Background: Resolution phase of acute inflammation has been recognized not passive but active process during the last 2 decades. This active process is highly regulated by novel families of potent bioactive lipid mediators, which are coined as specialized proresolving mediators (SPMs) including resolvins. Little has been known, however, about how resolvins are involved in chronic inflammation, such as rheumatoid arthritis (RA).

Objectives: To investigate whether lipid mediators (LM) are involved in the pathogenesis of RA.

Methods: We investigated lipid mediator profiling in the paws of SKG arthritis mice by using lipid chromatography (LC) /mass spectrometry (MS) /MS-based LM metaboloproteomics. CD4+ T cells from spleens of SKG mice were cultured on anti-CD3/CD28 precoated plate with IL-6/TGF-β, anti-IFNγ/IL-4 and analyzed by flow cytometry. CD4+ T cells were labeled with CFSE, and cell proliferation was analyzed by flow cytometry. Mouse bone marrow cells were cultured with M-CSF and RANKL, and TRAP-positive multinucleated cells were defined as osteoclasts. Osteoclast differentiation markers were analyzed by qRT-PCR.

Results: RvD5 or normal saline was administered daily into the peritoneal cavity of arthritic SKG mice.

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Objectives: We retrospectively evaluated treatment responses of patients with EORA for 3 years and their associated factors in a clinical setting.

Methods: The Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort is a large, single institute-based, observational cohort of RA patients established at Institute of Rheumatology, Tokyo Women’s Medical University, in 2000. The subjects were RA patients who first enrolled in the IORRA cohort from 2010 to 2014, were over 60 years old with less than 1-year disease duration, and had a DAS28-ESR over 3.2 at entry. The primary endpoint was DAS28-ESR <3.2 after 3-year observation. A multivariate logistic regression analysis was conducted to identify factors at baseline associated with the primary endpoint.

Results: Among a total of 250 patients in this study, 152 patients (60.8%) achieved DAS28-ESR <3.2 after 3-year observation (remission/low disease activity (RL) group), and 98 patients did not achieve DAS28-ESR <3.2 after 3-year observation (moderate/high disease activity (MH) group). Baseline characteristics of the patients were as follows (average ± SD or %): the RL group, age 69.9 ± 6.5, female 77%, DAS28-ESR 4.3 ± 0.8, J-HAQ 0.9 ± 0.7, PSL user 23.7%, MTX user 64.5%, and biologics user 4.0%; the MH group, age 69.4 ± 6.7, female 80.6%, DAS28-ESR 4.4 ± 0.8, J-HAQ 1.0 ± 0.7, PSL user 36.7%, MTX user 64.3%, and biologics user 6.1%. Proportions of the patients with cardiovascular disease and malignancy at baseline were 13.3% and 11.2% in the RL group and 5.9% and 13.3% in the MH group, respectively. DAS28-ESR and J-HAQ score after 3-year observation of the RL group were 2.3±0.5 and 0.4±0.5, respectively, and those of the MH group were 3.4±0.9 and 1.0±0.8, respectively. Corticosteroid use and having malignancy at baseline were associated with not achieving DAS28-ESR <3.2 after 3-year observation using multivariate analysis (Table 1). Similar results were obtained when MTX use and corticosteroid use were replaced by the average dose of each drug.

Conclusion: The majority of the patients with EORA achieved DAS28-ESR <3.2 after 3-year observation, and no use of corticosteroid and absence of malignancy at baseline were associated with the good outcome.


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