Background: Rheumatoid arthritis (RA) has been associated with increased cardiovascular (CV) risk and metabolic changes.

Objectives: We wished to determine how the Janus kinase (JAK) inhibitor tofacitinib influences vascular pathophysiology and metabolites of the arginine and methionine-homocysteine pathways.

Methods: Thirty RA patients with active disease were treated with either 5 mg bid or 10 mg bid tofacitinib and evaluated at baseline and after 6 and 12 months. We determined DAS28, CRP, IgM rheumatoid factor (RF) and anti-cyclic citrullinated peptide (aCCP) levels. We assessed brachial artery flow-mediated vasodilation (FMD), carotid intima-media thickness (IMT) and pulse-wave velocity (PWV) by ultrasound. We also determined plasma L-arginine, L-citrulline, L-ornithine, inducible nitric oxide synthase (iNOS), asymmetric (ADMA) and symmetric dimethylarginine (SDMA), L-N-monomethyl-arginine (L-NMMA), cysteine, homocysteine, and methionine levels.

Results: Twenty-six patients completed the study. Tofacitinib treatment maintained FMD and PWV. Ten mg bid tofacitinib significantly increased L-arginine, L-ornithine, iNOS and methionine levels after 12 months. Tofacitinib transiently increased L-citrulline and L-NMMA and decreased homocysteine levels after 12 months. Based on L-citrulline, L-ornithine, ADMA and SDMA levels, L-arginine remained highly available for endothelial NO production. Multivariate analysis indicated variable correlations of L-arginine, L-citrulline, ADMA, L-NMMA, homocysteine and methionine with DAS28, CRP, ESR and RF but not with aCCP. Regarding vascular pathophysiology, only PWV and methionine correlated with each other after 12 months.

Conclusion: Tofacitinib suppressed systemic inflammation in RA yielding stabilization of vascular function. It may exert CV protective effects in RA, at least in part, by shifting L-arginine metabolism to high arginine availability and decreasing homocysteine levels.

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POS0384

A NOVEL MECHANISM LINKING MUCOSAL BACTERIA WITH AUTOANTIBODY RESPONSES IN RA: ACETYLATED BACTERIAL LYSATE AS A MODEL ANTIGEN

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Background: Rheumatoid arthritis (RA) is characterized by autoantibodies against post-translationally modified proteins (AMPA) such as citrullinated, carbamylated and acetylated proteins. Importantly, these antibodies are highly multireactive, as they often recognize more than one of these post-translational modifications. Despite extensive research, the antigens inducing the breach of tolerance remain unknown, although microbial antigens are often suspected. Various bacteria are known to be capable of acetylation, therefore, it is intriguing to know what mechanisms can underlie the breach of tolerance towards acetylated proteins and development of anti-acetylated protein antibodies (AAPA).

Objectives: To investigate whether acetylated proteins of bacterial origin (1) are recognized by human derived AAPA and AAPA expressing B cells; and (2) can induce AAPA development when used to immunize mice.

Methods: Acetylated E. coli proteins were acquired with two separate methods (Figure 1A): by culturing E. coli in a condition promoting auto-acetylation (intrinsically acetylated bacterial proteins, IABP), or by directly acetylating lysate-derived proteins via a chemical reaction (extrinsically acetylated BP, EABP). Acetylated ovalbumin (AcOVA) served as positive control for AAPA induction in mice, non-acetylated BP (NABP) and phosphate buffer saline (PBS) served as negative

control. Mice were immunized with these proteins and the resulting antibody response was studied by ELISA. Furthermore, EABP/IABP/NABP were investigated for recognition by human-derived AAPA with ELISA and AAPA-expressing B cells with spleen tyrosine kinase (Syk) phosphorylation assay; acetylated human fibrinogen and native fibrinogen served as positive and negative control.

Results: Repetitive immunization of mice with EABP resulted in an AAPA response recognizing acetylated, carbamylated and citrullinated proteins. AAPA titers in these mice exceeded the titers in the positive control mice immunized with AcOVA and were substantially higher than in the NABP-immunized mice (Figure 1B). Human-derived monoclonal AAPA recognized EABP and IABP (not shown). B cell activation (measured by Syk phosphorylation) assay indicated that AAPA expressing B cells recognized EABP and (to a lesser extent) IABP, but not NABP (Figure 1C).

Conclusion: Acetylated bacterial proteins are potent antigens that can induce cross-reactive AAPA responses in mice and they are recognized by human AAPA. This suggests that acetylated bacterial proteins could possibly be involved in the breach of tolerance in RA.

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POS0385

DURING DEVELOPMENT OF RHEUMATOID ARTHRITIS, INTERMETATARSAL BURSTITIS MAY OCCUR BEFORE CLINICAL JOINT SWELLING: A LARGE MRI STUDY IN PATIENTS WITH CLINICALLY SUSPECT ARTHRALGIA

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Background: Inflammation of the synovial lining is a hallmark of rheumatoid arthritis (RA). A synovial lining is not only present at synovial joints and tendon sheaths but also at bursae. Inflammation of the synovium-lined intermetatarsal bursae in the forefoot, intermetatarsal bursitis (IMB), was recently identified with MRI. It is specific for early RA and present in the majority of RA patients at diagnosis. During development of RA, MRI-detectable subclinical synovitis and tenosynovitis often occur before clinical arthritis presents. Whether IMB is also present in a pre-arthritis stage is unknown.

Objectives: To assess the occurrence of IMB in patients with clinically suspect arthralgia (CSA) and its association with progression to clinical arthritis in a large MRI-study.

Methods: We studied 524 consecutive patients presenting with CSA. CSA was defined as recent-onset arthralgia of small joints that is likely to progress to RA based on the clinical expertise of the rheumatologist. Participants underwent unilateral contrast-enhanced 1.5T MRI of the forefoot, metacarpophalangeal (MCP) joints and wrist at baseline. Thereafter patients were followed for detection of clinical arthritis, as identified at physical joint examination by the rheumatologist. Baseline MRIs were evaluated for IMB at all 4 intermetatarsal spaces. Also synovitis, tenosynovitis and osteitis were