influence on Th17 decreasing and Treg cells increasing in patients with ERA, so we can hypothesise that part of the clinical response is own to the improvement in T cells balance. Previous data reported that Actinobacteria are strongly correlated with the production of IL-17 and a reduction of Nitrosipirae has been associated to increased inflammatory responses and to gut permeability in mice.\(^5\)

Lachnospiraceae family play an important role in the maintenance of intestinal homeostasis.\(^6\) The correlation between gut microbiota composition and Th17/Th16 axis observed in our patients may suggest the involvement of some bacteria family in Th17/Treg cells balance in the lamina propria of RA patients treated with MTX, even in the early phases of the disease.

REFERENCES:

Disclosure of Interest: None declared

AB0113
EFFICACY OF TREATMENT WITH PROBIOTICS IN THE INFLAMMATORY ACTIVITY OF PATIENTS WITH RHEUMATOID ARTHRITIS. SYSTEMATIC REVIEW OF THE LITERATURE

C. Fuego1, N. Mená-Vazquez2, R. Caparrós-Ruiz1, I. Ureña-Garnica1, G. Díaz-Cordovés1, F.G. Jimenez-Jimeñez3, M.C. Ordóñez-Cariles1, M. Rojas-Giménez1, R. Redondo-Rodríguez1, L. Cano-García1, M.V. Irigoyen-Oyarzábal1, C. M. Romero-Barco1, A. Belmonte1, S. Manrique-Aria1, A. Fernández-Nebro1, 1UGC de Reumatología del Hospital Regional Universitario de Málaga (HRUM), Instituto de Investigación Biomédica de Málaga (IBIMA), Universidad de Málaga; 2UGC de Reumatología del Hospital Regional Universitario de Málaga (HRUM), Instituto de Investigación Biomédica de Málaga (IBIMA), Departamento de Medicina y Dermatología, Universidad de Málaga, Málaga, Spain

Objectives: To study the effectiveness of the use of probiotics in the control of inflammatory activity of patients with rheumatoid arthritis and analyse its effect on their metabolic profile.

Methods: A bibliographic search was carried out in Medline and Embase. The search strategy included the terms MesH and the free text of “lactobacillus”, “bacillus”, “probiotics” and “rheumatoid arthritis.” The search strategies were carried out by two authors, which were included according to the type of studies: meta-analysis, systematic reviews and clinical trials, depending on the type of participant: adults with RA who have received probiotics, the main outcome measures: changes in the Disease Activity Score (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI)), as well as each of the parameters that constitute them: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), visual analogue scale of the doctor and the patient (EVA), number of painful joints (NAD) and inflamed (NAI) and functional status by Health Assessment Questionnaire (HAQ) Secondary variables: number of adverse reactions to probiotics.

Results: After the selection of 34 articles, 9 articles were finally included. All were randomised, double-blind, placebo-controlled clinical trials (RCTs) with a level of evidence between 1+ and 1++ and a recommendation grade of A and B. Seven CDs showed improvement in arthritis measurements. In Peltonen et al. observed a high rate of improvement in the experimental group than in the control group (3.1 vs 2.8, p=0.027). Mandal et al. described improvement of the EVA in the experimental group (p=0.046). Zamani et al. described an improvement in DAS28 (−0.3±0.4 versus −0.1±0.4, p=0.01). Vaghef-Mehrabany et al defined this improvement (p<0.01). Pineda et al showed an improvement in HAQ at 3 months in the experimental group (from 0.97 to 0.80, p=0.02), although not in ACR20 (p=0.33). Allipour et al. found improvements in CRP between the two groups (mean [95% CI]=−0.3±0.5 [p=0.007], MANOVA: mean [95% CI]=−0.2±0.3 [p=0.007]). Hatakka et al observed no significant improvement in the experimental group in HAQ, NAD and NAI, and Nenonent et al. Did not observe differences in DAS28. In the last, EC of Vaghef-Mehrabany of 2017 metabolic measurements were evaluated without finding significant improvements If an improvement in insulin resistance was observed as measured by the HOMA B index in the study by Zamani et al.

Conclusions: Treatment with probiotics seems to be effective in controlling the inflammatory activity of rheumatoid arthritis.

Disclosure of Interest: None declared

AB0114
MODULATION OF ENDOTHELIAL FUNCTION BY PROINFLAMMATORY CYTOKINES INVOLVED IN RHEUMATOID ARTHRITIS. FOCUS ON IL-17A, IL-20, IL-23 AND IL-9

P. Totonso, D. Wending1, G. Preul1, C. Demougeot1, 1EA 4267 PEPITE – Pathologies et Épithéliums: Prévention, Innovation, Traitements, Evaluation; 2Service de Rhumatologie, CHRU Besançon; 3EA 4266, Univ. Bourgogne Franche-Comté, Besançon, France

Background: Rheumatoid Arthritis (RA) is the most common inflammatory rheumatic disease, characterised by high circulating of pro-inflammatory cytokines. RA is associated with an increased cardiovascular risk secondary to the accelerated atherogenesis which is the consequence of endothelial dysfunction (ED)\(^1\). In addition to the well-known cytokines (TNF-α, IL-1β) and IL-6, emerging data identified new cytokines such as IL-17A, IL-20, IL-23 and IL-9 as putative key-players of the pathogenesis of RA. To date, whether these cytokines might contribute to RA-associated endothelial dysfunction is not known.

Objectives: This study investigated the effect of IL-17A, IL-20, IL-23 and IL-9 on endothelium-dependent relaxation in response to acetylcholine (Ach) in rat aortic rings.

Methods: Experiments were conducted on thoracic aortic rings from male Lewis rats (11 week old), incubated for 1 hour or 24 hour at 37°C with 2 concentrations of each cytokine (IL-17A: 250 pg/ml and 10 ng/ml; IL-20: 500 pg/ml and 5 ng/ml; IL-23: 80 pg/ml and 10 ng/ml; and IL-9: 300 pg/ml and 10 ng/ml). Incubation with 10 ng/ml TNF-α was used as a positive control and with vehicle as negative control. At the end of the incubation period, endothelial function was studied by assessing concentration-response curves to Ach (10−11–10−4 mol/L) after phe- nylephrine (PE, 10−5 mol/L) or KCl (30 mmol/L)-induced contractions.

Results: As described in the literature\(^2\), a 24h- but not 1h-incubation with TNF-α reduced Ach-induced relaxation. The same result was obtained with IL-17A (10 ng/ml). By contrast, IL-20 did not change Ach-induced relaxation whatever the concentration and the incubation time. Impairment in vascular relaxation was observed after exposure to IL-9 (10 ng/ml), both after 1h- and more severely after 24h-incubation. As regards IL-23, an effect was observed only after 1 hour incu- bation and with high concentration.

Conclusions: Our data demonstrated that IL-17A, IL-23 and IL-9 but not IL-20 induced endothelial dysfunction, with different kinetics profiles. Among the cyto- kines evaluated, IL-9 exhibited the most important effect thus revealing a new putative role of this pleiotropic cytokine in RA-associated cardiovascular risk. Further studies are needed to confirm these data on animal models of diseases.

REFERENCES:
[1] Steyers CM 3rd, Miller FJ Jr. Endothelial dysfunction in chronic inflamma-


Disclosure of Interest: None declared

AB0115
PROPHYLACTIC AND THERAPEUTIC ACTIVITY OF ALKALINE PHOSPHATASE IN ARTHRITIC RATS: SINGLE AGENT ACTIVITY AND IN COMBINATION WITH METHOTREXATE

D.M. Chandrupatla1, C.F. Molthoff2, W.I. Ritsema2, R. Voë1, E. Elshof2, D. Wendling2,3, D.M. Chandrupatla1, C.F. Molthoff2, W.I. Ritsema2, R. Voë1, E. Elshof2, D. Wendling2,3

1Amsterdam Rheumatology and Immunology Center, 2Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, Netherlands; 3Immunology, Kagoshima University, Kagoshima, Japan; 4Chemistry, Purdue University, West Lafayette, USA; 5Physiology, VU University Medical Center, Amsterdam, Netherlands; 6Rheumatology, KIMS Hospital, Kent, UK; 7AMRF BV, Wageningen, Netherlands

Background: Alkaline phosphatase (AP) is a gate-keeper of innate immune sys-
tem responses by detoxifying (dephosphorylating) inflammation triggering mole-
cules (ITMs) released from endogenous and external sources\(^1\) and maintaining physiological barriers.

Objectives: We examined whether AP’s broad mechanism of action may serve as a safe therapeutic, either as single agent or combined with methotrexate (MTX), in rheumatoid arthritis (RA).

Disclosure of Interest: None declared
Methods: A rat model for RA was used with repeated intra-articular methylated bovine serum albumin (mBSA) injections in one knee ("arthritic" knee), the contralateral knee serving as internal control. Recombinant human AP (200 μg, s.c.) was administered twice (spaced 4 days) before mBSA injections (prophylactic setting) or after arthritis induction (4x, 2x/wk, therapeutic setting), or combined with MTX (0.3 mg/kg or 1 mg/kg, i.p.) in 4 rats/group. Plasma pharmacokinetics of AP in arthritic and healthy rats was monitored by colorimetric enzymatic assay. As an endpoint of AP/MTX treatment outcome, macrophage infiltration (marking arthritic conditions) in knee sections, liver and spleen was assessed by immunohistochemistry (ED1 and ED2-macrophage specific antibodies), immunofluorescence (macropage marker; Folate Receptor-[r], FR), and positron emission tomography (PET) scans and ex vivo tissue distribution with the macrophage tracer [18F] fluoro-PEG-folate targeting FR).

Results: After AP administration, both in healthy and arthritic rats, plasma AP levels increased over 1 hour to reach a maximum of 50%–70% above baseline. Increased plasma AP levels in healthy rats were retained for at least 4 hours, whilst in arthritic rats AP plasma levels steadily returned to baseline levels within this time frame, suggesting consumption of available AP by conjugating to its ITM substrates. Prophylactic and therapeutic schedules of AP treatment, either as single agent or in combination with MTX, were well tolerated. Both prophylactic and therapeutic AP markedly reduced synovial macrophage infiltration in arthritic knees (ED1; 3.5–4 fold, ED2; 3.5–6 fold), comparable with MTX treatment effects.

Ex vivo tissue distribution studies corroborated the impact of AP, MTX and AP/MTX on reducing synovial macrophage infiltration. Beyond localised articular effects, AP also displayed systemic anti-inflammatory effects by a 2-fold reduction of ED1, ED2 and FR-positive macrophages in liver and spleen of arthritic rats.

Conclusions: AP as single agent and combined with MTX elicits local and systemic anti-arthritis activity in arthritic rats and appears promising as a new therapeutic compound against arthritic conditions.

REFERENCE:

Disclosure of Interest: D. Chandrupatla: None declared, C. Molhoff: None declared, W. Ritsema: None declared, R. Vos: None declared, E. Elshof: None declared, T. Matsuyma: None declared, P. Low: None declared, R. Musters: None declared, A. Hammonds: None declared, A. Windhorst: None declared, A. Lamermuts: None declared, C. van der Laken: None declared, R. Brands Employee of: employee, G. Jansen: None declared


ADIPONE STEM CELLSUPPRESSED SYNOVIAL INFLAMMATORY IN SKG/JCL MICE IN VIVO AND INFLAMMATORY CYTOKINE IN SYNOVIAL FIBROBLAST IN VITRO

H. Ueyama, T. Okano, K. Orita, H. Nakamura. Orthopedics, Osaka City University, Osaka, Japan

Background: Adipose derived stem cell (ADSC) is one of the stem cells produced by adipose tissue which can be collected easily and in large quantities. It has been reported that ADSC has anti-inflammatory effect in some disease models. However, the effect of ADSC for synovitis such as rheumatoid arthritis (RA) is unknown.

Objectives: The aim of this study is to investigate the effects of ADSC for joint synovitis and cartilage degeneration in SKG/Jcl mice in vivo and the effects of ADSC for synovial fibroblast in vitro.

Methods: SKG/Jcl mice which developed auto-immune arthritis by adjuvant stimulation were used as RA animal model. In vivo, the intra-articular injections of ADSC (ADSC group; n=10) or PBS (PBS group; n=10) were performed to the bilateral knee of SKG mice with arthritis. The knee joint was histologically assessed with synovitis score and Mankin score at 2 weeks after ADSC injection. In vitro, the anti-inflammatory effect of ADSC for stimulated human synovial fibroblast was analysed by real-time RT-PCR.

Results: In vivo, the synovitis score and Mankin score were statistically lower in ADSC group (synovitis score 2.0±0.7 vs 6.0±1.6, p<0.01 and Mankin score 2.2±0.8 vs 4.9±0.8, p<0.01) (figure 1). In vitro, the expression of tumour necrosis factor-stimulated gene-6 (TSG-6), the anti-inflammatory cytokine, was significantly higher in ADSC than in synovial cell (p<0.01). The inflammatory cytokine levels in stimulated synovial cell were significantly decreased by ADSC treatment (p<0.01) (table 1).

Abstract AB0116 – Table 1. Gene expressions in each cell by real-time RT-PCR

<table>
<thead>
<tr>
<th></th>
<th>Relative gene expressions referenced GAPDH as 1 (mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IL-6</td>
</tr>
<tr>
<td>ADSC</td>
<td>0.39±0.03</td>
</tr>
<tr>
<td>Synovial fibroblast</td>
<td>0.21±0.07</td>
</tr>
<tr>
<td>Stimulated synovial fibroblast (non-treatment, 24 hour)</td>
<td>7.8±1.5</td>
</tr>
<tr>
<td>Stimulated synovial fibroblast (non-treatment, 48 hour)</td>
<td>34.9±0.5</td>
</tr>
<tr>
<td>Stimulated synovial fibroblast (ADSC treatment, 48 hour)</td>
<td>5.2</td>
</tr>
</tbody>
</table>


*p<0.01 (the comparison to synovial cell by Mann-Whitney U test)

**p<0.01 (the comparison to non-treatment group by Mann-Whitney U test)

Conclusions: This is the first report to show the anti-inflammatory effect of ADSC for synovitis in RA animal model. ADSC can be collected with a minimally invasive technique more easily than other mesenchymal stem cells. ADSC might have potential to be one of the RA treatment.

REFERENCES:

Disclosure of Interest: None declared


ASSOCIATION OF VITAMIN D DEFICIENCY WITH CRP/ACPA POSITIVITY IN ALGERIAN PATIENTS WITH RHEUMATOID ARTHRITIS

I. Allam, R. Djidjik. Immunology, Beni Messous Teaching Hospital, Algiers, Algeria

Background: Vitamin D (VD) is a steroid hormone belonging to the class of secosteroids with myriad immune functions and seems to be involved in the development and severity of rheumatoid arthritis (RA).1–3

Abstract AB0117


---

* Disclosure of Interest: None declared