[2] O'Brien W, Fissel BM, Maeda Y, Yan J, Ge X, Gravallese EM, Aliprantis AO, Charles JF. RANK-Independent Osteoclast Formation and Bone Erosion in Inflammatory Arthritis. Arthritis Rheumatol. 2016 Dec;68(12):2889–2900.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.5383

AB0125 ANTI-DENGUE IGG ANTIBODY POSITIVITY AND RISK OF DEVELOPING RHEUMATOID ARTHRITIS: EVIDENCE FROM THE MALAYSIAN EPIDEMIOLOGICAL INVESTIGATION OF RHEUMATOID ARTHRITIS (MYEIRA) CASE-CONTROL STUDY

L.K. Tan[1,2], N.A. Ahmad Fauzi[1], W. Sulaiman[2], O. Ali[2], I.S. Lau[3], H. Hussein[4], N. S. Sharil[4], S.C. Gun[5], E. Mageswaren[4], M.-S. Mohd-Said[6], A. Mohd-Mokhtar[7], A. Rosman[3], M. Othman[8], C. Bengtsson[9], L. Alfredsson[9], L. Klareskog[10], S. Murad[11], L. Padyukov[10], C.L. Too[1,10]. *[1]Allergy and Immunology Research Center, Institute for Medical Research, Ministry of Health Malaysia, Kuala Lumpur; [2]Faculty of Medicine, University Kuala Lumpur Royal College of Medicine Perak, Ipoh, Perak; [3]Department of Medicine, Selayang Hospital, Selangor; [4]Department of Medicine, Putrajaya Hospital, Putrajaya; [5]Department of Medicine, Hospital Tunku Ja'afar, Seremban, Negeri Sembilan; [6]Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Center, Kuala Lumpur; [7]Department of Medicine, Tengku Ampuan Afzan Hospital, Kuantan, Pahang; [8]Department of Medicine, Hospital Raja Perempuan Bainun, Ipoh, Perak, Malaysia; [9]Institute of Environmental Medicine, Karolinska Institutet; [10]Department of Medicine, Rheumatology Unit, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; [11]Ministry of Health, Level 12th, Block E7, Parcel E, Federal Government Adminstrative Center, Putrajaya, Malaysia*

Background: Arthralgia is one of the common symptoms seen in RA and in mosquito-borne viral diseases (dengue and chikungunya infections). Studies have reported that both dengue and chikungunya infections are associated with long-term persistent rheumatic symptoms including joints, muscle and bone pain.
Objectives: We investigated the association between anti-dengue IgG antibody positivity and risk of developing anti-citrullinated peptide antibody (ACPA)-positive and ACPA-negative RA in the multi-ethnic Malaysian population.
Methods: A total of 1147 early RA cases (515 Malay, 254 Chinese and 378 Indians) and 1519 age, sex and residential area matched population-based controls (1,023 Malay, 208 Chinese, and 288 Indians) were included in this study. Anti-dengue IgG antibody was determined by ELISA method. The presence of anti-dengue IgG antibody and risk of developing ACPA-positive/ACPA-negative RA were estimated by calculating the odds ratio (OR) with 95% confidence interval (95% CI).
Results: Our data demonstrated that 79.1% (n=1,003) and 77.1% (n=1,255) RA and control subjects were positive for anti-dengue IgG antibody, respectively. Data analysis revealed that the Chinese RA patients has highest frequency of anti-dengue IgG antibody (86.6%) followed by the Indian (80.4%) and Malay (74.4%) RA patients while 83.7%, 87.5% and 73% Chinese, Indian and Malay healthy controls were positive for this antibody, respectively. The anti-dengue IgG antibody positivity was significantly associated with decreased risk of RA in the Indian population (OR 0.59, 95% CI: 0.38–0.91, p=0.02) and particularly for the ACPA-positive subset of RA (OR 0.60, 95% CI 0.37–0.96, p=0.03). Interestingly, we observed a non-significant increased risk for ACPA-positive RA in the Chinese (OR 1.49, 95% CI 0.81–2.72) and Malay populations (OR 1.06, 95% CI: 0.79–1.41) with anti-dengue IgG antibody. No association was observed between ACPA-negative RA and the antibody positivity.
Conclusions: Our study describes the association between anti-dengue IgG antibody occurrence and ACPA-positive RA, but not ACPA-negative RA in an ethnicity-dependent manner. Future research is needed to explore the biological mechanisms behind these findings.

REFERENCES:

[1] Mohd Zim MA, et al. Chikungunya infection in Malaysia: Comparison with dengue infection in adults and predictors of persistent arthralgia. Journal of Clinical Virology 2013;56(2013):141–145.
[2] Gissel Garcı´ et al. Long-term persistence of clinical symptoms in dengue-infected persons and its association with immunological disorders. International Journal of Infectious Diseases 2011;15(2011):e38–e43.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.6190

AB0126 LOW PREVALENCE OF ANTIBODIES AGAINST MALONDIALDEHYDE-ACETALDEHYDE ADDUCTS IN SPANISH PATIENTS WITH RHEUMATOID ARTHRITIS

L. Rodriguez-Martinez, E. Perez-Pampin, A. Mera-Varela, C. Conde, A. Gonzalez. *Experimental and Observational Rheumatology, Instituto Investigacion Sanitaria-H. Clinico Universitario de Santiago, Santiago de Compostela, Spain*

Background: Patients with rheumatoid arthritis (RA) present increased oxidative stress that leads to lipid peroxidation and the formation of malondialdehyde (MDA) and acetaldehyde (AA). These two compounds under oxidative stress form malondialdehyde-acetaldehyde (MAA) adducts with proteins, which are highly immunogenic. Recently, Thiele *et al.*[1] described the presence of antibodies against human albumin MAA adducts in patients with established RA from the Veterans Affairs Rheumatoid Arthritis (VARA) registry. Of particular relevance was the reported presence of IgG anti-MAA antibodies in 92% of the patients, including 88% of the anti-CCP negative patients. These results suggest MAA adducts could contribute to the pathogenesis of RA and the anti-MAA antibodies could drastically reduce the number of patients with seronegative RA.
Objectives: To replicate the association of anti-MAA antibodies with RA and explore their value as biomarkers.
Methods: Sera from 515 Spanish patients with established RA that fulfilled the 1987 ACR classification criteria and from 274 healthy controls were included. Available information included history of smoking, anti-CCP status, and genotype of HLA-DRB1 and PTPN22 rs2476601. Human serum albumin MAA adducts and hexyl-MAA standard were chemically synthesised. Anti-MAA antibodies against the albumin MAA adducts were determined by indirect ELISA using isotype-specific secondary antibodies for IgG, IgM and IgA.
Results: Anti-MAA antibodies were detected in a small fraction of the RA patients, who had slightly increased antibody titers compared to healthy controls, 6.4% were positive for IgG, 15.7% for IgM and 8.0% for IgA. The low prevalence of anti-MAA antibodies persisted in spite of multiple variations in the ELISA protocols including the use of different albumin sources, albumin MAA adducts produced in two different laboratories, and various secondary antibodies. IgM anti-MAA antibody titers were increased in smokers compared to non-smokers. Moreover, the presence of IgM and of IgA anti-MAA antibodies were associated with anti-CCP and RF positivity.
Conclusions: Anti-MAA antibodies were detected in a small fraction of the Spanish RA patients, but their low sensitivity questions the value of these antibodies as biomarkers of RA. Due to the contradictory findings, additional studies should be performed that will need to address also the role of MAA adducts on RA pathogenesis.

REFERENCE:

[1] Thiele GM, et al. Arthritis Rheumatol 2015;67(3):645–55.

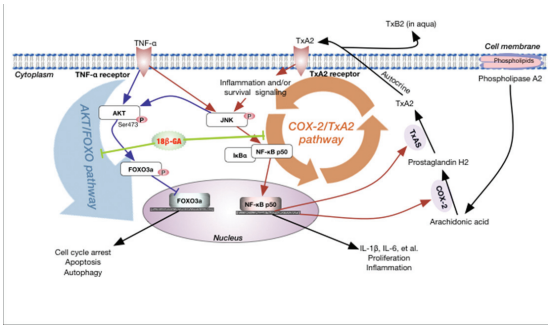
Acknowledgements: Supported by grants PI14/01651 and RD16/0012/0014 of the Instituto de Salud Carlos III (Spain) that are partially financed by the ERDF
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.4583

AB0127 ANTI-INFLAMMATORY AND PRO-APOPTOSIS EFFECTS OF 18BETA-GLYCYRRHETINIC ACID IN IN VIVO AND IN VITRO MODELS OF RHEUMATOID ARTHRITIS

M. Wang[1,2], R. Huang[1], on behalf of Runyue Huang Group. *[1]Rheumatology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China; [2]Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, Netherlands*

Background: Rheumatoid arthritis (RA) is one of the most common autoimmune diseases and it affects 0.5%–2.0% of the human population worldwide.[1]Though disease modifying anti-rheumatic drugs (DMARDs) can improve the clinical condition of patients with RA, toxicities of these drugs will be accumulated with long-term use and the unwanted side effects still cannot be avoided. 18β-glycyrrhetinic acid (18β-GA), an active component of licorice, exhibits potential anti-cancer, anti-inflammatory, anti-allergic, and anti-microbial activities.[2] Moreover, 18β-GA has been elucidated to attenuate hepatotoxicity or nephrotoxicity caused by chemical drugs, included methotrexate(MTX)[.[2] These evidences suggested 18 β-GA may become a candidate for low toxicity RA therapy as the mechanism was revealed.
Objectives: The aim of this study is to investigate the underline mechanism of 18β-GA on anti-inflammation and anti-proliferation in *in vivo* and *in vitro* models of RA.
Methods: CIA rats were treated with 18β-GA, methotrexate, celecoxib and three combination therapies for 30 days. Paw swelling volume, thromboxane synthase (TxAS), proliferating cell nuclear antigenprotein (PCNA), interleukin (IL)−1β, IL-6, and thromboxane B2 (TxB2) were detected to assess the anti-inflammation and

anti-proliferation effects of different treatments. To further study the potential mechanism, TNF-α-induced *in vitro* model was applied. With different treatments, cell proliferation was detected using MTS, meanwhile, cell cycle distribution and apoptosis were examined by flow cytometric analysis. Western blotting and real-time quantitative PCR were conducted to evaluate many moleculars that involved in interested pathways like COX-2/TxA2 pathway and AKT/FOXO3a pathway.
Results: The paw swelling volume and histological data indicate that 18β-GA administration attenuates arthritis severity in rats with CIA. Lower level of IL-1β, IL-6, and TxB2 were observed in serum of 18β-GA group as compared with model group. In addition, synovial immunohistochemistry data shows that 18β-GA decreased about half of PCNA intensity induced by collagen. However, *in vivo*, all data exhibited no significant differences among groups with monotherapy and combination therapy. In *vitro,* 18β-GA inhibited the mRNA and protein levels of COX-2 and TxAS that induced by TNF-α in MH7A cell line. Both p-JNK and NF-κ B1 (p50) were inhibited by 18β-GA as well as TxAS siRNA transfection. Moreover, 18β-GA inhibited MH7A proliferation in a time- and dose- dependent manner from MTS assay. Flow cytometric analysis revealed that 18β-GA induced cell apoptosis and caused G1-phase cell cycle arrest. Finally, AKT and FOXO3a were predominantly phosphorylated by TNF-α, whereas such effect was blocked by18β-GA treatment.



Abstract AB0127 – Figure 1

Conclusions: This study has for the first time shown that 18β-GA has an inhibitory role in synovial cell inflammation and proliferation, which is, at least in part, dependent on the regulation of COX-2/TxA2pathway and AKT/FOXO3a pathway. Thus,18β-GA should be regarded as a new potential drug candidate for RA therapy.

REFERENCES:

[1] Korczowska I. Rheumatoid arthritis susceptibility genes: An overview. World J Orthop 2014;5(4):544–9.
[2] Mahmoud AM, et al. Methotrexate hepatotoxicity is associated with oxidative stress, and down-regulation of PPARgamma and Nrf2: Protective effect of 18beta-Glycyrrhetinic acid. Chem Biol Interact 2017;270:59–72.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.5898

AB0128 CXCL1, BUT NOT AUTO-ANTIBODIES OR CD4+CCR6+ MEMORY TH CELLS WITHIN BLOOD, IS A MARKER TO DIFFERENTIATE MICE INTO COLLAGEN INDUCED ARTHRITISPOSITIVE OR NEGATIVE PRIOR TO CLINICALLY MANIFEST DISEASE

M. Molendijk, A.M. Mus, P.S. Asmawidjaja, E. Lubberts. *Erasmus MC, Rotterdam, Netherlands*

Background: There is currently a knowledge gap on early pathogenesis prior to Rheumatoid Arthritis (RA) diagnosis. Additionally, current medication available for RA treatment has not been developed for prevention. Collagen induced arthritis (CIA) could aid in extending knowledge on early RA pathogenesis and testing the preventive effects of medicines.
Objectives: In this study we sought a marker that can differentiate mice prior to clinically manifest disease into their future CIA status with the aim to facilitate research into early disease processes and preventive treatment strategies.
Methods: Blood was obtained at time points prior (days 12 and 19) and after clinically manifest disease (days 27 and 35) during CIA. Antibodies against bovine and mouse collagen type II (mCII) were measured from plasma by ELISA. $CD4^+CCR6^+$ memory Th cells as well as other T cell types were determined in blood. Cytokines and chemokines were detected in plasma by Luminex. Mice were divided into CIA negative and CIA positive groups based on CIA score reached on day 35.
Results: Antibodies against mCII of the IgG2a isotype differed prior to clinically manifest disease but are not suitable as a differentiation marker. $CD4^+CCR6^+$ memory Th cells in blood differed only at day 35. The same holds for IL-6, TNFα and CXCL2. In contrast, CXCL1 differed prior to clinically manifest disease with an AUC significantly better (p=0.003) than random.
Conclusions: Here we identified CXCL1 as a marker that can differentiate mice prior to clinically manifest disease into CIA positive and CIA negative mice. This might help facilitate research into early disease processes and preventive pre-clinical treatment strategies.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.6554

AB0129 ASSESSMENT OF MORPHOLOGY OF THE EARLY AND LATE STAGE OF JUVENILE RHEUMATOID ARTHRITIS

M. Salokhiddinov[1], U. Anarmetova[1], G. Haydarova[1], I. Xodjanazarov[2]. [1]*Tashkent Medica Academy*; [2]*Traumatology, Tashkent Medical Academy, Tashkent, Uzbekistan*

Background: One of the current problems of modern rheumatology is chronic inflammatory diseases of the knee joint in children. With juvenile rheumatoid arthritis (JRA), an uncontrolled inflammatory process can lead to the formation of contractures and deformities of the limbs
Objectives: Our aim is to study morphology of the early and late stage of juvenile rheumatoid arthritis
Methods: In total, 81 knee joint surgery was performed on 71 children of the child age in connexion with the JRA. The average age of the patients was 11 years (6–14). To verify the diagnosis during diagnostic arthroscopy, a multifocal biopsy from 7 points was performed. Pathomorphological study of the material was performed according to the conventional histological method of studying soft tissues
Results: The results of the pathomorphological examination were analysed for the time frame of the appearance of the JRA. Pathomorphological early and late synovitis criteria were found. Early criteria (typical for the first three months after the JRA debut) – the phenomenon of necrosis in synoviocytes and the subintimal layer, palisade-like cell structures in the sub-synovial layer, synoviocyte proliferation, fibrinoid superimpositions on the surface of the cover layer, productive endovascular endo- lytic endotheliosis, lymphocyte infiltration and plasmocytes. Late criteria (duration of the disease – more than 3–6 months): marked plasmacytic infiltration with the formation of lymphoid nodules with a hermetic centre, activation of fibrinoid and sclerotic processes with the formation of extensive fibrinoid necrosis with perifocal sclerosis, the formation of rheumatoid nodules, productive synovial hyperplasia, deposition of amyloid masses, formation of pannus granulation tissue with destructively invasive growth articular cartilage and synovium
Conclusions: Determining the stage of JRA is of great clinical importance for the early initiation of treatment and prevention of irreversible destructive complications. The proposed new method for determining the prevalence of pathological changes in the synovial membrane of the knee joint in children with JRA using a combined arthroscopic and pathomorphological evaluation of pathological changes in synovium in 7 joints allows to accurately determine the prevalence of the pathological process in the synovium, which has macroscopically only local manifestations

REFERENCES:

[1] Gormley GJ, Steele WK, Gilliland A, et al. Can diagnostic triage by general practitioners or rheumatology nurses improve the positive predictive value of referrals to early arthritis clinics? Rheumatology 2003;42(6):763–768.
[2] Houssien DA, Scott DL. Early referral and outcome in rheumatoid arthritis. Scandinavian Journal of Rheumatology 1998;27(4):300–302.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.2151

AB0130 SERUM LEPTIN AND ADIPONECTIN LEVELS IN RHEUMATOID ARTHRITIS PATIENTS, THEIR ASSOCIATION WITH INFLAMMATORY PROCESS

O. Galiutina, S. Shevchuk, Y. Seheda, I. Kuvikova. *Institute of Invalid Rehabilitation, Vinnitsya, Ukraine*

Background: It is well known that such bioactive substances as leptin and adiponectin are involved in different pathologic process including inflammation. At the same time, in a number of studies it was demonstrated anti-flammatory properties