Rheumatology, Madrid, Spain; ²Hospital Infantil Universitario Niño Jesús, Madrid, Spain

Background: Membrane-bound receptor for advanced glycation endproducts (mRAGE) expression increases in the presence of its ligands (e.g., High Mobility Group Box 1, HMGB1) and triggers an inflammatory immune response. In contrast, soluble RAGE (sRAGE) acts as a decoy receptor and downmodulates inflammation. Some studies have demonstrated that decreased sRAGE levels are negatively correlated with disease activity in juvenile idiopathic arthritis (JIA) but expression of mRAGE has not been studied.

Objectives: The aim of this study is to evaluate mRAGE and sRAGE on peripheral blood (PB) and synovial fluid (SF) mononuclear cells (MC) of patients with JIA and healthy controls and to assess whether there is an association with established inflammatory markers and clinical measures.

Methods: Matching samples of blood and synovial fluid were collected from patients with JIA (n=33) with active arthritis. RAGE expression on mononuclear cells was analyzed using flow cytometry. The intensity of RAGE expression was measured as mean fluorescence intensity (MFI). Levels of sRAGE and HMGB1 were determined with a specific ELISA kit in the serum and synovial fluid (SF) of patients with JIA. Relation between cellular RAGE and sRAGE with disease activity parameters [JADAS71, CHAQ, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] and HMGB1 were described. We compare mRAGE expression in PBMC and serum sRAGE levels between JIA patients and age-matched healthy controls (n=43).

Results: 24 patients with oligoarticular JIA and 9 patients with polyarticular JIA were studied, 8/23 females with a mean age of 7.7 ± 3.6 . MFI of mRAGE in PBMC and SFMC of JIA patients were significantly decreased in comparison with MFI of mRAGE in PBMC of healthy controls. Although serum levels of sRAGE were not different between patients and controls, sRAGE levels were lower in SF (570.2 [458.5-773.0]) compared to PB (759.7 [628.6-890.3]) in JIA patients, especially in the polyarticular group. By contrast, HMGB1 levels in SF were significantly higher than in PB of JIA patients. MFI of mRAGE in PBMC was correlated with JADAS71 (p 0.01) and CHAQ (p 0.07). There were no significant correlations between serum sRAGE and HMGB1 with JADAS71, CHAQ, CRP and ESR.

Conclusion: The sRAGE/RAGE system may be a modulator of inflammation in JIA patients. Differences between levels of sRAGE and HMGB1 in synovial fluid versus peripheral blood in patients with JIA may suggest a local role in the pathogenesis of JIA.

	JIA patients (n=33)	Healthy controls (n=43)
Age (years)	7.7 ± 3.6	7.9 ± 4.7 SD
Sex (boys/girls)	9/24	30/13
JIA category		
Oligoarticular	24	
Polyarticular	9	
Treatment		
NSAIDs	20	
MTX	12	
ANTI-TNFα	1	
ESR (mm/h)	26.3 (4-78)	
CRP (mg/dL)	1.4 (0.5-6.5)	
CHAQ	0.375 (0.2-3.75)	
JADAS-71	8.1 (2.8-16.3)	

Disclosure of Interests: Daniel Clemente Paid instructor for: Novartis, Speakers bureau: Novartis, Abvie, Roche, Sobi, Alberto García-Salido: None declared, Gustavo Melen: None declared, Manuel Ramírez-Orellana: None declared, J.C. López Robledillo: None declared

DOI: 10.1136/annrheumdis-2020-eular.6492

FRI0452

THE IMPACT OF SINGLE NUCLEOTIDE POLYMORPHISMS IN ADORA2A AND ADORA3 ON THE EARLY RESPONSE TO METHOTREXATE AND PRESENCE OF THERAPY SIDE EFFECTS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

J. Roszkiewicz¹, D. Michalek², A. Ryk², B. Szmyd³, E. Smolewska¹. ¹Medical University of Lodz, Department of Pediatric Cardiology and Rheumatology, Lodz, Poland; ²Medical University of Lodz, Department of Biostatistics and Translational Medicine, Lodz, Poland; ³Medical University of Lodz, Department of Pediatrics, Oncology and Hematology, Lodz, Poland

Background: Juvenile idiopathic arthritis (JIA) is the most frequent rheumatic disease in children, with an estimated prevalence between 16 and

150 per 100 000 [1]. Methotrexate (MTX) administered at the dose 10-15mg/m² is currently recommended as the first-line treatment in most of JIA subtypes [2]. Despite its widespread use in rheumatology, the mechanism of MTX immunomodulatory action remains incompletely understood [3]. Free adenosine is one of the particles possibly associated with the action of MTX, acting via three types of adenosine receptor: ADORA2A, ADORA2B, and ADORA3 [4].

Objectives: The aim of our study was to determine the association between single nucleotide polymorphisms in ADORA2A (rs2236624, rs2298383) and ADORA3 (rs3393) receptors genes on the disease activity and presence of MTX therapy side effects in patients with JIA.

Methods: One hundred children with JIA of all subtypes treated with MTX were recruited to the study. Demographic and clinical parameters were collected at the baseline of MTX therapy and on a control visit 4-6 months (median 5.09 months) after starting MTX. The clinical parameters included inflammatory markers values, number of joints with active arthritis, number of joints with restricted range of movement, physician's global assessment of disease activity, parent/patient global assessment of overall well-being, functional ability (measured by the Childhood Health Assessment Questionnaire – CHAQ) and the value of Juvenile Idiopathic Arthritis Disease Activity Score 71 (JADAS 71). Presence of MTX side effects was evaluated on the control visit. SNP genotyping was performed using genomic DNA isolated from peripheral blood samples.

Results: Both polymorphic variants of ADORA2A (rs2236624, rs2298383 - CC/CT) were significantly associated with 3.5 times higher odds of gastrointestinal side effects occurrence (OR: 3.52, 95%CI: 1.12-11.03, p=0.03 and OR: 3.49, 95%CI: 0.89-13.66 p=0.07) after adjustment to age, sex, dose and route of MTX administration. In addition, children with the ADORA3 rs3393 polymorphic variant (CT/CC) after six months of MTX treatment had significantly lower number of joints with active arthritis (0.0 vs 1.0, p=0.04), lower JADAS 71 score (3.0 vs 5.1, p=0.16) and lower value of CRP (0.6 vs 2.4, p=0.02).

Conclusion: Although future studies are needed to verify our findings, polymorphisms in ADORA2A and ADORA3 genes may become the determinants of MTX treatment efficacy and gastrointestinal toxicity in children with JIA.

References:

- [1] Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-392.
- [2] Ferrara G, Mastrangelo G, Barone P, et al. Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting. *PediatrRheumatol Online J*. 2018;16(1):46. Published 2018 Jul 11. doi:10.1186/s12969-018-0255-8.
- [3] Brown, P. M., Pratt, A. G., & Isaacs, J. D. (2016). Mechanism of action of methotrexate in rheumatoid arthritis and the search for biomarkers. *Nature Reviews Rheumatology*, 12(12), 731–742. doi:10.1038/nrrheum.2016.175.
- [4] Varani, K. et al. A2A and A3 adenosine receptor expression in rheumatoid arthritis: upregulation, inverse correlation with disease activity score and suppression of inflammatory cytokine and metalloproteinase release. *Arthritis Res. Ther.* 13, R197 (2011).

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.4772

FRI0453

COMPARATIVE GENE PROFILE IN MONOCYTES FROM CHILDHOOD- AND ADULT-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS: CLUES TO DIFFERENT SYSTEMIC INVOLVEMENT

I. C. Aranda-Valera¹, A. M. Patiño-Trives¹, R. M. Rosa¹, M. A. Aguirre¹, P. S. Laura¹, C. Pérez Sánchez¹, M. Luque-Tévar¹, I. Arias de la Rosa¹, M. D. C. Abalos-Aguilera¹, D. Ruiz-Vilchez¹, M. Espinosa¹, N. Barbarroja Puerto¹, E. Collantes-Estévez¹, C. Lopez-Pedraza¹. ¹IMIBIC/Reina Sofia Hospital/ University of Cordoba, Cordoba, Spain

Background:

Objectives: 1. This study, developed within the Innovative Medicines Initiative Joint Undertaking project PRECISESADS framework, aimed at identify specific inflammatory and oxidative stress determinants involved in the enhanced CV-risk present in SLE patients and to analyze the relevance of the sustained positivity for anti-dsDNA on the establishment of their atherothrombotic status.

Methods: One hundred and twenty-four SLE consecutive patients (not including patients with associated antiphospholipid syndrome), belonging to the PRECISESADS project, were evaluated for the presence of CVD and its association

with positivity for anti-dsDNA antibodies. A second cohort of 62 SLE patients was included, of which endothelial dysfunction, lipid profile, the presence of atheroma plaques (identified by a pathologic increase in the carotid intima media thickness -CIMT-), and the frequencies of anti-dsDNA positivity for 7 years, were evaluated. Serum inflammatory and oxidative stress biomolecules, and NETosis-derived bioproducts were further evaluated by multiplex assay and specific commercial kits, respectively. Besides, miRNomes were identified using next-generation sequencing. Clinical significance of the biomolecules analyzed was explored by correlation/association studies with immunological and CV-risk features.

Results: A significant relationship among the incidence of CVD (i.e. thrombosis or cardiac involvement) and the positivity for anti-dsDNA antibodies was recognized in the first SLE cohort. Accordingly, in the second SLE cohort, significantly impaired micro-vascular endothelial function (identified by reduction of hyperemia post-occlusion area), increased atherogenic index and pathologic increase in the CIMT were assessed in patients positive for anti-dsDNA in relation to anti-dsDNA negative patients. Around a 65% of SLE patients displayed a sustained positivity for anti-dsDNA antibodies for more than 7 years. These patients showed a distinctive and specific molecular profile compared with patients that had remained negative for anti-dsDNA, including increased inflammatory profile (IL1B, IL2, IL6, IL17, EOTAXIN, FGF, GMCSF, IFN γ , IP10, RANTES, TNF), enhanced oxidative status (lipoperoxides), and higher NETosis (nucleosomes, elastase). Levels of those biomolecules were closely interconnected and associated to their regulatory miRNAs, which accordingly exhibited differential expression in SLE anti-dsDNA(+) vs anti-dsDNA(-) patients. Finally, the frequency for positivity of anti-dsDNA significantly correlated both with markers of endothelial dysfunction and with the presence of atheroma plaques in SLE patients, pointing at the direct involvement of anti-dsDNA-Abs in the development of these processes.

Conclusion: 1. Positivity for anti-dsDNA antibodies confers a specific inflammatory/oxidative profile linked to an enhanced CV-risk in SLE patients. 2. Moreover, the sustained positivity for anti-dsDNA antibodies fosters the establishment of an atherothrombotic status in these autoimmune patients.

Acknowledgments: Supported by the EU/EFPIA -IMI-JU PRECISESADS (n° 115565) and ISCIII (PI18/0837 and RIER RD16/0012/0015), Co-funded with FEDER.

Disclosure of Interests: Inmaculada Concepcion Aranda-Valera: None declared, Alejandra M. Patiño-Trives: None declared, Roldán Molina Rosa: None declared, María A Aguirre: None declared, Pérez Sánchez Laura: None declared, Carlos Pérez Sánchez: None declared, María Luque-Tévar: None declared, Iván Arias de la Rosa: None declared, María del Carmen Abalos-Aguilera: None declared, Desiree Ruiz-Vilchez: None declared, Mario Espinosa: None declared, Nuria Barroja Puerto Grant/research support from: ROCHE and Pfizer., Speakers bureau: ROCHE and Celgene., Eduardo Collantes-Estévez Grant/research support from: ROCHE and Pfizer., Speakers bureau: ROCHE, Lilly, Bristol and Celgene., Chary Lopez-Pedreria Grant/research support from: ROCHE and Pfizer.

DOI: 10.1136/annrheumdis-2020-eular.4923

FRIDAY, 05 JUNE 2020

Paediatric rheumatology

FRI0454

UNDER DETECTION OF INTERSTITIAL LUNG DISEASE IN JUVENILE SYSTEMIC SCLEROSIS (JSSC) UTILIZING PULMONARY FUNCTION TESTS. RESULTS FROM THE JUVENILE SCLERODERMA INCEPTION COHORT

I. Foeldvari¹, B. Hinrichs², K. Torok³, M. J. Santos³, O. Kasapcopur³, A. Adrovic³, V. Stanevich³, F. R. Sztajn bok³, M. T. Terreri³, A. P. Sakamoto³, E. Alexeeva³, J. Anton³, M. Katsikas³, V. Smith³, R. Cimaz³, M. Kostik³, S. Appenzeller³, M. Janarthanan³, M. Moll³, D. Nemcova³, D. Schonenberg³, C. Battagliotti³, L. Berntson³, B. Bica³, J. Brunner³, P. Costa Reis³, D. Eleftheriou³, L. Harel³, G. Horneff³, D. Lazarevic³, K. Minden³, S. Nielsen³, F. Nuruzzaman³, A. Patwardhan³, Y. Uziel³, N. Helmus¹. ¹Hamburg Centre for Pediatric and Adolescence Rheumatology, Hamburg, Germany; ²Kinderklinik Heidelberg Pulmologie, Hamburg, Germany; ³JSSc Collaborative Group, Hamburg, Germany

Background: Juvenile systemic sclerosis (jSSc) is an orphan disease with a prevalence in around 3 in a million children. Pulmonary involvement in jSSc occurs in approximately 40 % in the inception cohort. Traditionally in jSSc, pulmonary function testing (PFT) with FVC and DLCO are used for screening and computed tomography (HRCT) was more reserved for those with abnormal PFTs. More recently, it has become apparent that PFTs might not be sensitive enough for detecting ILD in children.

Objectives: Utilizing a prospective international juvenile systemic scleroderma cohort (JSScC) [2], to determine if pulmonary screening with FVC and DLCO is

sufficient enough to assess the presence of interstitial lung disease in comparison to CT evaluation.

Methods: The international juvenile systemic scleroderma cohort database was queried for available patients with recorded PFT parameters and HRCT performed to determine sensitivity of PFTs detecting disease process.

Results: Of 129 patients in the jSScC, 67 patients had both CT imaging and an FVC reading from PFTs for direct comparison. DLCO readings were also captured but not in as many patients with tandem HRCT (n = 55 DLCO and HRCT scan). Therefore, initial analyses focused on the sensitivity, specificity and accuracy of the FVC value from the PFTs to capture the diagnosis of interstitial lung disease as determined by HRCT.

Overall, 49% of the patients had ILD determined by HRCT, with 60% of patients having normal FVC (>80%) with positive HRCT findings, and 24% of patients having normal DLCO (> 80%) with positive HRCT findings. Fourteen percent (n = 3/21) of patients with both FVC and DLCO values within the normal range had a positive HRCT finding.

Conclusion: The sensitivity of the FVC in the JSScC cohort in detecting ILD was only 39%. Relying on PFTs alone for screening for ILD in juvenile systemic sclerosis would have missed the detection of ILD in almost 2/3 of the sample cohort, supporting the use of HRCT for detection of ILD in children with SS. In addition, the cut off utilized, of less than 80% of predicted FVC or DLCO could be too low for pediatric patients to exclude beginning ILD. This pilot data needs confirmation in a larger patient population.

Supported by the "Joachim Herz Stiftung"

Disclosure of Interests: Ivan Foeldvari Consultant of: Novartis, Bernd Hinrichs: None declared, Kathryn Torok: None declared, Maria Jose Santos Speakers bureau: Novartis and Pfizer, Ozgur Kasapcopur: None declared, Amra Adrovic: None declared, Valda Stanevich: None declared, Flávio R. Sztajn bok: None declared, Maria T. Terreri: None declared, Ana Paula Sakamoto: None declared, Ekaterina Alexeeva Grant/research support from: Roche, Pfizer, Centocor, Novartis, Speakers bureau: Roche, Novartis, Pfizer., Jordi Anton Grant/research support from: grants from Pfizer, abbvie, Novartis, Sobi. Gebro, Roche, Novimmune, Sanofi, Lilly, Amgen, Grant/research support from: Pfizer, abbvie, Novartis, Sobi. Gebro, Roche, Novimmune, Sanofi, Lilly, Amgen, Consultant of: Novartis, Sobi, Pfizer, abbvie, Consultant of: Novartis, Sobi, Pfizer, abbvie, Speakers bureau: abbvie, Pfizer, Roche, Novartis, Sobi, Gebro, Speakers bureau: abbvie, Pfizer, Roche, Novartis, Sobi, Gebro, Maria Katsikas: None declared, Vanessa Smith Grant/research support from: The affiliated company received grants from Research Foundation - Flanders (FWO), Belgian Fund for Scientific Research in Rheumatic diseases (FWRO), Boehringer Ingelheim Pharma GmbH & Co and Janssen-Cilag NV, Consultant of: Boehringer-Ingelheim Pharma GmbH & Co, Speakers bureau: Actelion Pharmaceuticals Ltd, Boehringer-Ingelheim Pharma GmbH & Co and UCB Biopharma Sprl, Rolando Cimaz: None declared, Mikhail Kostik: None declared, Simone Appenzeller: None declared, Mahesh Janarthanan: None declared, Monika Moll: None declared, Dana Nemcova: None declared, Dienneke Schonenberg: None declared, Cristina Battagliotti: None declared, Lillemor Berntson Consultant of: paid by Abbvie as a consultant, Speakers bureau: paid by Abbvie for giving speeches about JIA, Blanca Bica: None declared, Juergen Brunner Grant/research support from: Pfizer, Novartis, Consultant of: Pfizer, Novartis, Abbvie, Roche, BMS, Speakers bureau: Pfizer, Novartis, Abbvie, Roche, BMS, Patricia Costa Reis: None declared, Despina Eleftheriou: None declared, Liora Harel: None declared, Gerd Horneff Grant/research support from: AbbVie, Chugai, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Speakers bureau: AbbVie, Bayer, Chugai, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Dragana Lazarevic: None declared, Kirsten Minden Consultant of: GlaxoSmithKline, Sanofi, Speakers bureau: Roche, Susan Nielsen: None declared, Farzana Nuruzzaman: None declared, Anjali Patwardhan: None declared, Yosef Uziel: None declared, Nicola Helmus: None declared

DOI: 10.1136/annrheumdis-2020-eular.1788

FRI0455

IS THERE AN INCREASE IN THE FREQUENCY OF INFLAMMATORY DISEASES IN THE FAMILIES OF PATIENTS WITH FMF?

S. Yildirim¹, M. Yildiz¹, A. Aliyeva¹, F. Haslak¹, O. Koker¹, A. Adrovic¹, S. Sahin¹, K. Barut¹, O. Kasapcopur¹. ¹Istanbul University-Cerrahpasa, Pediatric Rheumatology, Istanbul, Turkey

Background: Familial Mediterranean Fever (FMF) is the most common periodic fever syndrome in childhood with an autosomal recessive inheritance pattern and is characterized by unprovoked fever attacks, serositis episodes. The causative gene of the disease is MEFV that encodes pyrin protein. The pyrin protein takes a role in pathways related to inflammation, and mutations of it lead to increased inflammation. It is already shown that frequencies of some certain diseases like PAN, HSP increase in patients with FMF. Nevertheless,