Rag2^{-/-}Fra2 tg mice showed no fibrosis or Lin⁺gp38⁺ cell expansion. ECG parameters of Rag2^{-/-}Fra2 tg mice were not changed compared to control mice, indicating that inflammation is necessary to acquire Fra2-driven fibrotic phenotype and defects in the conduction system.

Conclusion: Fra2 overexpression and inflammation foster stromal cell-to-myofibroblast differentiation, leading to cardiac fibrosis and defects of the conduction system. Targeting this process might be a therapeutic strategy for SSc patients with disorders of cardiac involvement.

Disclosure of Interests: Mara Stellato: None declared, Michal Rudnik: None declared, Florian Renoux: None declared, Przemyslaw Blyszczuk: None declared, Elena Osto: None declared, Matthias Dewenter: None declared, Petra Seebeck: None declared, Elena Pachera: None declared, Oliver Distler Grant/ research support from: Prof. Distler received research funding from Actelion, Bayer, Boehringer Ingelheim and Mitsubishi Tanabe to investigate potential treatments of scleroderma and its complications, Consultant for: Prof. Distler has/had consultancy relationship within the last 3 years with Actelion, AnaMar, Bayer, Boehringer Ingelheim, ChemomAb, espeRare foundation, Genentech/Roche, GSK, Inventiva, Italfarmaco, iQvia, Lilly, medac, MedImmune, Mitsubishi Tanabe Pharma, Pharmacocyclics, Novartis, Pfizer, Sanofi, Serodapharm and UCB in the area of potential treatments of scleroderma and its complications. In addition, he had/had consultancy relationship within the last 3 years with A. Menarini, Amgen, Abbvie, GSK, Mepha, MSD, Pfizer and UCB in the field of arthritides and related disorders, Gabriela Kania: None declared
DOI: 10.1136/annrheumdis-2019-eular.6403

OP0187

RITUXIMAB AND CYCLOPHOSPHAMIDE COMPARISON FOR EFFICACY AND SAFETY IN THE PATIENTS WITH SYSTEMIC SCLEROSIS ASSOCIATED WITH INTERSTITIAL LUNG DISEASE

Olga Koneva, Lidia P. Ananyeva, Liudmila Garzanova, Oxana Desinova, Olga Ovsyannikova, Mayya Starovoytova. V.A. Nasonova Research Institute of Rheumatology, Moscow, Russian Federation

Background: Cyclophosphamide (CyP) is considered as a drug of choice for the treatment of interstitial lung disease (ILD) in the patients with systemic sclerosis (SSc). However, according to the literature, the use of CyP leads to rather limited and transient improvement of the pulmonary fibrosis. In this context the search for novel, more efficacious agents has been continued, such as attracting much attention rituximab (RTM).

Objectives: To compare the impact of CyP and RTM on SSc clinical manifestation and activity, and the safety of these agents in the open-label prospective non-randomized study.

Methods: 107 patients with the confirmed SSc diagnosis and ILD evidence based on HRCT findings were enrolled into the study. All patients received low-dose and moderate-dose prednisolone regimens. 36 patients (**Group A**) received **parenteral CyP** for 12±6 months at total dose 10.6±5 g (the average age 47±12 years, females 92%, SSc duration 5.0±4.8 years, diffused/localized forms 1.6/1). 71 patients (**Group B**) received **RTM** at total dose 1.43±0.66 g over the follow-up period 13.2±2 months (the average age 46±13 years, females 83%, SSc duration 5.6±4.4 years, diffused/localized forms 1.4/1); to 32 (45%) of them RTM was added to immunosuppressants due to inadequate efficacy of the latter. The time courses FVC(%), modified skin count (mRss, points), activity index (EScSG, points), left ventricle ejection fraction (LVEF,%), mean pulmonary arterial pressure (EchoCG), and cardiac rhythm and conductivity disorders (ECG) were evaluated.

Results: In Groups A and B the therapy was associated with significant decrease in mRss (p=0.009 and 0.001, respectively) and EScSG (p=0.000165 and 0.001, respectively). Increase in LVEF (61.8±7.3 и 63.6±7.3. p=0.02) was observed only in RTM-treated patients.

Evaluation of FVC time course in Groups A and B revealed significant FVC increase (p=0.034 and 0.000045, respectively), with median increment about 5%. In Group A FVC 10% FVC increase was found in the third of the patients thus exceeding respective parameter in Group B (p=0.2). The patient percentage with FVC decrease by ≥10% was similar in both groups.

During the follow-up period no change of the other studied parameters was observed.

The therapy was better tolerated in RTM-treated group: during RTM therapy adverse reactions emerged in significantly lower proportion of the patients (11/14%) compared with CyP-treated group (19/53%), p=0.0000.

Parameters	Group A	Group B
EScSG 1	2.8±2*	2.8±1.8*
M ± SD		
EScSG 2	1.4±1.17*	1.3±1.1*
M ± SD		
mRss 1	11.2±9.8 *	11.3±9.6 *
M ± SD		
mRss 2	7.9±6.8. *	8.0±6.6*
M ± SD		
FVC 1	80.5±20.1*	77.3±20 *
M ± SD		
FVC 2	85.9±20.5*	82.6±21.*
M ± SD		
Δ FVC%	5.4	5.3
	[-0.6; 12.3]	[0.1; 10.2]
FVC increment by ≥10%, n/%	11/31	14/19.7
FVC decrement by ≥10% n/%	2/5.6	4/5.6

Notes: in Parameters column 1 = before treatment, 2 = after treatment; M ± SD = mean value and standard deviation; * = significant difference between the values measured before and after the treatment

Conclusion: Both agents effectively alleviated skin induration and EScSG, and significantly improved FVC. However, CyP use for a year slightly more frequently resulted in clinically significant FVC increase, probably due to low RTM cumulative dose. RTM was better tolerated compared to CyP. The study findings substantiate potential use of anti-B-cell therapy both as a first-line agent for ILD treatment in the patients with SSc, and in the event of CyP inefficacy of poor tolerability, especially in the patients with cardiopathy.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.6816

OP0188

PATHOGENICITY OF FUNCTIONAL AUTOANTIBODIES AGAINST AT1R IN A MOUSE MODEL OF SYSTEMIC SCLEROSIS

Junping Yin¹, Xiaoqing Wang¹, Xiaoyang Yue¹, Gabriela Riemekasten², Xinhua Yu¹, Frank Petersen¹. ¹Research Center Borstel, Borstel, Germany; ²University of Lübeck, Lübeck, Germany

Background: Systemic sclerosis (SSc) is an autoimmune connective tissue disease featured by autoimmunity, fibrosis and vasculopathy. Although many autoantibodies have been detected in the sera of patients with SSc, it is not clear whether they play a role in the pathogenesis of disease. It has been reported that autoantibodies against the angiotensin-II receptor type 1 (AT1R) are present in the sera of SSc patients and are associated with several clinical symptoms of the disease, suggesting that these autoantibodies may act as pathogenic drivers. Recently, our group has developed a novel mouse model for SSc by immunizing mice with human AT1R (hAT1R). From this model we were able to generate functional monoclonal antibodies agonizing AT1R.

Objectives: In the current study, we aim to clarify, whether B cells and antibodies directed against AT1R are involved in the pathogenesis of experimental SSc *in vivo*.

Methods: To investigate the role of B cells in the hAT1R-induced mouse model of SSc, we immunized B-cell deficient mice with hAT1R. Nine weeks after the first immunization, mice were sacrificed and sera and tissues were collected for further evaluation. To investigate the pathogenicity of anti-AT1R antibodies in the disease, monoclonal autoantibodies against hAT1R were applied to the ear of C57Bl/6 mice by single or repetitive injection. Mice were sacrificed 24 hours or 14 days after the first injection for single and repeated application, respectively, and ear and lung tissues were collected for further evaluation.

Results: Compared to the wild type C57Bl/6 mice, hAT1R-immunized B-cell deficient mice were resistant against experimental SSc with regard to autoantibody production, inflammation in the lung and skin, and skin fibrosis. Furthermore, both single and repetitive injection of monoclonal antibodies against hAT1R induced inflammation in ears of mice. Despite this local effect, repetitive injection of anti-AT1R monoclonal antibodies provoked also inflammation in the lung of mice.

Conclusion: Our data demonstrate that i) B cells are indispensable for the pathogenesis of the hAT1R-induced mouse model for SSc and ii) monoclonal antibodies against hAT1R can induce inflammation in mice. Therefore, our results support a role of autoantibodies against AT1R in the pathogenesis of SSc.

REFERENCES:

[1] Yannick Allanore, et al. Nat Rev Dis Primers 2015.

- [2] Gabriela Riemekasten, et al. *Ann Rheum Dis* 2011.
 [3] Mike O. Becker, et al. *Am J Respir Crit Care Med* 2014.

Disclosure of Interests: Junping Yin: None declared, Xiaoqing Wang: None declared, Xiaoyang Yue: None declared, Gabriela Riemekasten Consultant for: Chugai, F. Hoffmann-La Roche, Speakers bureau: Chugai, F. Hoffmann-La Roche, Xinhua Yu: None declared, Frank Petersen: None declared
DOI: 10.1136/annrheumdis-2019-eular.1132

THURSDAY, 13 JUNE 2019

Genetics, epigenetics and immunity

OP0189

GENETICS OF JUVENILE IDIOPATHIC ARTHRITIS: THE IDENTIFICATION OF A NOVEL RISK LOCUS AND CLINICAL SUBGROUP ANALYSIS

John Bowes, Annie Yarwood, Samantha Smith, Damian Tarasek, Wendy Thomson. *The University of Manchester, Arthritis Research UK Centre for Genetics and Genomics, Manchester, United Kingdom*

Background: Juvenile idiopathic arthritis (JIA) is a clinically heterogeneous group of childhood onset inflammatory joint diseases with strong evidence to support a genetic contribution to susceptibility. JIA is divided into seven clinical subgroups based on observed patterns of clinical symptoms using the International League of Associations for Rheumatology (ILAR) classification system. The genetic overlap between these groups is not completely understood and this lack of knowledge typically leads to the different ILAR groups being analysed as discrete entities and reducing the overall power of genetic association studies.

Objectives: The aim of this study was to conduct a large case-control association study on susceptibility to JIA to identify novel susceptibility loci and to investigate differences of these associations between the ILAR groups.

Methods: JIA participants were genotyped on the Illumina Infinium CoreExome or OmniExpress arrays at The University of Manchester. UK population control genotype data was obtained from the Understanding Society Longitudinal Study. Quality control of data was performed conforming to conventional standards based on call rate, cryptic relatedness and ancestry outliers. Imputation was performed using the Haplotype Reference Consortium panel on the Michigan Imputation Server followed by exclusion of SNPs with low imputation accuracy ($r^2 < 0.5$) and low minor allele frequency ($< 1\%$). Association testing of all SNPs was performed with an additive model incorporating imputation uncertainty using SNPTEST. A subset of SNPs independently associated with all JIA (p-value $< 5 \times 10^{-6}$) were tested to evaluate if they were specific to a particular ILAR group or shared across multiple ILAR groups using Bayesian multinomial regression and model selection methods implemented in the Trinculo software package.

Results: Following quality control the dataset consisted of > 7.4 million SNPs for 3305 JIA cases and 9196 controls. Association testing in a combined dataset of all ILAR groups identified seven SNPs associated at genome-wide significance (5×10^{-8}); six of these have previously been reported for JIA while one is a novel association. The novel association (rs497523, p-value = 7.12×10^{-9} , OR 0.85, 95% CI 0.8:0.9) maps to chromosome 16p11 and is located within intron one of the *CCDC101* gene. In a subset of 44 independently associated SNPs we found no strong evidence to support association of any SNP to a specific ILAR group with the majority of the SNPs showing evidence for sharing across multiple groups.

Conclusion: In the largest case control association study for susceptibility to JIA performed to date, we identified a novel association to a SNP in the intron of *CCDC101*. This gene is involved in transcriptional regulation through histone acetyltransferase. *CCDC101* may be the causal gene at this locus; however introns contain enhancer elements that regulate other genes in the transcriptional domain. Therefore fine mapping with the integration of genomic data is currently being performed for this locus. The results provide little evidence to support ILAR subgroup specificity for any of the associated variants; on the contrary the results support a general model of sharing across multiple groups. The combined analysis of data across subgroups, informed by model sharing, will maximise power to identify novel associations.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.4900

OP0190

META-ANALYSIS OF IMMUNOCHIP DATA OF FOUR AUTOIMMUNE DISEASES REVEALS NOVEL SINGLE-DISEASE AND CROSS-PHENOTYPE ASSOCIATIONS

Ana Márquez^{1,2}, Martin Kerick², Alexandra Zernakova³, Javier Gutierrez-Achury⁴, Wei-Min Chen⁵, Suna Onengut-Gumuscu⁵, Isidoro González-Álvarez⁶, Luis Rodríguez-Rodríguez⁷, Miguel A González-Gay⁸, Maureen Mayes⁹, Soumya Raychaudhuri^{10,11,12}, Stephen S. Rich⁵, Cisca Wijmenga³, Javier Martin Ibanez². ¹Instituto de Investigación Biosanitaria de Granada, Systemic Autoimmune Disease Unit. Hospital Clínico San Cecilio, Granada, Spain; ²Instituto de Parasitología y Biomedicina "López-Neyra", Granada, Spain; ³University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, Netherlands; ⁴Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, United Kingdom; ⁵Center for Public Health Genomics, University of Virginia, Charlottesville, United States of America; ⁶Hospital Universitario La Princesa, IIS-IP, Madrid, Spain; ⁷Hospital Clínico San Carlos, IdiSSC, Madrid, Spain; ⁸IDIVAL, Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Santander, Spain; ⁹The University of Texas Health Science Center-Houston, Division of Rheumatology and Clinical Immunogenetics, Houston, United States of America; ¹⁰Brigham and Women's Hospital, Harvard Medical School, Division of Rheumatology, Immunology, and Allergy, Boston, Spain; ¹¹Brigham and Women's Hospital, Harvard Medical School, Division of Genetics, Boston, United States of America; ¹²Broad Institute of MIT and Harvard, Program in Medical and Population Genetics, Cambridge, United States of America

Background: In recent years, research has consistently proven the occurrence of genetic overlap across autoimmune diseases, which supports the existence of common pathogenic mechanisms in autoimmunity.

Objectives: The objective of this study was to further investigate this shared genetic component.

Methods: We performed a cross-disease meta-analysis of ImmunoChip data from 37,159 patients diagnosed with a seropositive autoimmune disease (11,489 celiac disease (CeD), 15,523 rheumatoid arthritis (RA), 3,477 systemic sclerosis (SSc), and 6,670 type 1 diabetes (T1D)) and 22,308 healthy controls of European origin using the R package ASSET.

Results: We identified 38 risk variants shared by at least two of the conditions analyzed, five of which represent new pleiotropic loci in autoimmunity. We also identified six novel genome-wide associations for the diseases studied. Cell-specific functional annotations and biological pathway enrichment analyses suggested that pleiotropic variants may deregulate gene expression in different subsets of T cells, especially Th17 and regulatory T cells. Finally, drug repositioning analysis evidenced several drugs that could represent promising candidates for CeD, RA, SSc and T1D treatment.

Conclusion: We have been able to advance in the knowledge of the genetic overlap existing in autoimmunity, thus shedding light on common molecular mechanisms of disease and suggesting novel drug targets that could be explored for the treatment of the autoimmune diseases studied.

REFERENCES:

- [1] Richard-Miceli C, Criswell LA. Emerging patterns of genetic overlap across autoimmune disorders. *Genome Med.* 2012;4(1):6.
- [2] Bhattacharjee S, Rajaraman P, Jacobs KB, et al. A subset-based approach improves power and interpretation for the combined analysis of genetic association studies of heterogeneous traits. *Am J Hum Genet.* 2012;90(5):821-35

Disclosure of Interests: Ana Márquez: None declared, Martin Kerick: None declared, Alexandra Zernakova: None declared, Javier Gutierrez-Achury: None declared, Wei-Min Chen: None declared, Suna Onengut-Gumuscu: None declared, Isidoro González-Álvarez: None declared, Luis Rodríguez-Rodríguez: None declared, Miguel A González-Gay Grant/research support from: Prof. MA Gonzalez-Gay received grants/research supports from Abbvie, MSD, Jansen and Roche., Speakers bureau: Consultation fees/participation in company sponsored speaker's bureau from Pfizer, Lilly, Sobi, Celgene, Novartis, Roche and Sanofi., Maureen Mayes Grant/research support from: Maureen Mayes is a clinical trial investigator for Boehringer-Ingelheim; Galapagos, Reata, Sanofi, Merck-Serono, Consultant for: Maureen Mayes is a member of scientific advisory boards for Galapagos NV (Pharma), Boehringer-Ingelheim, Mitsubishi-Tanabe, Astellas; Grant Review Board for Actelion., Speakers bureau: Maureen Mayes received personal fees for being a conference speaker on the use of autoantibodies in connective tissue diseases for Medtelligence, Soumya Raychaudhuri: None declared, Stephen S. Rich: None declared, Cisca Wijmenga: None declared, Javier Martin Ibanez: None declared

DOI: 10.1136/annrheumdis-2019-eular.402