regarding IL23 (276 vs 262 pg/ml, $p>0.4$) and IL17 levels (184 vs 233 pg/ml, $p>0.2$). Only 22 (6.6%) AS patients carried the protective rs11209032 A allele, while 206 (61.7%) carried the rs11209032 A risk allele ($p=0.03$). There was no demonstrable influence of individual genotypes (A vs G, AA vs AG vs GG) or haplotypic combinations on BASFI, spinal function tests, CRP, ESR, IL-23 or IL-17 levels (all $p>0.3$).

Conclusions: While there is a high prevalence of the IL-23R rs11209032 A risk allele in Caucasian AS patients, this has no demonstrable bearing on clinical disease measures or serum IL-23 and IL-17 levels.

Acknowledgements: The authors wish to acknowledge the technical assistance by Mrs K Nilsen and the financial support of the North Norwegian Health Authority Research Fund

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.5882

FRI0427 FIRST DESCRIPTION OF GAMMA DELTA T CELLS AT NORMAL HUMAN ENTHESES

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Background: Recent animal studies have suggested that $\gamma\delta$ T-cells accumulate at entheses, secrete IL-17 and are responsible for driving the spondyloarthritis (SpA) phenotype resulting from IL-23 overexpression in mice (1, 2). In humans examination of the immunological profile of entheses has been hampered by lack of tissue. Recently, we used a novel strategy to show that group 3 innate lymphoid cells are present at the human entheses (3). Here we extend our methodology to examine the broader immunological profile of human entheses and to determine if $\gamma\delta$ T-cells are also present.

Objectives: To characterise $\gamma\delta$ T-cells at human entheses and adjacent perienthesal bone

Methods: Human enthesal soft tissue (EST) and peri-enthesal bone (PEB) was harvested from normal spinous process in patients undergoing elective spinal orthopaedic procedures. Interspinous EST was dissected from PEB and enzymatically digested, followed by isolation of mononuclear cells. Flow cytometry was then used to determine the proportion of B-cells (CD45+, CD19+) NK cells (CD45+, CD3-, CD56+) and T-cells (CD45+, CD3+). T-cells were then sub divided based on expression of CD4 (T-helper cells), CD8 (Cytotoxic T-cells) and TCR $\gamma\delta$ ($\gamma\delta$ T-cells). All enthesal data was compared to age-matched peripheral blood from healthy controls.

Results: Enthesal digests contained on average a lower proportion of T-cells compared to peripheral blood ($p=0.018$). However, the proportion of T-cells not expressing either CD4 or CD8 was greater in enthesal tissues ($p=0.021$), this population was largely composed of $\gamma\delta$ T-cells. As a proportion of T-cells $\gamma\delta$ T-cells were 6 fold more numerous in EST compared to peripheral blood ($p=0.024$), and PEB had 3 fold more. 37% of EST $\gamma\delta$ T-cells expressed CCR6 this compared to 26% and 34% in PEB and peripheral blood respectively.

Conclusions: $\gamma\delta$ T-cells are present in normal human entheses and $\gamma\delta$ T-cells constitute a greater proportion of the T-cell pool compared to peripheral blood, making it likely that they represent a tissue resident population. Additionally, we observed a very similar proportion $\gamma\delta$ T-cells that expressed CCR6, a functional marker for IL-17 production, as was observed in mice (2). This is the first description of $\gamma\delta$ T-cells at the human entheses and offers tentative confirmation of findings in mouse models where these cells play a key role in SpA pathogenesis.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.6421

FRI0428 THE JAK1-SELECTIVE INHIBITOR, FILGOTINIB, INHIBITS INFLAMMATION PATHWAYS OBSERVED IN AN IL23-INDUCED PSORIATIC ARTHRITIS MOUSE MODEL

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Background: Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease characterized by musculoskeletal involvement and extra-skeletal manifestations such as psoriasis, uveitis and Inflammatory Bowel Disease (IBD). The importance of several pro-inflammatory cytokines, in addition to TNF α , IL-12

and IL-23 which are targets of current treatments, suggests that novel therapies may benefit patients. The JAKs (a family of 4 non-receptor tyrosine kinases) are crucial for the signaling of many pro-inflammatory cytokines. In this regard, the JAK1-selective inhibitor filgotinib (GLPG0634, GS-6034) has shown efficacy in patients with rheumatoid arthritis (RA), a disease that shares some hallmarks with PsA, as well as in Crohn's disease (CD), making this molecule a potential therapy for PsA.

Objectives: To gain insight into filgotinib mode of action using a PsA preclinical model by analysing the gene expression signature of filgotinib in mouse phalanges and colon tissues from an IL23-induced PsA mouse model.

Methods: Spondyloarthritis was induced by hydrodynamic injection of IL-23 enhanced Episomal Expression Vector (EEV). Animals were treated with filgotinib or vehicle from day 10 (therapeutic mode) and sacrificed after 16 days of treatment. RNAs were extracted from the phalanges and the proximal colon, and transcriptome assays were performed using the Agilent SurePrint G3 mouse chip. Data analysis was performed using empirical Bayes methods and linear models (limma BioConductor package).

Results: In mice, IL-23 induced changes in the transcriptome in both phalanges and colon that were marked by effects on genes related to the IL-23/T H 17 axis. Microarray analysis performed on mouse phalanges and colon revealed that filgotinib partially reversed the impact of IL-23 on gene expression in colon and in phalanges. In both tissues, filgotinib signature was different but some impacted biological programs were similar. A consistent interferon signature was counteracted by filgotinib in both tissues with decreased expression of common genes such as Apobec3, Gbp8, ligp1 and Oas3. Several markers of inflammation or associated with IL-23 activity were also decreased with common on Kynu and Cd96 gene expression in both tissues. Of interest, filgotinib repression on inflammatory gene expression was stronger in colon compared to phalanges (IL1b, Clec4e). Moreover expression of some genes involved in gut homeostasis that were induced by IL-23 were decreased by filgotinib in the colon, notably Fpr2 (receptor for formyl peptides) and Mmp7. In phalanges, gene expression associated with IL-23-induced disease was also reversed by filgotinib treatment. Il19, Mtlc1 and Tlr1 which are key mediators in psoriasis, or Rankl that is involved in bone remodeling in PsA were differently regulated by IL-23 and filgotinib.

Conclusions: Systemic expression of IL-23 in mice generated a PsA phenotype that was associated with altered gene expression in diseased tissues. A strong interferon signature was reversed by filgotinib as were several inflammation and disease markers. Together with the previous Phase 2 clinical results in RA and CD, these data support the study of filgotinib for the treatment of PsA patients.

Disclosure of Interest: R. Blanqué Employee of: Galapagos SASU, M. Ongenaert Employee of: Galapagos NV, C. David Employee of: Galapagos SASU, C. Robin-Jagerschmidt Employee of: Galapagos SASU, A. Cauvin Employee of: Galapagos SASU, C. Saccomani Employee of: Galapagos SASU, P. Clement-Lacroix Employee of: Galapagos SASU, S. Dupont Employee of: Galapagos SASU, R. Galien Employee of: Galapagos SASU

DOI: 10.1136/annrheumdis-2017-eular.4911

FRI0429 DYSREGULATION OF THE SPLICING MACHINERY IN LEUKOCYTES FROM ANKYLOSING SPONDYLITIS PATIENTS IS ASSOCIATED TO DISEASE PATHOGENESIS

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Background: Ankylosing spondylitis (AS) is a chronic inflammatory disease, of unknown aetiology, associated to the development of several comorbidities such as atherosclerosis. Splicing is a post-transcriptional process involved in the RNA maturation. Recent studies have revealed that a pathological dysregulation of the splicing machinery or spliceosome is associated to several human diseases. Yet, the spliceosome alterations have not been described in AS.

Objectives: 1) To analyze whether dysregulation of the spliceosome is present in AS. 2) To evaluate the association between the alteration of this process and the clinical, inflammatory, oxidative, and atherogenic profiles present in this pathology.

Methods: Fourteen AS patients and 14 healthy donors (HDs) were included in the study. Disease function and activity status were analyzed using the BASFI and BASDAI. The expression of selected components of the major-(n=12) and minor-spliceosome (n=4), and splicing factors (n=28) was evaluated in purified monocytes, lymphocytes and neutrophils from patients and HDs (n=14 each) by Fluidigm methodology. Oxidative stress, inflammation and atherogenesis were evaluated by flow cytometry and RT-PCR. Endothelial function was determined by the post occlusive hyperaemia test using Laser-Doppler.

Results: Compared to HDs, a significant dysregulation in the expression of relevant splicing factors and spliceosome components was found in all the leukocyte subtypes from AS patients, being neutrophils which displayed higher number of altered molecules. Interestingly, a specific altered profile of major- and minor-spliceosome members, and splicing factors was observed when compared lymphocytes (U4, U6, NOVA1, RMB17), monocytes (PRP8, SF3B TV2, CELF4, ESRP2, RBM3, SAM68 TV1, SRSF10, TIA1) and neutrophils (U11, U2, U2AF2, U11, CA 150, ESRP1, PSF, PTB, SRM160).

Correlation studies revealed that disease activity (CRP, ESR, BASDAI) was associated to the alteration of a vast number of spliceosome components in the three subtypes of analyzed leukocytes. In addition, the BASFI index correlated with the expression of splicing factors ESRP1, SRSF1 and TRA2B in neutrophils. The inflammatory, atherogenic and oxidative profile of AS leukocytes was related to the expression of a number of spliceosome molecules in the three leukocyte subsets, although neutrophils exhibited the highest number of deregulated spliceosome components related to inflammation (STAT3, TNF- α , IL-1 α , IL-1 β , IL-5) and cell adhesion (ICAM-1, SELL, THBS4, CDH5). Finally, endothelial dysfunction correlated with the expression of several components of the major-spliceosome and splicing factors in monocytes and neutrophils.

Conclusions: 1) AS patients display a dysregulation of the splicing machinery components associated to disease function and activity. 2) The expression of spliceosome members in the different leukocyte subsets is related to the inflammatory, oxidative and proatherogenic profile of AS patients.

Alteration of the spliceosome may provide new biomarkers for diagnosis and clinical monitoring of AS

Acknowledgements: Funding by: JA PI-0314–2012, SER, ISCIII (RIER RD16/0012/0015)

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.4845

FRI0431 ALTERED EXPRESSION OF CIRCULATING MICRORNAS IS RELATED TO DISEASE ACTIVITY AND STRUCTURAL DAMAGE IN ANKYLOSING SPONDYLITIS PATIENTS

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Background: Ankylosing spondylitis (AS) remains difficult to diagnose before irreversible damage to sacroiliac joint is noticeable. MicroRNAs (miRNAs) are a group of single-stranded non-coding RNAs of 20–25 nucleotides in length that can potentially regulate every aspect of cellular function. Recent studies have demonstrated that miRNAs can be detected in the circulation and serve as potential biomarkers of various inflammatory pathologies.

Objectives: To evaluate whether AS pathogenesis is related to the aberrant expression of plasma miRNAs.

Methods: The expression profile of 800 miRNAs in plasma was determined in pooled samples from AS patients and healthy donors (HDs) (n=3 each) using the nCounter technology. Next, candidate miRNAs were validated by real time RT-PCR in a cohort of AS patients and HDs (n=26 each). In parallel, the expression of validated miRNAs was examined in a cohort of 24 psoriatic arthritis (PsA) patients. To evaluate their relevance in the AS pathogenesis, an analysis was performed by using the web-based bioinformatics tool *Ingenuity Pathways Analysis* (IPA). Association and correlation studies of altered miRNAs with clinical and analytical profile of the AS patients were also performed. AS activity was defined as CRP >5 mg/L and/or BASDAI $\geq$ 4 and ESR >20 mm/h. Structural damage was evaluated by mSASSS.

Results: In discovery phase, nine miRNAs were differentially expressed (fold change $\geq$ 2) in the plasma of AS patients vs. HDs. After validation, higher expression levels of miRNA (miR)-146a-5p, miR-125a-5p, miR-151-3p and miR-22-3p, and lower of miR-150-5p and miR-451a were found in AS vs. HDs. Interestingly, higher miR-146a-5p, miR-125a-5p, miR-151-3p and miR-22-3p expression levels in AS than in PsA patients were further observed. The areas under the curve, generated to assess the accuracy of miRNAs as diagnostic biomarkers for AS, ranged from 0.717 to 0.798; the six-miRNAs signature reached 0.947. Bioinformatics analysis revealed that miRNAs targeted inflammatory and bone remodeling genes, underlying their potential role in this pathology. Indeed, correlation studies showed an association between these six miRNAs and potential target proteins associated to AS pathophysiology. In addition, miR-146a-5p, miR-146a-5p, miR-125a-5p and miR-22-3p expression was increased in active vs. non-active patients. Moreover, miR-150-5p and miR-451a expression was related to the presence of syndesmophytes in AS patients, underlying their association with structural damage.

Conclusions: 1) Several miRNAs are found differentially expressed in plasma from AS patients vs. HDs and other chronic inflammatory pathologies as PsA, indicating that these miRNAs may be considered potential biomarkers for AS diagnose. 2) The differential expression of certain miRNAs is associated to disease activity and structural damage. Overall, this study identified a six-plasma

miRNAs signature that could be attractive candidates as non-invasive biomarkers for the AS diagnosis, and may help to elucidate the disease pathogenesis.

Acknowledgements: Funded by JA PI-0314–2012, SER, and ISCIII (RIER RD16/0012/0015).

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.4780

FRIDAY, 16 JUNE 2017

Spondyloarthritis - clinical aspects (other than treatment)

FRI0430 DUAL TRAJECTORIES OF DISEASE ACTIVITY AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: The ultimate goal of managing Ankylosing Spondylitis (AS) is to improve and maintain the patient's health-related quality of life (HRQoL). To reach this goal, rheumatologists target towards low disease activity, as this is the main modifiable factor. To date, there is insufficient insight into (1) the co-evolution of disease activity and HRQoL, and (2) the heterogeneity in such trajectories among patients.

Objectives: To explore the heterogeneous character of AS by identifying different temporal patterns of co-dependence between disease activity and HRQoL over 8 years follow-up.

Methods: Data from Outcome in AS International Study (OASIS; n=161) and Groningen Leeuwarden AS (GLAS; n=264) cohorts were used. All patients had an established diagnosis of AS. In GLAS, all patients started a biological. HRQoL and disease activity were measured bi-annually using ASQoL and ASDAS-CRP

Figure 1. Joint trajectory latent classes of ASQoL-ASDAS

Abstract FRI0430 – Table 1. Baseline characteristics of patients within each ASQoL-ASDAS trajectory

Characteristics	Trajectory 1 (N=55)	Trajectory 2 (N=105)	Trajectory 3 (N=86)	Trajectory 4 (N=124)	Trajectory 5 (N=55)	p-value
Age – yr	43.9 $\pm$ 12.4	46.0 $\pm$ 12.7	40.9 $\pm$ 10.7	47.9 $\pm$ 11.3	45.1 $\pm$ 13.7	<0.01*
Male sex (%)	46 (83.6)	71 (67.6)	62 (72.1)	83 (66.9)	29 (52.7)	0.01*
Smoking – yes (%)	16/42 (38.1)	23/85 (27.1)	26/74 (35.1)	44/98 (44.9)	20/46 (43.5)	0.13
HLA-B27 – positive (%)	50/54 (92.6)	73/103 (70.9)	72/82 (87.8)	94/119 (79.0)	44/55 (80.0)	0.01*
Symptom duration – yr	20.3 $\pm$ 10.9	21.4 $\pm$ 12.1	17.0 $\pm$ 10.9	22.2 $\pm$ 13.1	21.3 $\pm$ 12.6	0.04*
(Bridging) syndesmophytes present (%)	16/39 (41.0)	45/73 (61.6)	38/70 (54.3)	64/90 (71.1)	18/34 (52.9)	0.02*
Start biological (%)	15/54 (27.8)	41/101 (40.6)	81/86 (94.2)	85/120 (70.8)	35/55 (63.6)	<0.01*