reduced bone, cartilage destruction ($p < 0.001$) and less new bone formation ($p < 0.001$) in peripheral joints. Comparably, therapeutic treatment with rapamycin decreased spondylitis severity (1 versus 2.8; $p < 0.05$) and arthritis severity (4 versus 8.8; $p < 0.05$) compared to controls. In the rapamycin treatment group, *IL-17A* ($p < 0.05$) and *IL-17F* ($p < 0.05$) mRNA were decreased in the MCP joints.

Conclusions mTOR blockade decreases IL-17A and TNF production *in vitro* in SpA PBMCs and reduces osteoblastic differentiation of human SpA FLS. In the *M. tub* induced HLA-B27 transgenic rat model of SpA, mTOR blockade reduces arthritis and spondylitis development and severity by targeting inflammation and bone remodeling.

Disclosure of Interest None declared.

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LUNG DISEASE IN SYSTEMIC JIA: AN EMERGING PROBLEM LINKED WITH YOUNG AGE AND ANTI-IL-1/IL-6

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10.1136/annrheumdis-2018-EWRR2019.115

Career situation of first and presenting author Post-doctoral fellow.

Introduction The advent of anti-IL-1/IL-6 therapies transformed the management of systemic juvenile idiopathic arthritis (sJIA), a debilitating childhood inflammatory condition. However, concurrent with practice change, pediatric rheumatologists noted an increase in sporadic cases of types of lung disease in sJIA, that were rarely seen in previous decades.

Objectives The study aims to provide an up-to-date characterization of lung disease and identify novel risk factors.

Methods We organized a multi-center retrospective study and obtained information on 61 cases of lung disease in children with sJIA or sJIA-like disease.

Results Clinical data from our cohort showed that lung disease in the setting of sJIA is associated with distinctive features, including acute clubbing (in 61%), atypical rash (in 56%) and an unusually high frequency of serious adverse reactions to tocilizumab (40%, OR=79 compared to the control). This lung disease has unique radiological findings and lung pathology similar to pulmonary alveolar proteinosis and/or endogenous lipid pneumonia (PAP/ELP, 64%) often with associated pulmonary vascular changes. Whole-exome sequencing on 18 patients ruled out a novel monogenic disorder or known causes of congenital PAP. Thus, the etiology of the disease is not clear, while its mortality is high (5 years survival: 42%, 25%–68%). When compared to a control cohort of children entered as sJIA in a patient registry, the lung disease cohort has similar overall anti-IL-1/IL-6 exposure level. However, in the anti-IL-1/IL-6 exposed subset, but not in the non-exposed, young sJIA onset age potentially increased the risk of lung disease (age < 5 years, OR=7.3). The high-risk patients (early sJIA onset and exposed to anti-IL-1/IL-6) were highly enriched for PAP/ELP pathology (89%, 17/19 vs. low-risk: 35%, 6/17). In addition, children with Trisomy 21 (T21) and sJIA have dramatically elevated risk for lung disease (OR=50). Marked serum ferritin elevation and/or profound lymphopenia occur several months prior to lung disease detection and may be early indicators of lung disease.

Conclusions Lung disease associated with anti-IL-1/anti-IL-6 therapies often presents as an alveolar and pulmonary vascular complication with high mortality in children with sJIA/sJIA-like disease. Risk is significantly increased in children with young age at sJIA onset or concurrent T21. In sJIA patients (including those with initial treatment response), emergence of atypical clinical features, rising ferritin and dropping absolute lymphocyte count should raise suspicion of this complication.

Disclosure of Interest G. Chen: None declared, V. Saper: None declared, G. Deutsch: None declared, R. P. Guillerman: None declared, K. Jagadeesh: None declared, G. Schulert: None declared, S. Canna: None declared, Y. Lu: None declared, J. Birgmeier: None declared, A. Leung: None declared, A. Grom: None declared, G. Bejerano: None declared, M. Davis: None declared, P. Khatri: None declared, E. Mellins Grant/research support from: Novartis, GlaxoSmithKline, Codexis, Inc.

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AN ADD-ON TRAINING PROGRAM INVOLVING BREATHING EXERCISES, COLD EXPOSURE, AND MEDITATION ATTENUATES INFLAMMATION AND DISEASE ACTIVITY IN AXIAL SPONDYLOARTHRITIS – A PROOF OF CONCEPT TRIAL

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10.1136/annrheumdis-2018-EWRR2019.116

Career situation of first and presenting author Student for a master or a PhD.

Introduction Previous research in healthy individuals showed that the innate immune response can be voluntarily modulated by a training program involving breathing exercises, exposure to cold and meditation¹. It is unknown whether the same intervention could potentially lead to suppression of inflammation and whether it can safely be applied in patients with chronic inflammatory diseases.

Objectives The objective of this study was to assess safety and anti-inflammatory effects of an add-on training program comprising breathing exercises, cold exposure and meditation in patients with axial spondyloarthritis.

Methods This was an open-label randomised one-way cross-over proof-of-concept trial. Participants were randomised to either the early or late intervention group. The intervention consisted of an 8 weeks training program comprising cold exposure, meditation and breathing exercises.

Results There was no significant difference in adverse events between groups, with one serious adverse event occurring 8 weeks after end of the intervention and judged 'unrelated'. After 8 weeks there was a significant decline of the hs-CRP in the intervention group (median [interquartile range] from 10.2 [6.5–17.1] to 6.0 [3.9–15.6] mg/L; $p = 0.02$), but not in the control group (from 8.7 [5.2–17.2] to 13.2 [7.9–20.1] mg/L; $p = 0.70$). A similar trend was seen for serum calprotectin ($p = 0.07$ in intervention versus $p = 0.31$ in control), but not for ESR. In addition, ASDAS-CRP ($p = 0.02$), BASDAI ($p = 0.04$), SF-36 physical component score ($p = 0.01$), EQ-5D ($p = 0.049$), and EQ-5D VAS ($p = 0.02$) decreased significantly in the intervention group, but not the control group.

Conclusions In the present trial we show that the add-on training program involving breathing exercises, cold exposure, and meditation can safely be applied in patients with axial

spondyloarthritis, a prototype chronic inflammatory disease. Furthermore, it attenuated inflammation and improved disease activity, function, and quality of life.

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Acknowledgements Professor Piet van Riel, Lisa van Maanen, Sanne Pons, Wim Hof, Isa Hof, Henk van den Berg, Marianne Peper, Linda Hochstenbach, and Iris Premssler.

Disclosure of Interest None declared.

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PEFICITINIB TARGETS SYNOVIAL FIBROBLASTS IN RHEUMATOID ARTHRITIS

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10.1136/annrheumdis-2018-EWRR2019.117

Career situation of first and presenting author Post-doctoral fellow.

Introduction Tofacitinib and baricitinib are the first approved Janus kinase inhibitors (JAKi) in Europe for treatment of rheumatoid arthritis (RA). Other JAKi differing in the inhibition profile of the four isoforms JAK1, JAK2, JAK3 and TYK2 are currently examined in clinical trials. Especially filgotinib, inhibiting mainly JAK1/2, and the panJAKi peficitinib are well tolerated up to doses causing C_{max} values higher than 1 μ M. However, less is known about the effect of JAKi in RA on synovial fibroblasts (RASf) activated by IL-1 β . RASf contribute to the growing pannus and develop an aggressive cartilage-destructive phenotype.

Objectives The aim of the study was to examine the effect of JAKi on activated RASf and further characterize the most effective inhibitor.

Methods Isolated human RASf were pretreated with JAKi for 2 hour and then stimulated with IL-1 β and JAKi with/without soluble IL-6 receptor (sIL-6R). IL-6 and MMP-3 were measured in supernatants by ELISA. Stimulation with oncostatin M served as control. The proliferation of RASf was detected using a BrdU-incorporation assay. The effect of peficitinib on RASf migration was investigated by cell culture inserts using a FCS gradient. For adhesion assays, RASf were treated with JAKi, detached and seeded in culture plates. Then, plates were extensively shaken and adherent RASf quantified by counting crystal violet stained cells. Cell viability, cytotoxicity and apoptosis were measured using commercially available assays.

Results Addition of the sIL-6R caused an additional release of IL-6 in RASf treated with IL-1 β compared to IL-1 β alone. This release was fully blocked by tofacitinib at 0.5 and 1 μ M (both $p < 0.01$). However, tofacitinib was not able to reduce the IL-6 release of IL-1 β activated RASf without sIL-6R. In contrast, peficitinib attenuated the IL-6 levels by 62% at 5 μ M ($p < 0.001$, $n = 7$) and by 24% at 1 μ M. Filgotinib resulted in a reduction of 30% at 5 μ M only ($p < 0.05$). The MMP-3 release was reduced by peficitinib (88%, $p < 0.001$) at 5 μ M. Peficitinib was the only JAKi able to reduce the proliferation of activated RASf by 23% at 1 μ M ($p < 0.05$).

Furthermore, peficitinib at 1 and 5 μ M decreased the migration of RASf by 38% and 92% ($p < 0.001$, $n = 4$). Peficitinib up to 5 μ M did not act cytotoxic on RASf even after 48 hour.

Conclusions JAKi suppress the inflammatory response induced by transsignaling of IL-6 in RASf. Peficitinib appears to be superior to other JAKi in suppressing the IL-1 β induced response and the proliferation of activated RASf. Thus, patients suffering specifically from severe synovial proliferation could benefit from treatment with peficitinib.

Disclosure of Interest None declared.

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TARGETING ACTIVATED SYNOVIAL FIBROBLASTS USING PHOTODYNAMIC THERAPY IN HUMAN RHEUMATOID ARTHRITIS SYNOVIAL TISSUE

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10.1136/annrheumdis-2018-EWRR2019.118

Career situation of first and presenting author Student for a master or a PhD.

Introduction Activated synovial fibroblasts (ASF) play an important role in the pathogenesis of rheumatoid arthritis (RA). They contribute to the pro-inflammatory environment in the joint and degradation of cartilage and bone. Depleting ASF could ameliorate both these hallmarks of RA. ASF are characterized by the expression of fibroblast activation protein (FAP).

Objectives Here, we investigated the potential of FAP-targeted photodynamic therapy (tPDT) using the photosensitizer IRDye700DX conjugated to the anti-FAP antibody 28 H1 (28H1–700DX) to selectively kill these cells.

Methods To demonstrate the proof-of-concept of FAP-based tPDT in *ex vivo* human tissue, RA synovial tissue obtained during joint replacement surgery was trypsin digested and fibroblasts were cultured for at least 5 passages. Cells were incubated with or without 1 μ g/well 28H1–700DX for 4 hour, washed with PBS and either exposed to 690 nm light or not exposed. A luminescent cell viability assay (CellTiter-Glo) was used to measure cell viability. In parallel, 6 mm biopsies of synovial tissue were taken and used for FAP-based tPDT ($n = 8$ patients). They were subjected to tPDT as described above and formalin fixed after 1 hour. To measure cell death, 5 μ m paraffin slices were stained for FAP, gamma-H2AX and caspase-3 expression for activated fibroblasts, DNA double-strand breaks and early apoptosis, respectively.

Results FAP-tPDT performed on the cultured fibroblasts showed a light dose dependent increase in cell death when incubated with 28H1–700DX for 4 hour. Cell viability was not affected when cells were incubated with 28H1–700DX without illumination ($101.37\% \pm 3.9\%$ remaining compared to $100\% \pm 5.07\%$ in the normalized control). Radiant exposure of 17.6 J/cm^2 did not significantly decrease cell viability ($6.4\% \pm 9.8\%$ decrease, ns). Radiant exposures of 52.8, 105.6 and 158.4 J/cm^2 significantly decreased cell viability ($38.6\% \pm 6.9\%$, $67.5\% \pm 10.9\%$ and $80.6\% \pm 5.8\%$ respectively, $p < 0.001$ for all). After FAP-tPDT, the human synovial biopsies showed a significantly increased staining of the caspase-3 marker, but not of gamma-H2AX (Friedman's ANOVA, $p = 0.007$ and $p = 0.810$ respectively). Pairwise comparison