the MMP-3 levels induced by IL-1 β by 88% ($n=7$, $p<0.001$) at 5 μ M and by 31% at 1 μ M ($n=7$, ns). In direct comparison to tofacitinib and baricitinib the IL-1 β (20 ng/ml) induced IL-6 increase was only decreased by peficitinib and filgotinib but not by tofacitinib or baricitinib even at 10 μ M. Tofacitinib only blocked the specific IL-6 effect e.g. induced by the combination of the soluble IL-6 receptor (sIL-6R) and low doses of IL-1 β ($p<0.01$).

The proliferation of RASF was attenuated by tofacitinib, baricitinib and peficitinib at 5 μ M. Peficitinib exerted the strongest decrease of about 70% ($p<0.001$, $n=4$) and it was the only inhibitor attenuating the proliferation at 1 μ M (23%, $p<0.05$, $n=4$). Peficitinib also decreased the migration of RASF by 38% at 1 μ M and by 92% at 5 μ M. The observed effects were not mediated by apoptosis and even after 48h peficitinib did not act cytotoxic on RASF. In contrast to migration, short-term adhesion onto a plastic surface was not affected by peficitinib.

Conclusion: Peficitinib and filgotinib modulated the IL-1 β -induced response of RASF. Peficitinib also inhibited the proliferation and the migration of RASF. Therefore, especially peficitinib could be able to reduce the aggressive pannus formation in RA patients.

REFERENCES:

- [1] Cao YJ, et al.: Pharmacokinetics, Pharmacodynamics, and Safety of ASP015K (Peficitinib), a New Janus Kinase Inhibitor, in Healthy Subjects. *Clin Pharmacol Drug Dev* 2016;5:435-449.
- [2] Vanhoutte F, et al.: Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Filgotinib, a Selective JAK-1 Inhibitor, After Short-Term Treatment of Rheumatoid Arthritis: Results of Two Randomized Phase IIa Trials. *Arthritis Rheumatol* 2017;69:1949-1959.
- [3] Lamba M, et al.: Evaluation of Pharmacokinetics Compared With Immediate-Release Tofacitinib and Impact of Food. *J Clin Pharmacol* 2016;56:1362-1371.
- [4] Shi JG, et al.: The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J Clin Pharmacol* 2014;54:1354-1361.

Disclosure of Interests: Magnus Diller: None declared, Rebecca Hasseli: None declared, Iris Aykara: None declared, Marie Hülser: None declared, Stefan Rehart: None declared, Ulf Müller-Ladner Grant/research support from: Projekt supported by an unrestricted educational grant from Celgene GmbH., Elena Neumann: None declared

DOI: 10.1136/annrheumdis-2019-eular.3934

THU0027

INHIBITION OF TH17 CELLS IN PSORIATIC ARTHRITIS THROUGH ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR IS DEPENDENT UPON DISEASE ACTIVITY

Amara Ezeonyeji^{1,2}, Michael Ehrenstein¹. ¹University College London, Centre for Rheumatology, London, United Kingdom; ²St George's University Hospital NHS Trust, London, United Kingdom

Background: Th17 cells have been implicated in the development of psoriatic arthritis (PsA) and psoriasis and are a major target for therapy. Th17 cells exhibit plasticity and can transdifferentiate to other effector cell types. Th17 cells that lose expression of IL-17 in favour of IFN- γ (non-classical Th1 cells) contribute to the pathogenesis of autoimmune diseases and are found in the joints of patients with inflammatory arthritis. Conversely, induction of IL-10 in Th17 cells has been shown to suppress their pathogenic potential. The Aryl Hydrocarbon Receptor (AhR) is a nuclear receptor with pleiotropic effects on immune function. The AhR ligand, 6-formylindolo[3,2-b]carbazole (FICZ) has been shown to induce or suppress Th17 cell differentiation and promote generation of tolerogenic FoxP3+ T regs or Type 1 regulatory cells (Tr1) that produce IL-10. FICZ also reduces psoriasis inflammation in a model of skin inflammation through AhR activation¹. FICZ could thus play a regulatory role to control inflammation in PsA.

Objectives: To evaluate the immunomodulatory effects of FICZ on IL-17, IL-10 and IFN- γ production from human CD4+ T cells in PsA and healthy controls (HCs)

Methods: Whole PBMCs and purified CD4+ T cells were isolated from HCs, untreated or DMARD treated (UNT/DMARD) PsA patients and anti-TNF α (adalimumab and etanercept) treated patients. Cells were stimulated with anti-CD3/CD28 (α CD3/28) (1 μ g/ml) and cultured for 3-5 days in the presence or absence of FICZ (250nM). To some cultures 2,3,7,8-Tetrachlorodibenzodioxin (TCDD) (10nM) was used as a control AhR ligand, and IL-21 (30ng/ml) as a positive control for IL-10 production. Cells were then re-stimulated with PMA/ionomycin and intracellular production of IL-17, IFN- γ and IL-10 measured by FACS.

Results: The percentage of IL-17+ CD4+ T cells was reduced in the peripheral blood of HCs and PsA patients after 3 days (healthy $p=0.0098$, UNT/DMARD $p=0.0004$, anti-TNF α $p=0.0012$) and 5 days (healthy $p=0.0005$, UNT/DMARD $p=0.0012$, anti-TNF α $p=0.0012$). The percentage of IFN- γ + CD4+ T cells was reduced in HCs and PsA patients (HC $p=0.016$, UNT/DMARD $p=0.001$, anti-TNF α $p=0.001$) after 3 days culture with FICZ but this effect was only sustained for HCs ($p=0.02$) and anti-TNF α treated patients ($p=0.01$) after 5 days of culture. No ligand specific difference in IL-17 suppression was seen between FICZ and TCDD. No difference in baseline IL-10 expression was seen between treatment groups. However, IL-10 production was significantly enhanced by FICZ in the anti-TNF α patients group ($p=0.02$). This effect was not seen with TCDD nor IL-21 alone. The addition of IL-21 to cultures from anti-TNF α patients treated with FICZ further enhanced IL-10 expression ($p<0.05$). Increase in IL-10 by FICZ was associated with a reduction in IL-17. Upon stratifying patients by swollen joint count (SJC) and Psoriasis Area Severity Index (PASI) into high (SJC $\geq$ 3, PASI $\geq$ 5) and low (SJC $<$ 3, PASI $<$ 5) disease activity, the percentage of IL-17+ CD4+ T cells after 3 days culture with FICZ was reduced for patients with low PASI score ($p=0.02$). A similar trend was seen for those with low SJC ($p=0.06$). In contrast, stimulation with FICZ did not regulate Th17 cells in patients with high PASI score or SJC.

Conclusion: The AhR ligand FICZ suppresses IL-17 production in CD4+ T cells of PsA patients and HCs and IFN- γ in HCs and anti-TNF α treated patients. FICZ promotes IL-10 production in CD4+ T cells from anti-TNF α treated patients and this effect is enhanced in the presence of IL-21. CD4+ T cells from patients with high disease activity are more resistant to FICZ mediated IL-17 suppression. Use of AhR ligands may thus be a useful therapeutic adjunct to conventional and biological therapy in PsA.

REFERENCE:

- [1] Di Meglio P, et al. Activation of the AhR dampens the severity of inflammatory skin conditions, *Immunity*, 2014, Jun 19;40(6):989-1001.

Disclosure of Interests: Amara Ezeonyeji: None declared, Michael Ehrenstein Grant/research support from: A different project receives support from GSK

DOI: 10.1136/annrheumdis-2019-eular.262

THU0028

COMPARISON OF IL-17A AND TNF INDUCED CYTOKINE SECRETION BY RHEUMATOID AND PSORIATIC ARTHRITIS SYNOVIAL FIBROBLASTS AND THEIR INHIBITION BY BIOLOGICS

Klaus Frommer¹, Stefan Rehart², Ulf Müller-Ladner¹, Elena Neumann¹. ¹Justus-Liebig-University Giessen, Dept. of Rheumatology and Clinical Immunology, Bad Nauheim, Germany; ²Agaplesion Markus Hospital, Dept. of Orthopaedics and Trauma Surgery, Frankfurt, Germany

Background: Rheumatoid arthritis (RA) and psoriatic arthritis (PsA), although similar in several respects, display clinical as well as therapeutic differences. This includes, for example, the higher effectiveness of the anti-IL-17A biologic secukinumab in PsA than in RA patients. Synovial fibroblasts (SF) are one of the key effector cell types in the pathophysiology of RA and PsA. We hypothesized that RASF and PsASF respond differentially to IL-17A and its biologic secukinumab and that this might contribute to the difference seen in the therapeutic response.

Objectives: To examine the effect of the two cytokines IL-17A and TNF- α on RASF in comparison to PsASF as well as the effect of their corresponding biologics. To analyze the effect of the IL-17A homolog IL-17F.

Methods: SF were isolated from synovium from PsA or RA patients undergoing surgery. SF from RA and PsA patients were stimulated with recombinant IL-17A, IL-17F and TNF- α alone or with respective combinations. Dose-response curve analysis was performed with IL-17A. The biologics secukinumab and adalimumab were used to block the effects on the SF. As a measure of the proinflammatory response, secretion of the cytokine IL-6 was quantified using an immunoassay.

Results: IL-6 secretion was induced by IL-17A in RASF as well as PsASF (IL-17A: 13.7-fold $\uparrow$ vs 6.9-fold $\uparrow$; $n=3$). Although sharing the same receptor, the IL-17A homolog IL-17F alone caused no induction of IL-6 secretion in SF. However, when combined with TNF- α , both IL-17 isoforms, IL-17A and IL-17F, increased IL-6 secretion due to a strong synergistic effect with TNF- α . RASF ($n=3$) responded more strongly than PsASF ($n=3$) to the combined stimulation (IL-17A: 544-fold $\uparrow$ vs 127-fold $\uparrow$, IL-17F: 54-fold $\uparrow$ vs 27-fold $\uparrow$). Adalimumab and secukinumab were