patients we have used it intravenously, and in higher doses, where the half-life is shorter and twice daily dosing is required. Anakinra was well tolerated and its short half-life makes it ideal for use in suspected sepsis-driven HLH. One case was managed entirely steroid-free using anakinra. This allowed for the identification of an underlying lymphoma which may have missed had high-dose steroids been used. Larger studies will help us ascertain whether earlier anakinra use may spare steroid and chemotherapy side-effects and improve patient outcomes.

REFERENCES:

- [1] Clinical Commissioning Policy: NHS England Reference: 170062P. 2018.
- [2] Grom AA, et al. *Nat Rev Rheumatol*. 2016; 12(5): 259–268.

Disclosure of Interests: Shabnam Shabbir: None declared, Ahmad Al-Abdulla: None declared, Anne Kinderlerer: None declared, Mamta Sohal: None declared, Mark Layton: None declared, Peter Hill: None declared, Richard Corbett: None declared, Liz Lightstone: None declared, Tom Cairns : None declared, Justin Mason Consultant for: Prof Mason has worked as a paid Consultant for Roche/Chugai and Novartis, Speakers bureau: Prof Mason has been a paid speaker for Roche/Chugai, Nichola Cooper: None declared, Taryn Youngstein: None declared
DOI: 10.1136/annrheumdis-2019-eular.4245

THU0052

USTEKINUMAB AND GUSELKUMAB TREATMENT RESULTS IN DIFFERENCES IN SERUM IL17A, IL17F AND CRP LEVELS IN PSORIATIC ARTHRITIS PATIENTS: A COMPARISON FROM USTEKINUMAB PH3 AND GUSELKUMAB PH2 PROGRAMS

Stefan Siebert¹, Matthew J Loza², Qingxuan Song², Iain McInnes¹, Kristen Sweet².
¹Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, United Kingdom; ²Janssen Research and Development, LLC, Spring House, United States of America

Background: Ustekinumab (UST) is a monoclonal antibody (mAb) that binds the p40 epitope which is shared by IL12 and IL23, whereas guselkumab (GUS) is a mAb that selectively binds the p19 subunit of IL23. In recent studies, both UST (Phase 3 programs)¹ and GUS (Phase 2 program)² have demonstrated a reduction in musculoskeletal clinical signs and symptoms and improvement of psoriatic lesions in patients with active psoriatic arthritis (PsA), implicating the IL12/23 pathway in disease pathogenesis.

Objectives: To explore the post-treatment pharmacodynamic changes of IL17A, IL17F, and CRP with GUS and UST in the context of PsA.

Methods: Serum protein levels of IL17A, IL17F, and CRP were measured in 142 subjects and 38 matched healthy controls from the GUS Ph2 study² at Weeks 0, 4, and 16. In the UST Ph3 studies¹, biomarkers were assayed at Weeks 0, 4, and 24 as follows: IL17A (n=474), IL17F (n=237), CRP (n=927). IL17A and IL17F were assayed using Single Molecule CountingTM Human Immunoassay Kits (formerly Singulex). CRP was measured using CardioPhase hsCRP assay (UST studies) or Meso Scale Discovery Platform (GUS study).

Results: At baseline, the Th17 effector cytokines IL17A and IL17F were elevated in the serum of PsA subjects in the GUS Ph2 cohort compared to healthy controls. IL17A and IL17F levels significantly correlated with affected skin body surface area, but not swollen or tender joint scores, in both studies. While none of the baseline levels of evaluated cytokines were associated with American College of Rheumatology (ACR) or Psoriasis Area Severity Index (PASI) clinical responses to UST, baseline IL17F levels were modestly associated with ACR20 response to GUS at week 24. Both UST and GUS treatment resulted in pharmacodynamic decreases in IL17A, IL17F, and CRP levels, with GUS treatment restoring IL17A and IL17F levels to that of healthy controls by week 16. Consistent with being a component of ACR scores, CRP changes were significantly associated with ACR20 responses to both UST and GUS treatment. Weeks 4 and 16 changes in IL17F with GUS treatment were significantly associated with ACR20 response at week 24. Week 24 PASI75 response to GUS was significantly associated with week 4 changes in IL17A, with a similar trend observed at Week 16.

Conclusion: These results underscore the relevance of the IL23/Th17 pathway in PsA, with GUS treatment providing a stronger suppression of the pathway than UST treatment. The significant associations of changes in IL17A and IL17F levels with GUS treatment with PASI75 and ACR20 response, respectively, support the importance of the IL23/Th17 pathway for both skin and joint pathologies. The associations of reduction in CRP levels with both UST and GUS treatment also reinforce the role of acute phase inflammation in joint pathology.

REFERENCES:

- [1] Deodhar A, Kavanaugh A, et al. *Lancet*. 2013; 382(9894):780-9.
- [2] Deodhar A, Gottlieb AB, et al. *Lancet*. 2018; 391(10136):2213-2224.

Disclosure of Interests: Stefan Siebert Grant/research support from: AbbVie, Novartis, Pfizer, Janssen, BMS, Celgene, UCB, and Boehringer Ingelheim, Consultant for: AbbVie, UCB, Pfizer, Janssen, Boehringer Ingelheim, Celgene, and Novartis, Speakers bureau: AbbVie, UCB, Pfizer, Janssen, Boehringer Ingelheim, Celgene, and Novartis, Matthew J Loza Shareholder of: Johnson & Johnson, Employee of: Janssen Research & Development, LLC, Qingxuan Song Employee of: Janssen Research & Development, LLC, Iain McInnes Grant/research support from: AstraZeneca, Celgene, Compugen, Novartis, Roche, UCB Pharma, Consultant for: AbbVie, Celgene, Galvani, Lilly, Novartis, Pfizer, UCB Pharma, Kristen Sweet Employee of: Janssen Research & Development, LLC
DOI: 10.1136/annrheumdis-2019-eular.479

THU0053

APREMILAST INHIBITS THE TGFβ1 MEDIATED TRANSITION OF CULTURED HUMAN SKIN FIBROBLASTS INTO PROFIBROTIC MYOFIBROBLASTS: IN VITRO STUDY

Maurizio Cutolo¹, Paola Montagna¹, Giulia Martinelli¹, Samuele Tardito¹, Claudio Corallo², Nicola Giordano², Emanuele Cozzani³, Carmen Pizzorni¹, Sabrina Paolino¹, Massimo Patanè¹, Alberto Sulli¹, Elisa Alessandri¹, Vanessa Smith^{4,5,6}, Stefano Soldano¹. ¹University of Genova, IRCCS Policlinic San Martino Hospital, Research laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, Genoa, Italy; ²University of Siena, Scleroderma Unit, Department of Medicine, Surgery and Neurosciences, Siena, Italy; ³University of Genova, IRCCS Policlinic San Martino Hospital, Department of Health Science, Unit of Dermatology, Genoa, Italy; ⁴Ghent University Hospital, Department of Rheumatology, Ghent, Belgium; ⁵Ghent University Hospital, Department of Internal Medicine, Ghent, Belgium; ⁶VIB Inflammation Research Center (IRC), Unit for Molecular Immunology and Inflammation, Ghent, Belgium

Background: Fibroblast-to-myofibroblast transition and extracellular matrix (ECM) overproduction represent fundamental events in chronic inflammation, that characterise several diseases, including psoriasis (1,2). Transforming growth factor-β1 (TGFβ1), plays an important role as a profibrotic mediator (3).

Phosphodiesterases (PDE)4 act as proinflammatory enzymes via degradation of cAMP. PDE4 are expressed in normal skin fibroblasts (Fbs) and overexpressed in psoriatic skin Fbs and myofibroblasts (2).

Objectives: This study investigated how apremilast (an oral PDE4 inhibitor small molecule used for the treatment of psoriasis and psoriatic arthritis) might interfere with intracellular signalling for the fibroblast-to-myofibroblast transition and the synthesis of profibrotic ECM proteins induced by TGFβ1 in primary cultures of healthy human skin Fbs.

Methods: Human skin Fbs were isolated from 7 voluntary healthy subjects after signing informed consent and EC approval. The cultured Fbs were stimulated with TGFβ1 10ng/ml alone or in combination with apremilast 1μM and 10μM for 4, 16 and 24 hours. Other aliquots of Fbs were also previously stimulated with TGFβ1 for 4 hours and then treated with apremilast 1μM and 10μM for 4, 16 and 24 hours always in the presence of TGFβ1. Genes and related protein expression of α-smooth muscle actin (αSMA), type I collagen (COL-1) and fibronectin (FN) were investigated by qRT-PCR and Western blotting (WB). Smad proteins (the main signal transducers for receptors of TGFβ1) and extracellular signal-regulated kinases (ERKs), which are implicated in mediating TGFβ1 effects, were investigated by WB after 15, 30 and 60 minutes of apremilast treatment combined with TGFβ1 stimulation.

Results: Apremilast significantly downregulated the phosphorylation of Smad 2 and 3, at 15 minutes, and that of Erk1/2, after 30 minutes (p<0.05), both induced by TGFβ1 stimulation in cultured skin Fbs. Apremilast significantly downregulated the TGFβ1-induced increase in the gene expression of αSMA, COL-1 and FN at 4 and 16 hours, and the related protein synthesis at 24 hours (p<0.05) in cultured skin Fbs (treated in combination with TGFβ1). Similar effects were observed in differentiated myofibroblasts treated with apremilast.

Conclusion: Apremilast inhibited the fibroblast-to-myofibroblast transition *in vitro*, as well as the profibrotic activity induced by TGFβ1 in cultured skin Fbs by downregulating specific intracellular signalling pathways Smad 2/3 and Erk 1/2. These results might partially explain some of the downregulating effects on skin Fbs overactivity during treatment of skin lesions of psoriasis and that of psoriatic patients with apremilast.

REFERENCE:

- [1] Clarke DL, et al. *Fibrogenesis & Tissue Repair* 2013, 6:20. 2. Schafer PH, et al. *Cell Signal.* 2016;28:753-63. 3. Carthy JM. *J Cell Physiol.* 2018;233:98-106.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.7505

THU0054

THE SYNOVIAL FLUID FROM RHEUMATOID ARTHRITIS PATIENTS CONTAINS SOLUBLE TAM RECEPTOR TYROSINE KINASES OF WHICH SOLUBLE TYRO3 AND ITS LIGAND GAS6 CORRELATES WITH THE PROINFLAMMATORY CYTOKINE LEVELS

Julia Vullings, Claire Waterborg, Marije Koenders, Peter van Lent, Peter van der Kraan, Fons van de Loo. *Radboud Institute for Molecular Life Sciences (RIMLS), Rheumatology, Nijmegen, Netherlands*

Background: We recently showed that the tyrosine-protein kinase receptors MER and AXL, both members of the TAM (including TYRO3) receptor family, play a protective role in mouse models of rheumatoid arthritis (RA) [1, 2]. In both humans and mice, TAM receptors can be proteolytically cleaved from the cell membrane and shed as a soluble (s) receptors. These sTAM receptors may act as decoy receptors, bind their ligands Growth Arrest-Specific 6 (GAS6) and Protein S (PROS1), and thereby inhibit the immunoregulatory and anti-inflammatory effect of TAM receptor activation, and prevent TAM receptor-mediated phagocytic clearance of dying cells.

Objectives: To determine the soluble TAM receptor levels in synovial fluids from RA and osteoarthritis (OA) patients and correlate this to the inflammatory process.

Methods: The level of sMER, sAXL, sTYRO3, GAS6, IL-8, TNF α and IL-1 β was measured in synovial fluids of RA (n = 28) and OA patients (n = 12) by ELISA or multiplex array. Synovial explants were cultured for 24 hrs and the release of sMER and GAS6 was measured by ELISA. Human synovial explants of RA (n = 15) and osteoarthritis (OA) (n = 17) patients were immunostained for MER.

Results: Soluble MER and sTYRO3 were significantly enhanced in synovial fluids (P<0.0001 and P=0.0042) of RA patients as compared to OA patients. The sAXL and GAS6 levels in synovial fluid of RA and OA patients was equally high (P = 0.267 and P = 0.074). In RA patients, but not in OA patients, the synovial fluid levels of sTYRO3 and GAS6 (a ligand for all three TAM receptors) positively correlated with TNF α (r=0.555, r=0.477), IL-1 β (r=0.597, r=0.481) and IL-8 (r=0.567, r=0.529). Soluble MER levels, however, did not correlated with local inflammatory markers. Although synovial explants from RA released more sMER into the culture media than explants from OA (P = 0.0045), the explants of both RA and OA patients contained comparable amounts of immunopositive MER cells.

Conclusion: We showed that synovial fluid sTYRO3 and GAS6 levels correlates with higher proinflammatory cytokine levels in RA but not in OA patients. This is in line with the recent observation done by Xu et al. [3], that circulating levels of sTYRO3, but not sMER or sAXL, correlates with disease activity and bone destruction in RA patients. In accordance to serum, the synovial sMER levels were significantly higher in RA - than in OA patients with sAXL levels comparable between both patient groups. Interestingly, only for sMER the synovial fluid levels were much higher than in serum suggesting local production as we confirmed in the synovial explants cultures. This illustrates that release of soluble TAM receptors is either the results of different processes (enzymatic shedding or alternative splicing isoforms) or reflects the different cell populations in the arthritic joint. We found that naïve macrophages express high MER and inducible AXL, while synovial fibroblast express high AXL and TYRO3. Further studies are warranted to determine if sMER levels impair the clearance of apoptotic cells in the arthritic joint as we have found in our mice studies. Our study shows that synovial sTYRO3 is a marker for joint inflammation and possibly a novel therapeutic target for RA.

REFERENCES:

- [1] Waterborg, C.E., et al., *Protective role of the Mer Tyrosine Kinase via efferocytosis in rheumatoid arthritis Models.* *Frontiers in immunology*, 2018. 9.

- [2] Waterborg, C.E., et al., *03.05 The tam receptors axl and mer play a protective role in a temporal and spatial manner in inflammatory arthritis.* 2017, BMJ Publishing Group Ltd.
- [3] Xu, L., et al., *Soluble TAM receptor tyrosine kinases in rheumatoid arthritis: correlation with disease activity and bone destruction.* *Clinical & Experimental Immunology*, 2018. 192(1): p. 95-103.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.7288

THU0055

TPL2 INHIBITION SUPPRESSES MEK-ERK INFLAMMATORY SIGNALING AND PROINFLAMMATORY CYTOKINE PRODUCTION IN PRIMARY HUMAN MONOCYTES

Matthew R. Warr, Angie Hammond, Grace Park, Nathan Wright, James Taylor. *Gilead Sciences, Inc., Foster City, United States of America*

Background: Tumor progression locus 2 (TPL2, also known as MAP3K8) is a mitogen-activated protein kinase kinase kinase and the primary regulator of ERK-mediated gene transcription downstream of multiple proinflammatory stimuli including bacterial products (eg, LPS and bacterial peptidoglycans), damage-associated molecular patterns (DAMPs), TNF α , and IL-1 β .¹ Dysregulated signaling downstream of these inflammatory signals can drive uncontrolled immune cell activation and inflammation, which is associated with multiple chronic inflammatory and autoimmune diseases. As such, TPL2 inhibition represents a strategy to modulate inflammation in a variety of disease settings.

Objectives: We evaluated the effect of a highly selective TPL2 inhibitor on inflammatory signaling and cytokine production in LPS and TNF α -stimulated primary human monocytes.

Methods: Monocytes were precultured with a TPL2 inhibitor and stimulated with LPS or TNF α , and phosphosignaling and cytokine production were then evaluated at 30 minutes and 4 hours poststimulation. A431 cells (human epidermoid carcinoma cell line) were stimulated with TNF α or EGF and phospho-ERK was evaluated after 30 minutes.

Results: TPL2 inhibition selectively inhibited LPS and TNF α -stimulated phosphorylation of TPL2, MEK, and ERK, with little to no inhibition of phosphorylated p38, JNK, or p65 observed. TPL2 inhibition similarly inhibited both the RNA production and secretion of TNF α , IL-1 β , IL-6, and IL-8 following LPS stimulation in primary human monocytes. To confirm TPL2 requirement for inflammatory, but not Ras-mediated (growth factor stimulated) ERK signaling, A431 cells were stimulated with either TNF α or EGF. Although TPL2 inhibition reduced TNF α -stimulated pERK, no effect on ERK activation downstream of EGF was observed.

Conclusion: This work demonstrates the selective effects of TPL2 inhibition on ERK-mediated signaling and proinflammatory cytokine gene transcription in primary human monocytes and highlights the potential for TPL2 inhibition to treat diseases associated with dysregulated inflammatory signaling and chronic inflammation.

REFERENCE:

- [1] Gantke T, Sriskantharajah S, Ley S. *Cell Res.* 2011;21:131-145.

Disclosure of Interests: Matthew R. Warr Shareholder of: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Angie Hammond Grant/research support from: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Grace Park Grant/research support from: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Nathan Wright Shareholder of: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., James Taylor Grant/research support from: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc.

DOI: 10.1136/annrheumdis-2019-eular.2512