Results: In SLE patients respect to HC, plasma IL-1β levels were unmodified whereas IL-6 was higher, resulting significantly increased in SLE-S. Monocytes isolated from SLE patients released lower quantities of IL-1β after stimulation with BzATP, whereas the release of both IL-6 and TNF-α was significantly augmented in SLE-NS respect to both HC and SLE-S subjects after all types of stimulation. RT-PCR showed reduced P2X7R and augmented NLRP3 mRNA expression in SLE patients. Accordingly, P2X7R activity was significantly reduced in all SLE patients and did not appear to be influenced by a chloroquine pre-treatment.
Conclusion: In SLE patients, compared to HC subjects, we found reduced P2X7R mRNA expression, increased NLRP3 mRNA, as a possible compensating mechanism, and correspondingly, significantly lower BzATP-induced intracellular Ca^{2+} increase, without an apparent influence by chloroquine, one of the drugs most diffusely used for SLE treatment. The in vitro IL-1β release was reduced, whereas plasma IL-1β was unaltered, indicating an alternative source, other than monocytes, of this cytokine. Conversely, IL-6 and TNF-α levels were increased in vitro, and IL-6 was present in plasma at higher levels. The possible consequences of reduced P2X7R, mainly on cytokines network deregulation and lymphocyte proliferation, will be further investigated as well as the role of IL-6 and TNF-α as possible therapeutic targets.

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Disclosure of Interests: Anna Lisa Giuliani: None declared, Federica Furini: None declared, Alessandra Bortoluzzi: None declared, Marcello Govoni: None declared, Francesco Di Virgilio Consultant for: FDV is a member of the Scientific Advisory Board of Biosceptre Ltd, a UK-based biotech Company involved in the development of P2X7R-targeted therapeutics.
DOI: 10.1136/annrheumdis-2019-eular.1736

THU0017 IN VITRO MECHANISTIC STUDIES DEMONSTRATE FILGOTINIB ACTIVITY THAT HAS POTENTIAL IMPLICATIONS FOR DIFFERENTIATION AMONG JAK INHIBITORS

Pei Han, Amy Meng, Nevena Mollova, Yuanjiang Yu, Julie A. DI Paolo. *Gilead Sciences, Inc., Foster City, United States of America*

Background: Inhibition of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway has demonstrated efficacy in immune-mediated diseases and has been identified as a therapeutic target for the treatment of rheumatoid arthritis (RA). Differences in JAK inhibitor specificity for JAK1, JAK2, JAK3, and TYK2 may influence their safety profiles, but the mechanism is not known. Selective JAK1 inhibition by filgotinib (FIL) may modulate a subset of proinflammatory cytokines associated with RA pathogenesis and improve the risk-benefit profile by minimizing other non–JAK1-related adverse events. JAK2 inhibition is associated with cytopenias, while JAK3 inhibition has been associated with increased risk for opportunistic infections (eg, tuberculosis and herpes zoster) and chronic low-grade inflammation. In clinical trials, FIL did not negatively impact hemoglobin, LDL/HDL ratios, or natural killer (NK) cell counts.[1-3]
Objectives: To compare the in vitro profile of JAK inhibitors with different JAK selectivity profiles, for effects on erythroid progenitor cell expansion, NK cell proliferation, and liver X receptor (LXR) agonist-induced cholesteryl ester transfer protein (CETP) expression, an enzyme responsible for the conversion of HDL to LDL.
Methods: JAK inhibitors (FIL, FIL metabolite [GS-829845], baricitinib [BARI], tofacitinib [TOFA], and upadacitinib [UPA]) were evaluated in vitro in human cell-based assays: growth of erythroid progenitors from human cord blood $CD34^+$ cells using a HemaTox™ liquid expansion assay, IL-15–induced NK cell proliferation, and LXR agonist-induced CETP expression in the hepatic cell line (HepG2). Using IC_{50}s generated from these assays and the reported human plasma concentrations of the JAK inhibitors from clinical studies,[4-6] we calculated the target coverage for each compound at clinically relevant doses. The activity of FIL in humans was based on a PK-PD modeling algorithm[7] of FIL + GS-829845.
Results: In vitro assay results are described in the table. Based on these results, human exposure data, and modeled PK-PD relationships, FIL 100 mg and FIL 200 mg result in lower calculated cellular inhibition than the other JAK inhibitors at clinical exposures. Notably, FIL 100 mg and FIL 200 mg, but not the other inhibitors, are calculated to reduce CETP expression by 17% and 27%, respectively, while BARI, TOFA, and UPA are not expected to alter CETP levels.

Abstract THU0017 Table 1. IC_{50} ± SD in in vitro assays (nM, unless otherwise noted).

Assay	FIL	GS-829845	BARI	TOFA	UPA
Early erythroid progenitors	1960 ±137	19300 ±1730	38.6±2.9	210 ±15.2	42 ±2.9
Mature erythroid progenitors	1140 ±112	10600 ±1270	25.7±2.9	110 ±10	24.5 ±2.75
NK cell proliferation	314.8 ±53	9697 ±8100	6.6±1.9	12.2 ±2.1	4.1 ±1.7
Inhibition of LXR agonist-induced CETP expression	15.3 ±7.1 μM	19.4 ±4.2 μM	>1 μM weak induction[a]	No effect	

[a] Weak stimulation of LXR agonist-induced CETP expression.
Conclusion: JAK1 selectivity of FIL and GS-829845 resulted in less inhibition of erythroid progenitor expansion and NK cell proliferation compared with BARI, TOFA, and UPA. FIL also reduced LXR agonist-induced CETP expression, while the other inhibitors did not alter these levels. These results provide a potential mechanistic link to the observed reduction of CETP concentration and activity following FIL treatment, and the observed reduction in LDL:HDL in RA patients.[8]

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Disclosure of Interests: Pei Han Shareholder of: Gilead Sciences, Inc., Grant/research support from: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Amy Meng Shareholder of: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Nevena Mollova Shareholder of: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Yuanjiang Yu Grant/research support from: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc., Julie A. Di Paolo Shareholder of: Gilead Sciences, Inc., Employee of: Gilead Sciences, Inc.
DOI: 10.1136/annrheumdis-2019-eular.3361

THU0018 ANTI-GALECTIN-9 ANTIBODY AS A NOVEL TREATMENT OPTION IN RHEUMATOID ARTHRITIS TARGETING PATHOGENIC FIBROBLAST-LIKE SYNOVIOCYTES

Ditte Køster[1], Malene Hvid[1,2], Aida Solhøj Hansen[1], Tue Wenzel Kragstrup[1,3], Pierre Busson[4,5,6], Bent Deleuran[1,3], Morten Aagaard Nielsen[1]. *[1]Aarhus University, Biomedicine, Aarhus, Denmark; [2]Aarhus University, Clinical Medicine, Aarhus, Denmark; [3]Aarhus University Hospital, Rheumatology, Aarhus, Denmark; [4]UMR 8126, CNRS, Villejuif, France; [5]Universite Paris-Saclay, Gustave Roussy, Villejuif, France; [6]Universite Paris-Saclay, Univ Paris Sud, Le Kremlin-Bicêtre, France*

Background: Fibroblasts-like synoviocytes (FLS) present in the stromal environment are key effector cells in the persistence of synovial inflammation and joint damage in rheumatoid arthritis (RA). A particular subset of FLS characterized as $Thy\text{-}1^+Podoplanin^+CD34^-$ is significantly expanded in RA patients and has been described to be disease-associated[1]. Currently, no treatment targeting the stromal environment in RA is available[2].
Objectives: To identify a novel treatment option targeting the stromal environment in RA to modify the disease-associated subset of fibroblasts.
Methods: An *in vitro* model was established with FLS derived from synovial fluid mononuclear cells (SFMC) from RA and osteoarthritis (OA) patients (n=6). FLS between passage 2-5 were used for further analyses. Untreated FLS in cultures were analyzed by flow cytometry for expression