($\rho = -0.260$, $p = 0.015$), moreover, positive correlation with serum LPS ($\rho = 0.284$, $p = 0.008$) and LBP ($\rho = 0.247$, $p = 0.021$) and inverse correlation with ENC ($\rho = -0.321$, $p = 0.002$) were found. On the other hand, IgG anti-Pg-LPS antibody levels which reflect systemic infection, inversely correlated SDAI ($\rho = -0.308$, $p = 0.004$), PainVAS ($\rho = -0.433$, $p < 0.0001$), and so on.

Figure 1. Relationships between intestinal bacterial population and disease activity, Disease marker, LPS related marker and anti-Pg LPS antibody levels

Conclusion: Serum LBP highly associated with RA activity and markers, which suggests bacterial LPS as roles in triggering and perpetuating disease activity in RA. In contrast, IgA anti-Pg-LPS, IgG anti-Pg-LPS antibody reflecting infection of Pg, negatively associated with intestinal total bacteria ($\rho = -0.4405$, $p < 0.0001$), RA disease activities, respectively. These results may show a possible oral-gut relationship resulting in aggravation of disease activity in RA.

Disclosure of interest: None declared

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.1368

THU0067

JAK SELECTIVITY AND THE IMPACT ON CYTOKINE SIGNALING INHIBITION AT CLINICAL RHEUMATOID ARTHRITIS DOSES

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Background: Janus kinase 1 (JAK1) inhibitors are efficacious in rheumatoid arthritis (RA). Despite having similar efficacy, in vitro studies have shown differences in JAK selectivity profiles for the small-molecule JAK inhibitors (JAKi) baricitinib (BARI), tofacitinib (TOFA), and upadacitinib (UPA).¹ For example, BARI and UPA are JAK1/JAK2 selective, while TOFA is JAK1/JAK3 selective, but each JAKi has some activity against other JAKs. As JAKs form signaling pairs, differences in selectivity could lead to distinct pharmacologic profiles that may impact clinical efficacy and safety.

Objectives: As a first step to understand the basis of potential differences at therapeutic doses, we compared the selectivity and potency of filgotinib (FIL) and its major metabolite (MET) to those of BARI, TOFA, and UPA in cytokine-stimulated peripheral blood mononuclear cells (PBMCs) and whole blood (WB).

Methods: PBMCs and WB from healthy donors were incubated in vitro with 8 doses of each JAKi, and levels of signal transducer and activator of transcription phosphorylation (pSTAT) were measured following cytokine stimulation. Half maximal inhibitory concentration (IC₅₀) values were calculated in phenotypically sorted leukocyte populations by flow cytometry. Therapeutic dose relevance of the in vitro analyses was assessed using calculated mean concentration-time profiles from JAKi population pharmacokinetic data in RA subjects. For each JAKi, the time above IC₅₀ and average daily pSTAT inhibition were calculated for each cytokine/STAT pair in B cells, CD4+ T cells, CD8+ T cells, monocytes, and/or NK cells.

Results: Cellular assays in PBMCs and WB showed dose-dependent inhibition of cytokine-induced pSTATs with all JAKi (correlation between the protein-adjusted IC₅₀ values from PBMCs and IC₅₀ values from WB, $r^2 = 0.98$). Among the most potently inhibited pathways were JAK1/TYK2-dependent cytokine, interferon alpha (IFN α), and the JAK1/2-dependent cytokine, interleukin (IL)-6. FIL and MET had weaker potencies against JAK2/TYK2 (G-CSF/pSTAT3), JAK1/2 (IFN γ /pSTAT1), and JAK2/2 (granulocyte-macrophage colony-stimulating factor [GM-CSF])-dependent pathways compared to JAK1/TYK2 (IFN α /pSTAT5). FIL and MET showed the greatest selectivity vs the JAK2/2 pathway (GM-CSF/pSTAT3) in monocytes.

The mean concentration-time profiles and time above IC₅₀ over 24 hr for each cytokine/STAT pathway showed that JAK1/2 (IL-6/pSTAT1) and JAK1/TYK2 (IFN α /pSTAT1) pathways were strongly modulated with all tested JAKi. FIL (200 mg) showed similar activity in average target coverage and time above IC₅₀ to the approved low doses of TOFA (5 mg) and UPA (15 mg); conversely, FIL had reduced mean average inhibition and time above IC₅₀ levels against JAK1/2 (IFN γ /pSTAT1), JAK1/3 (IL-2, -4, and -15), JAK2/TYK2 (G-CSF/pSTAT3), and JAK2/2 (GM-CSF/pSTAT5)-dependent pathways compared to TOFA and UPA, and in certain cases to BARI (2 mg).

Conclusion: Different JAKi modulate distinct cytokine pathways to varying degrees, and no agent potently and continuously inhibited an individual cytokine signaling pathway throughout the dosing interval. FIL (200 mg) showed a similar inhibition profile to TOFA, BARI, and UPA against the JAK1/TYK2- (IFN α /pSTAT1) or JAK1/2-dependent (IL-6/pSTAT1) responses, consistent with the role of these pathways in clinical efficacy.² However, FIL displayed a differentiated pharmacologic profile from the other JAKi, showing biologically reduced activity on the JAK1/2 (IFN γ)-, JAK1/3 (IL-2, -4 and -15)-, JAK2/TYK2 (G-CSF)-, and JAK2/2 (GM-CSF)-dependent pathways, which play important roles in hematopoiesis and immune function. These data suggest that FIL (200 mg) may have less impact on a subset of homeostatic immune functions signaling via JAK2 and JAK3 than those observed at the clinically approved doses of TOFA (5 mg and 10 mg), UPA (15 mg), and BARI (4 mg).

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Disclosure of Interests: Paqui Gonzalez-Traves Employee of: Gilead, Bernard Murray Employee of: Gilead, Federico Campigotto Employee of: Gilead, Amy Meng Shareholder of: Gilead Sciences, Employee of: Gilead, Julie A. Di Paolo Employee of: Gilead

DOI: 10.1136/annrheumdis-2020-eular.2074

THU0068

COMPARISON OF INFLAMMATION DURING METABOLIC CHANGES IN RHEUMATOID AND OSTEOARTHRITIS MOUSE MODELS

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Background: Arthritis is influenced by metabolic changes. Adipokines are bioactive factors produced by adipose tissue with important effects on energy homeostasis and immune responses but are also involved in the pathogenesis of rheumatoid arthritis (RA) and osteoarthritis (OA).

Objectives: To evaluate inflammation during metabolic and adipokine induced changes in experimental models of RA and OA at different time points, an obesity model (high-fat-diet, HFD) was therefore combined with an OA (DMM, destabilization of the medial meniscus) and RA (collagen induced arthritis, CIA) mouse model.

Methods: Mice were fed with HFD or ND (normal diet) for 12 (OA) or 6 (RA) weeks prior to arthritis induction. DMM was performed in C57BL/6 mice and CIA was induced in DBA/1J mice. After 4, 6 and 8 (DMM) or after 4, 5 and 7 weeks (CIA) of arthritis induction animals were sacrificed to collect histological and serological data. Clinical scoring for CIA and histological scorings for both models were performed to evaluate disease development and progression. Diet-induced effects were monitored by weight, fatty liver score and crown-like structures (CLS) counts in adipose tissue. To evaluate HFD-induced adipokine levels adiponectin, leptin and visfatin serum concentrations were measured in parallel to the CRP. Local tissue adipokine expression was evaluated by immunohistochemistry.

Results: Induction of OA and RA was successful in an HFD setting, shown by histological joint destruction and the increased fatty liver score and bodyweight. Compared to healthy animals, CRP levels were significantly increased after CIA induction, confirming systemic inflammation. In DMM, the number of CLS