features ($p=0.002$ for both). There were no other significant associations between S100 levels and other conventional markers such as C3, C4 and the anti-dsDNA antibodies.

Conclusions We demonstrate increased S100 proteins expression in SLE patients. Although they were not strongly associated with disease activity, S100 proteins and namely S100A4 could be proposed as a diagnostic biomarker for SLE.

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Disclosure of interest None declared

P059

EX VIVO COMPARISON OF BARICITINIB, UPADACITINIB, FILGOTINIB AND TOFACITINIB FOR CYTOKINE SIGNALLING IN HUMAN LEUKOCYTE SUBPOPULATIONS

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Introduction Baricitinib (BARI), an oral selective Janus kinase (JAK) 1/2 inhibitor, approved in the EU for moderate to severe active RA.

Objectives To compare *in vitro* cellular pharmacology of BARI to upadacitinib (ABT), filgotinib (FILGO), and tofacitinib (TOFA), three JAK inhibitors (JAKis) currently approved or in clinical development.

Methods Peripheral blood mononuclear cells from healthy donors ($n=6-12$) were incubated with different JAKis. After cytokine stimulation, phosphorylated signal transducer and activator of transcription (pSTAT) levels were measured and IC_{50} calculated in phenotypically gated leukocyte subpopulations. Therapeutic dose relevance of *in vitro* analysis was assessed using calculated mean concentration-time (CT) profiles over 24 hour JAKi-treated subjects (BARI 4 mg QD; ABT 15 and 30 mg QD; FILGO 100 and 200 mg QD; TOFA 5 and 10 mg BID). Time above IC_{50} ($T>IC$; h/day) and average daily% inhibition of pSTAT formation (%SI) were calculated for each JAKi, cytokine, and cell type.

Results Tested cytokines did not signal in all cell types. When signalling was detected, IC_{50} , %SI, and $T>IC$ for a particular JAKi exhibited similar dose dependent inhibition across cell types. For JAK1/3 dependent signalling across 4 cytokines (IL-2, 4, 15, 21), IC_{50} for ABT and TOFA were more potent than BARI; FILGO was the least potent. Overlaid on CT profiles, this indicated generally higher %SI and longer $T>IC$ for ABT and TOFA compared to BARI and FILGO. For IL-6 (JAK1/2), %SI and $T>IC$ was TOFA>BARI/ABT>FILGO and for IL-10 (JAK1/TYK2), %SI was TOFA>BARI/ABT>FILGO. IFN- γ (JAK1/2) was modulated only by BARI, ABT, and TOFA. IFN- α (JAK1/TYK2) signalling was most potently inhibited by BARI and ABT. FILGO did not appear to modulate GM-CSF signalling (JAK2/2), while %SI and $T>IC$ were similar between BARI and ABT.

Conclusions JAKis modulate distinct cytokine pathways to differing degrees and durations over 24 hour. BARI and FILGO inhibited JAK1/3 signalling less than ABT and TOFA. No JAKis agent potently or continuously inhibited an individual cytokine signalling pathway throughout dosing interval, implying the varying efficacy and safety profiles of JAKis across disease states.

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Disclosure of interest None declared

P060

IL-38 IN ARTHRITIS MATURATION AND DEGRADATION OF THIS NEW IL-1 FAMILY ANTI-INFLAMMATORY CYTOKINE

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Introduction Interleukin 38 (IL-38) is an IL-1 family cytokine with potential anti-inflammatory activity. Recently we showed that over-expression of full length IL-38 reduces inflammation in arthritic mice by 20%-30%, reduces macrophage infiltration and the expression of cytokines implicated in the biology of Th17 cells.¹ However, IL-38 does not have a classical signal peptide, and it is unclear how it is released for example from monocytes/macrophages. It needs post-translational processing (N-terminal truncation) to acquire full biological activity, but the required proteases are unknown.

Objectives The aim is to study the maturation of IL-38 in the inflammatory process.

Methods THP1 macrophagic cells were transduced with a lentivirus encoding full length IL-38 to over-express this cytokine. Secretion and maturation (truncation) of endogenous or over-expressed IL-38 has been studied by western blot. The potential proteases implicated in IL-38 N-terminal truncation have been analysed *in silico* (Prosper webserver) and by biochemical tests using recombinant proteases and their inhibitors.

Results In the synovial fluid of RA patients, we observed 2 truncated forms of IL-38. To determine if apoptosis is a mechanism responsible for the maturation of IL-38, we tested different stress conditions on THP1 macrophages that overexpress IL-38. In conditioned media, three truncated forms of IL-38 were revealed by Western Blot under conditions of apoptosis, exacerbated oxidative stress, or necrosis. However, none of these conditioned media appears to have a high anti-inflammatory effect on macrophages. Our results rather suggest that cell death by apoptosis or necrosis results in IL-38 degradation and loss of biological effect. *In silico*, several potential cleavage sites were found for calpain, MMP-2, MMP-9 and cathepsin G. Incubation of recombinant full length IL-38 with MMP-2 or cathepsin G leads to significant degradation of this cytokine. On apoptotic THP1 cells overexpressing IL-38, an inhibitor of MMPs and TACE (TAPI) also reduces the release and degradation of IL-38.

Conclusions The degradation and loss of the anti-inflammatory effect of IL-38 appears to occur during cell death in the extracellular space, and could involve MMPs. The processes involved in the maturation of IL-38 need to be further explored and could open new therapeutic opportunities for the treatment of arthritis.

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