FRI0428

THE JAK1-SELECTIVE INHIBITOR, FILGOTINIB, INHIBITS INFLAMMATION PATHWAYS OBSERVED IN AN IL23-INDUCED PSORIATIC ARTHRITIS MOUSE MODEL

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Background: Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease characterized by musculoskeletal involvement and extra-skeletal manifestations such as psoriasis, uveitis and Inflammatory Bowel Disease (IBD). The importance of several pro-inflammatory cytokines, in addition to TNFa, IL-12 and IL-23 which are targets of current treatments, suggests that novel therapies may benefit patients. The JAKs (a family of 4 non-receptor tyrosine kinases) are crucial for the signaling of many pro-inflammatory cytokines. In this regard, the JAK1-selective inhibitor filgotinib (GLPG0634, GS-6034) has shown efficacy in patients with rheumatoid arthritis (RA), a disease that shares some hallmarks with PsA, as well as in Crohn's disease (CD), making this molecule a potential therapy for PsA.

Objectives: To gain insight into filgotinib mode of action using a PsA preclinical model by analysing the gene expression signature of filgotinib in mouse phalanges and colon tissues from an IL23-induced PsA mouse model.

Methods: Spondyloarthopathy was induced by hydrodynamic injection of IL-23 enhanced Episomal Expression Vector (EEV). Animals were treated with filgotinib or vehicle from day 10 (therapeutic mode) and sacrificed after 16 days of treatment. RNAs were extracted from the phalanges and the proximal colon, and transcriptome assays were performed using the Agilent SurePrint G3 mouse chip. Data analysis was performed using empirical Bayes methods and linear models (limma BioConductor package).

Results: In mice, IL-23 induced changes in the transcriptome in both phalanges and colon that were marked by effects on genes related to the IL-23/T_H17 axis. Microarray analysis performed on mouse phalanges and colon revealed that filgotinib partially reversed the impact of IL-23 on gene expression in colon and in phalanges. In both tissues, filgotinib signature was different but some impacted biological programs were similar. A consistent interferon signature was counteracted by filgotinib in both tissues with decreased expression of common genes such as Apobec3, Gbp8, Iigp1 and Oas3. Several markers of inflammation or associated with IL-23 activitywere also decreased with common on Kynu and Cd96 gene expression in both tissues. Of interest, filgotinib repression on inflammatory gene expression was stronger in colon compared to phalanges (IL1b, Clec4e). Moreover expression of some genes involved in gut homeostasis that were induced by IL-23 were decreased by filgotinib in the colon, notably Fpr2 (receptor for formyl peptides) and Mmp7. In phalanges, gene expression associated with IL-23-induced disease was also reversed by filgotinib treatment. Il19, Mtcl1 and Tlr1 which are key mediators in psoriasis, or Rankl that is involved in bone remodeling in PsA were differently regulated by IL-23 and filgotinib.

Conclusions: Systemic expression of IL-23 in mice generated a PsA phenotype that was associated with altered gene expression in diseased tissues. A strong interferon signature was reversed by filgotinib as were several inflammation and disease markers. Together with the previous Phase 2 clinical results in RA and CD, these data support the study of filgotinib for the treatment of PsA patients.

Disclosure of Interest: R. Blanqué Employee of: Galapagos SASU, M. Ongenaert Employee of: Galapagos NV, C. David Employee of: Galapagos SASU, C. Robin-Jagerschmidt Employee of: Galapagos SASU, A. Cauvin Employee of: Galapagos SASU, C. Saccomani Employee of: Galapagos SASU, P. Clement-Lacroix Employee of: Galapagos SASU, S. Dupont Employee of: Galapagos SASU, R. Galien Employee of: Galapagos SASU

DOI: 10.1136/annrheumdis-2017-eular.4911