WHOLE BLOOD TRANSCRIPTIONAL CHANGES FOLLOWING SELECTIVE INHIBITION OF JANUS KINASE 1 (JAK1) BY FILGOTINIB IN ADULTS WITH MODERATELY-TO-SEVERELY ACTIVE RHEUMATOID ARTHRITIS WITH PRIOR INADEQUATE RESPONSE TO METHOTREXATE (FINCH1).

P.C. Taylor[1], B. Downie, E. Elboudwarej, S. Kim, A. Hertz, A. Mirza[2], J. Siegel, R. Hawtin, J. Liu[2]
[1]Botnar Research Centre, Nuffield Dept Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK
[2]Gilead Sciences, Inc., Foster City, CA

Background: Filgotinib (FIL), an oral selective JAK1 inhibitor, has shown safety and efficacy in multiple phase 3 studies in adults with moderately-to-severely active rheumatoid arthritis (RA). We have previously described the molecular response to FIL in large-scale RNA sequencing studies of gene expression in other RA populations[1-3] and herein conducted a similar study in RA pts with prior inadequate response to MTX.

Objective: Identify RA-associated gene transcripts and biological pathways that are altered in response to FIL treatment.

Methods: RA pts who had an inadequate response to MTX were enrolled in FINCH1 (clinicalTrials.gov NCT02889796) and randomized to receive either a stable dose of MTX with placebo (PBO+MTX), adalimumab (ADA+MTX) or one of two doses of FIL (FIL100mg+MTX, FIL200mg+MTX) once daily (QD). Whole blood samples were collected from pts using PAXgene tubes at baseline, week 4 and week 12. RNA from these samples was extracted and sequenced on the Illumina HiSeq 2500 platform following globin RNA depletion. Correlations between baseline gene expression and disease measurements were performed using Spearman's rank partial correlation with covariates. Differentially expressed genes (DEGs) were identified using voom-limma. Pathway analysis was performed on v6.1 of the Molecular Signature Database using single sample GSEA with the focus on immune signaling pathways from KEGG. A false-discovery rate of 5% was applied for all analyses.

Results: Differential gene expression analyses comparing baseline samples with after-treatment samples revealed more rapid transcriptional kinetics for FIL-treated pts compared to ADA+MTX treated pts. No significant DEGs were observed in PBO-treated pts. Many more significant DEGs were observed in the FIL200mg+MTX arm compared to the FIL100mg+MTX arm, consistent with the superior clinical efficacy of the FIL 200mg dosage. Consistent with other FIL clinical trial RNA-seq studies and the selective MoA of FIL, JAK-STAT pathway-induced genes SOCS2 and CISH were significantly downregulated across both FIL treatment arms and timepoints, but not in the ADA+MTX arm. RA disease activity associated genes FAM20A and METTL7B were significantly reduced at both 4 and 12 weeks only in the FIL200mg+MTX arm. While no significant changes in KEGG immune signaling pathways were observed in the PBO+MTX arm, a dose dependent effect on pathway modulation was observed in the FIL arms. The most prominently down-regulated KEGG pathways included JAK/STAT signaling and leukocyte transendothelial migration.

Conclusions: More rapid onset and sustained changes of transcriptional activity were observed in the whole blood transcriptional profile of RA pts following FIL200mg+MTX compared to ADA+MTX treatment. FIL dose-dependent changes were observed, most notably in the KEGG JAK/STAT signaling pathway. These observations confirm an inhibition of JAK-STAT signaling by FIL and are consistent with the observed clinical efficacy of FIL in these pts.

References

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