Selective Inhibition of Janus Kinase 1 (JAK1) by Filgotinib Modulates the Disease-Associated Whole Blood Transcriptional Profile of Patients With Active Rheumatoid Arthritis

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Background: Filgotinib (FIL), an oral JAK1-selective inhibitor, was safe and efficacious in FINCH2, a randomized, double-blind, placebo-controlled, phase 3 study in patients with active rheumatoid arthritis (RA) who had an inadequate response to biologic disease-modifying antirheumatic drugs (bDMARDs).[1] The whole blood transcriptional profile of patients was evaluated.

Objective: Identify RA-associated gene transcripts and biological pathways that are altered in response to FIL treatment and interrogate FIL-modulated biomarkers correlated with disease activity.

Methods: RA patients enrolled in FINCH2 (n=449) were randomized 1:1:1 and received FIL (100 mg, 200 mg) or placebo (PBO) once daily plus a stable background dose of methotrexate. Whole blood samples from enrolled patients were collected at baseline (BL) and weeks 4 and 12 for RNA sequencing. Spearman's rank correlation of BL disease activity (DAS28-CRP) was calculated to define disease-associated genes (DAGs) and pathways (DAPs). Differential expression of 5155 genes and FIL-specific changes were determined after subtracting gene expression changes in the PBO group. Biological pathways (910 total) were analyzed by Gene Set Enrichment Analysis (GSEA) or single-sample GSEA. A false-discovery rate of 5% was applied for all analyses.

Results: At weeks 4 and 12, more genes were significantly differentially expressed in the FIL 200 mg arm vs the 100 mg arm; and, consistent with increased clinical efficacy, the average magnitude of change in gene expression was larger. No single gene reached a threshold of significance for differential expression in PBO-treated patients. FIL treatment induced a stronger reversal of DAG expression (rho range: –0.35 to –0.59) compared to PBO (rho ~ –0.3) at weeks 4 and 12. DAGs most prominently reversed by FIL included *FAM20A* and *METTL7B*. Top-ranked pathways associated positively with disease activity at BL included inflammatory response, complement activity, and cell cycle. Hallmark pathways most significantly reduced following FIL treatment included IL-6/JAK/STAT, inflammatory, and interferon response consistent with known effects of FIL. In contrast, IL-6/JAK/STAT signaling increased at weeks 4 and 12 with PBO. DAPs showed a similar reversal of gene expression (rho range: –0.43 to –0.58) with FIL at weeks 4 and 12 compared to PBO (rho range: –0.007 to –0.024) suggesting that FIL treatment may attenuate RA-mediated IL-6/JAK/STAT signaling, inflammation, and other RA-associated pathways correlated with clinical outcome measures.

Conclusions: The whole blood transcriptional profile of patients following FIL treatment showed a dose-dependent reduction in the expression of JAK/STAT signaling and inflammation genes. No significant changes in the expression of DAGs were observed in PBO-treated patients. FIL also broadly reversed DAGs and DAPs, and ongoing research is exploring the relationship between changes in gene and pathway modulation across a range of clinical endpoints.

Reference

1. Genovese MC, et al. American College of Rheumatology, 2018; Chicago, IL. Abstract L06.