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The JAK1-Selective Inhibitor Filgotinib Reverses the Disease-Associated Transcriptional Profile Found in the Blood of Patients with Active Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Time: 9:00AM-11:00AM

Background/Purpose:

Filgotinib (FIL), an oral JAK1- selective inhibitor, has shown good safety and efficacy in active rheumatoid arthritis (RA) patients with inadequate response to MTX in two phase 2b studies: with methotrexate (DARWIN 1) and as monotherapy (DARWIN 2). To better understand and define the differences in molecular pathways in these RA patients, their correlation to disease severity, and the impact of FIL on these pathways, a large-scale RNA sequencing study was conducted.

Methods:

PAXgene blood samples from 150 RA patients in DARWIN 1 (D1) on either a stable dose of MTX and placebo (PBO) or FIL 200mg once daily (QD); and 92 RA patients in DARWIN 2 (D2) on either PBO or FIL monotherapy 100mg or 200mg QD, were collected and analyzed at baseline, week 1 and/or week 12. RNA in whole blood was sequenced (Illumina HiSeq 2500) after globin depletion. Differential gene expression analysis was performed on all time-paired subject data after subtracting gene expression changes in the PBO group. Pathway analysis was performed using GSEA and GO enrichment. Spearman's rank correlation of gene expression to disease activity score (DAS28-CRP or VectraDA) was calculated on samples without missing values to define disease-associated molecular pathways. A false-discovery rate (FDR) of 10% was applied for all analyses.

Results:

Of the 14,984 genes evaluated, 6,413 genes correlated with DAS28-CRP or VectraDA baseline disease activity and defined a Transcriptional Disease Profile (TDP). FIL treatment reversed the expression of 70% of the TDP genes in D1 and 74% in D2, with 3,801 (59%) reversed in both D1 and D2. Of the 607 genes differentially expressed in D1 or 2, FIL significantly reversed 337 genes in the TDP, suggesting an impact on disease biology with or without MTX. DAS28-CRP or VectraDA-associated genes

reversed by FIL were enriched in processes for neutrophil and granulocyte activation, blood coagulation and inflammatory responses. Genes associated with innate immune responses and c-Jun N-terminal kinase signaling correlated with the TDP but were not significantly impacted by FIL. Following FIL treatment, disease-correlated gene set enrichment scores were also significantly reversed for PD1 signaling, JAK/STAT signaling via IL-6, epithelial-mesenchymal transition, and extracellular matrix regulation. Patients with increased expression of a RA-associated interferon gene set showed a reduced clinical response (median ACR-N) at 12 weeks with PBO (D1 p=0.15, D2 p=0.35) but trended toward an increased clinical response with FIL (D1 p=0.049, D2 p=0.33). Patients receiving FIL showed a reduced interferon profile at 12 weeks (D1 p =0.032, D2 p < 0.001), while no significant change was observed for patients on PBO.

Conclusion:

Disease-associated molecular pathways relevant to DAS28-CRP and VectraDA were shown to be significantly improved at 12 weeks after FIL therapy. This work helps elucidate the molecular correlates of RA disease activity as well as the selective impact of FIL on key relevant pathways. Consistent with previous data, a blood based RA interferon signatures was prognostic for reduced clinical response with PBO and here predicted and showed an improved response with FIL.

Disclosure: P. C. Taylor, Celgene, Eli Lilly, Galapagos, UCB, 2,AbbVie, Eli Lilly, Galapagos, Glaxo Smith Kline, Pfizer Inc, UCB, Biogen, Sandoz, Novartis, Janssen, Gilead Sciences Inc, 5; **B. Downie**, Gilead Sciences Inc, 1, 3; **L. Zhuo**, Gilead Sciences Inc, 1, 3; **Y. Gindin**, Gilead Sciences Inc, 1, 3; **J. Tarrant**, Gilead Sciences Inc, 1, 3; **J. Liu**, Gilead Sciences Inc, 1, 3; **R. Galien**, Galapagos, 3; **A. M. Mirza**, Gilead Sciences Inc, 1, 3.

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