Filgotinib, a Janus Kinase 1 (JAK1)-Selective Inhibitor, Modulates Disease Associated Cytokines in Patients With Active Rheumatoid Arthritis

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Background: Filgotinib (FIL), an oral JAK1-selective inhibitor, was safe and effective in FINCH2, a randomized, double-blind, placebo-controlled, phase 3 study in patients with active rheumatoid arthritis (RA) who had an inadequate response to methotrexate (MTX) and ≥1 biologic disease-modifying antirheumatic drug (bDMARD).[1]

Objective: A longitudinal study of cytokines from patients in FINCH2 was conducted to identify RA-associated biomarkers related to bone biology, immune cell migration, and inflammation that are altered by FIL therapy; and FIL-associated biomarkers that correlate with clinical response (DAS28CRP, swollen and tender joint counts, pain, and fatigue).

Methods: Plasma and serum samples from RA patients (n=449) who received FIL (100 mg, 200 mg) or placebo (PBO) once daily plus MTX were analyzed at baseline (BL) and week 12 for 42 disease-relevant cytokines using validated, commercially available single- or multiplex assays. Changes in cytokine levels from BL to week 12 were compared between treatment arms using a Wilcoxon rank sum test (Median differences of on-treatment change, relative to PBO were reported). Spearman rank correlation was used to compare changes in cytokine level from BL to week 12 and clinical response. P-values < 0.05 were considered significant.

Results: At week 12, 18 of 42 cytokines significantly decreased with FIL 100 mg treatment relative to PBO; FIL 200 mg decreased these cytokines to a similar or greater degree. An additional 6 cytokines were significantly decreased by FIL 200 mg. Conversely, 2 cytokines increased relative to PBO with FIL 100 mg, and 6 cytokines increased with FIL 200 mg (sIL-6R, IL10, GMCSF, IL2, leptin, and IL17A)). Biomarkers most significantly modulated by FIL 200mg ($p<0.0001$) included markers related to bone biology (MMP1 [–22.8%], MMP3 [–24.7%], CTX1 [–27.4%], and NTX [–16.4%]), immune cell migration (VCAM1 [–20.0%], ICAM1 [–14.2%], CXCL13 [–45.0%], and CXCL10 [–32.3%]), and inflammation (TNFRI [–20.7%], CRP [–77.4%], SAA [–61.8%], and resistin [–20.2%]).

Hierarchical clustering of BL biomarker levels revealed distinct groups of cytokines that were strongly correlated with each other. Among them, SAA, IL6, and CXCL10 were significantly positively correlated with RA disease activity (DAS28CRP) at BL (rho > 0.3). Several of these biomarkers were also significantly correlated with individual components of DAS28CRP, including CRP (IL6, SAA), PainVAS (CRPSAA), and SJC28 (CRP IL6, CXCL10). Among the biomarkers associated with RA disease activity at BL, treatment with FIL 100 mg led to decreases at week 12 relative to PBO: CRP [–48.7%], SAA [–36.9%], and IL6 [–

2.6%]. All 4 were also decreased in FIL 200 mg: CRP [–77.4%], SAA [–61.8%], IL6 [–13.6%], CXCL10 [–32.3%], suggesting FIL impacts these disease activities at a molecular level.

Conclusions: Twelve weeks of FIL treatment significantly reduced 24 disease-relevant cytokines in patients with active RA. These effects were dose-dependent and suggest a shift toward restored immune homeostasis. These findings are consistent with the clinical efficacy of FIL in FINCH2.

Reference

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