DDW2020 Digestive Disease Week®

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AGA

EFFECTS OF THE JANUS KINASE (JAK1)-SELECTIVE INHIBITOR FILGOTINIB (FIL) ON CIRCULATING CYTOKINES AND WHOLE-BLOOD GENES/PATHWAYS OF PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE (CD)

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Inflammatory Bowel Diseases
IBD: Controlled Clinical Trials in Humans
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Ask the Author

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Background: A Phase 2 study of the JAK1-selective inhibitor FIL dosed at 200 mg once daily for 10 weeks in moderately to severely active CD (FITZROY, ClinicalTrials.gov #NCT02048618) demonstrated significantly higher clinical remission rates compared with placebo,[1] and early decrease in systemic and mucosal inflammation biomarkers that was more pronounced in endoscopic responders.[2] We investigated baseline correlation of whole-blood transcriptome pathway activities with clinical disease indexes and circulating cytokines. The effect of FIL on changes in disease-related pathways in responders and nonresponders was also explored.

Methods: PAXgene blood samples were collected from 104 CD patients at baseline and Week 10. RNA was sequenced (Illumina HiSeq 2500) after globin depletion (ThermoFisher GlobinClear). Differential gene expression analysis was performed using limma R package,[3] and Hallmark pathway[4] activity scores were calculated using single sample Gene Set Enrichment Analysis (ssGSEA).[5] All correlations were performed using the Spearman method.

Results: At baseline, pathways with activity scores positively correlated with Simple Endoscopic Score for Crohn's Disease (SES-CD) were immune (IL6/JAK/STAT3, inflammatory response), metabolic and reactive oxygen species (ROS). These were also positively correlated with systemic inflammation (CRP, SAA, IL6 and OSM) and epithelial turnover (IL22, C4M2 and C3M) markers. Ten weeks of FIL treatment led to significant decreases of these pathways in endoscopic responders (50% reduction in SES-CD; **Figure**), whereas there were no significant changes by placebo treatment. While interferon (IFN) response pathway scores showed weak correlation (rho <0.2) with SES-CD at baseline, they are significantly reduced by FIL treatment, particularly in FIL responders.

Conclusion: In whole blood, inflammation, metabolic and ROS pathways are reduced by FIL in endoscopic responders at Week 10, while reduction in IFN response pathways were observed in all patients regardless of endoscopic response.

References

1. Vermeire S, *et al*. *Lancet* 2017; 389:266–275.
2. Roblin X. ECCO 2018.
3. Ritchie ME, *et al*. *Nucleic Acids Research* 2015; 43:e47.
4. Liberzon A, *et al*. *Cell Syst* 2015; 1:417–425.
5. Barbie DA, *et al*. *Nature* 2009; 462:108–112.

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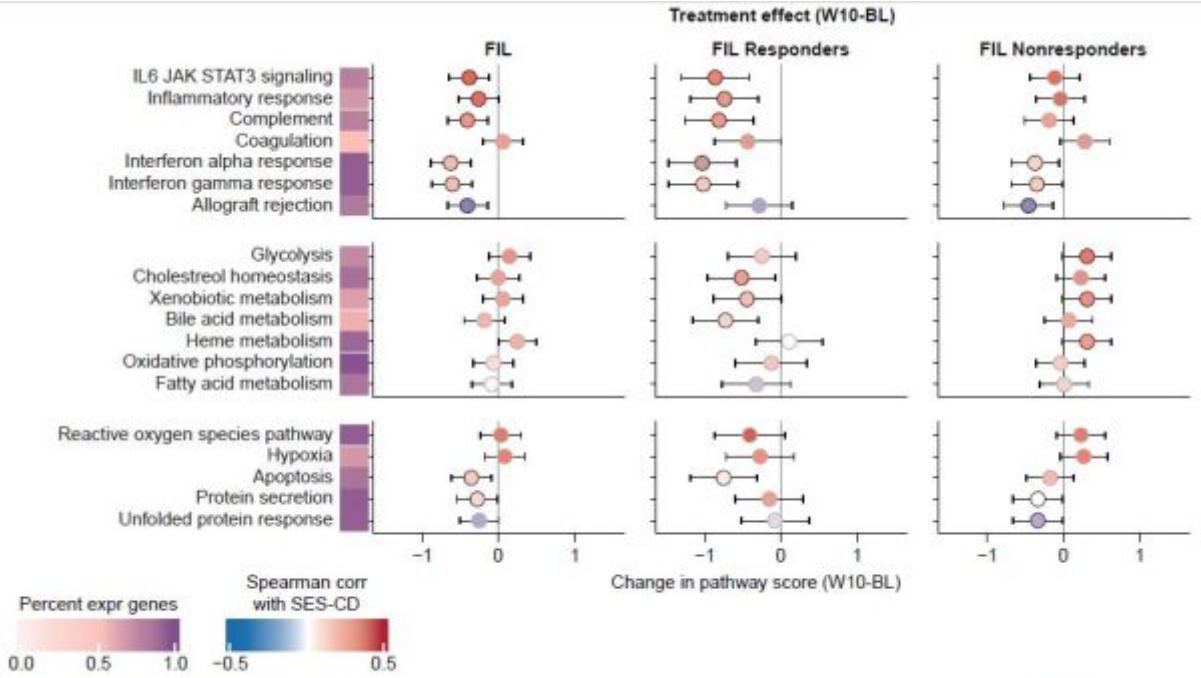

BL, baseline; FIL, filgotinib; IL6, interleukin 6; JAK, Janus Kinase; SES-CD, Simple Endoscopic Score for Crohn's Disease; STAT3, Signal Transducer And Activator of Transcription 3; W10, Week 10.

Disclosure: X. Roblin: Abbvie: Board Membership; Amgen: Consulting; Janssen: Board Membership; MSD: Board Membership; Pfizer: Consulting; Sandoz: Consulting; takeda: Board Membership; Theradiag: Consulting; A. Serone: Gilead Sciences Inc.: Employment; O. Yoon: Gilead Sciences: Employment; L. Zhuo: Gilead Sciences: Employment; E. Grant: Gilead Sciences, Inc: Employment, Stock Shareholder; J. Woo: Gilead Sciences: Stock Shareholder; J. Liu: Gilead: Employment; R. Galien: Galapagos: Employment, Employment; G. R. D'Haens: Abbvie: Consulting; Ablynx: Consulting; Allergan: Consulting; Alphabiomics: Consulting; Arena Pharmaceuticals: Consulting; Boehringer Ingelheim: Consulting; Bristol Meiers Squibb: Consulting; Celltrion: Consulting; Echo Pharmaceuticals: Consulting; Eli Lilly: Consulting; Galapagos: Consulting; Genentech/Roche: Consulting; Gilead: Consulting; Glaxo Smith Kline: Consulting; Gossamerbio: Consulting; Immunic: Consulting; Johnson and Johnson: Consulting; Kintai Therapeutics: Consulting; Mitsubishi Pharma: Consulting; Nextbiotics: Consulting; Pfizer: Consulting; Prodigest: Consulting; Progenity: Consulting; Prometheus laboratories/Nestle: Consulting; Takeda: Consulting;

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