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FILGOTINIB DECREASES MOLECULAR MARKERS OF JAK1 SIGNAL TRANSDUCTION IN CROHN'S DISEASE: CONCORDANCE WITH ENDOSCOPY AND HISTOPATHOLOGY

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Inflammatory Bowel Diseases
IBD: Controlled Clinical Trials in Humans
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Background: Filgotinib (FIL) is a JAK1 inhibitor under Phase 3 clinical evaluation for treatment of IBD. We conducted a posthoc analysis in a subset of patients with moderately to severely active CD from FITZROY (NCT02048618) to assess the effect of FIL (200mg QD) on molecular markers of JAK1-related signalling (STAT1 & STAT3 phosphorylation) within epithelium and non-epithelium regions of intestinal mucosa and explore their correlation to histologic and endoscopic indices.

Methods: Biopsies were collected at baseline and Week 10 from the most affected area of each predefined bowel segment (ileum, ascending, transverse, descending colon and rectum). Within-subject matched biopsies for all segments from FIL (n=42) and placebo (PBO; n=18) treated patients were scored for histologic (GHAS) and endoscopic (SES-CD) disease activity totalling to 300 segments. Using specific antibodies and IHC, %pSTAT1 and %pSTAT3 positive nuclei within epithelium and non- epithelium regions of each biopsy were quantified using machine learning (Visiopharmv.2019.06). Basal pSTAT levels assessed from 182 nondiseased (SES-CD=0 & GHAS=0) segments were used to determine a threshold for categorising segments as either low or high molecular disease activity (MDA). Agreement between endoscopy or histology and MDA was evaluated by k and % agreement by segment and all segments combined.

Results: Median basal pSTAT1 was similar between colonic epithelium and non-epithelium regions (1%–2%), but higher in ileal epithelium (5%). Median basal pSTAT3 was higher in non-epithelium (3%–5%) vs epithelium (1%–2%) regions across all segments. At baseline, MDA was elevated in segments with ulceration (~10%, pSTAT1 & pSTAT3). In segments with GHAS activity subscore ≥2 at baseline, both epithelium MDA (10%–30%) and non-epithelium MDA were elevated (25%–35%) and correlated to histologic activity. In segments with low baseline MDA, significantly fewer segments with FIL showed MDA worsening at Week 10 compared with PBO (both pSTAT1 & pSTAT3). In segments with high baseline MDA, FIL treatment improved significantly more segments than PBO; this was evident for pSTAT3 only (Table). Concordance between MDA and endoscopy was mostly fair to moderate (κ 0.3–0.5), whereas MDA and histology showed moderate to good concordance (κ 0.4–0.8).

Conclusion: Filgotinib treatment improved JAK1-related MDA within the mucosa of patients with CD. Concordance between MDA and clinical indices was highest with histology.

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Table. Effect of FIL on epithelium and non-epithelium regions within segments

			Ep			Non-Ep		
pSTAT	BL MDA	W10 change	FIL	PBO	P	FIL	PBO	P
pSTAT 1	Low	Worsen	−0.168	−0.348	<0.05	−0.173	−0.394	<0.05
	High	Improve	0.436	0.286	NS	0.390	0.327	NS
pSTAT 3	Low	Worsen	−0.115	−0.375	<0.005	−0.109	−0.382	<0.005
	High	Improve	0.449	0.241	<0.05	0.442	0.232	<0.05

Data are proportions of segments; bold indicates significant difference between FIL v PBO
BL: baseline; Ep: epithelium; FIL: filgotinib; PBO: placebo; W10: Week 10;

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