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THE JAK1-SELECTIVE INHIBITOR FILGOTINIB REDUCES MULTIPLE MARKERS OF INFLAMMATION LINKED TO VARIOUS PATHOLOGIC CELL TYPES AND PROCESSES IN RHEUMATOID ARTHRITIS PATIENTS

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Background: JAK1, 2, 3 and TYK2 are cytoplasmic tyrosine kinases that mediate intracellular signaling of many cytokines and growth factors. Filgotinib (GLPG0634, GS-6034) is a JAK inhibitor with high selectivity for JAK1 over other JAK family members. Filgotinib has a favorable safety and efficacy profile in two Phase 2B studies in active rheumatoid arthritis (RA) patients who were methotrexate (MTX) inadequate responders.

Objectives: To assess the effect of filgotinib on a background of MTX treatment on markers of inflammation in RA patients.

Methods: Serum samples from RA patients who were on a stable dose of MTX and received either placebo (PBO), filgotinib 100mg or 200mg once daily (QD), were collected at baseline, week 4 and week 12 and analyzed for 35 soluble serum biomarkers by validated single-plex or multiplex immunoassays. Median % changes from baseline for biomarkers are reported. Wilcoxon rank-sum test assessed the significance of difference between filgotinib treated groups and PBO.

Results: Filgotinib treatment induced a dose-dependent and significant decrease in a variety of biomarkers implicated in RA pathogenesis including inflammation (IL-1β, IL-6, TNFα and SAA), matrix degradation and cartilage destruction (MMP1 and MMP3), immune cell trafficking (CXCL10, ICAM-1 and VCAM-1) and angiogenesis (VEGF). Cytokines involved in T_H1 (IFN-γ, IL-2, IL-12) and T_H17 (IL-1β, IL-6, IL-21, IL-23) cell subset differentiation and activity were significantly decreased. Additionally, decrease in the B-cell chemoattractant CXCL13 and the myeloid growth factor GM-CSF supports the anti-inflammatory effects of filgotinib treatment.

Table: Median percent change of biomarkers at week 12 from baseline for PBO and 200mg QD dose.

	PBO (N=78)	filgotinib 200mg QD (N=75)		PBO (N=78)	filgotinib 200mg QD (N=75)		PBO (N=78)	filgotinib 200mg QD (N=75)
BAFF	-2	-6^{NS}	IL-2	-7	-20**	MIP-1β	0	-7*
CRP	-8	-78***	IL-21	0	-28**	MMP-1	-6	-26***
CXCL-13	3	-40***	IL-23	-6	-25***	MMP-3	-9	-43***
EGF	0	0^{NS}	IL-4	0	0^{NS}	RESISTIN	-1	-16***
GM-CSF	0	-26***	IL-5	2	-14**	SAA	7	-67***
ICAM-1	0	-14***	IL-6	-20	-63***	sgp130	0	4^{NS}
IFN-γ	-2	-21*	IL-7	1	-17***	TNF-α	1	-15***
IL-10	-3	-17**	IL-8	-2	-12^{NS}	TNF-RI	0	-15***
IL-12	0	-24***	IP-10	-2	-31**	VCAM-1	0	-16***
IL-13	-1	-8**	LEPTIN	6	23*	VEGF	-2	-26***
IL-17A	2	-18*	MCP-1	4	-8^{NS}	YKL-40	-7	-33***

IL-1β	-2	-26***	MIP-1α	1	-8**	

p-values comparing % changes between filgotinib and PBO groups: NS, $p>0.05$; *$p<0.05$; **$p<0.01$; ***$p<0.001$

Conclusions: Treatment with filgotinib decreased several factors that have key roles in RA for matrix degradation, cartilage destruction, angiogenesis, leukocyte adhesion and recruitment. The changes were accompanied by decreases in cytokines that promote and activate T_H1, T_H17, B-cells and myeloid cells that are important in RA. These findings provide insights into filgotinib mechanism of action and are consistent with its efficacy observed in RA patients.

Disclosure of Interest: P. Taylor Consultant for: Galapagos NV, Pfizer, Eli Lilly, UCB, GSK, R. Westhovens: None declared, A. Van der Aa Employee of: Galapagos NV, C. Jamoul Employee of: Galapagos NV, W. Li Employee of: Gilead Sciences, L. Goyal Employee of: Gilead Sciences, Y. Pan Employee of: Gilead Sciences, P. Harrison Employee of: Galapagos NV, C. Tasset Employee of: Galapagos NV, J. Tarrant Employee of: Gilead Sciences, R. Galien Employee of: Galapagos SASU

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