THU0182

MONOTHERAPY WITH THE JAK1-SELECTIVE INHIBITOR FILGOTINIB DISPLAYS AN ANTI-INFLAMMATORY BIOMARKER PROFILE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Janus kinases (JAKs) are key proteins in the signal transduction of many cytokines and growth factors. The selective JAK1 inhibitor filgotinib (GLPG0634, GS-6034) has been evaluated in a 24-week phase 2B study (DARWIN 2) as monotherapy in active rheumatoid arthritis (RA) patients with inadequate response to methotrexate and has shown a good safety and efficacy profile[1].

Objectives: To gain insight into filgotinib mode of action as monotherapy in RA patients by analysing the impact of filgotinib on a broad panel of immune modulators in the serum.

Methods: RA patients received either placebo (PBO), or filgotinib monotherapy at 50mg, 100mg or 200mg once daily (QD). Serum samples were collected at baseline, week 4 and week 12 and analysed using the 18-plex bead-based immunoassay (HSTCMAG-28SK Merck-Millipore) on BioPLEX-200 instrument to measure cytokine concentration. Median % change from baseline for biomarkers are reported for week 4 and 12. Wilcoxon rank-sum test assessed the significance of difference between filgotinib treated groups and PBO.

Results: Following treatment with filgotinib at 100 mg QD and 200mg QD, there were significant reductions in cytokines important in expansion and activity of multiple T cell subsets and innate immunity compared to PBO (see Table). These changes include decreases in proinflammatory cytokines (IL-6, IL-1β, and TNFα), T_H1-related (IL-2, IFN-γ and IL-12), T_H2-related (IL-4, IL-5, and IL-13) and T_H17-related cytokines (IL-1β, IL-6, IL-17A, IL-21 and IL-23). All doses of filgotinib also reduced the B- and T-cell development cytokine IL-7. In contrast, IL-8 was not affected by filgotinib. Reductions in MIP1α, MIP1β and GM-CSF are in line with a down modulation of innate immune activity.

Table: Median percent change of biomarkers from baseline

	Week 4			Week 12		
	PBO (N=61)	filgotinib 100mg QD (N=62)	filgotinib 200mg QD (N=65)	PBO (N=61)	filgotinib 100mg QD (N=63)	filgotinib 200mg QD (N=65)
GM-CSF	0	-11***	-9***	6	-11***	-21***
IFN-γ	13	-15***	-13***	6	-21***	-23***
IL-1β	6	-10**	-13***	8	-24***	-16***
IL-2	4	-9**	-13***	10	-22***	-21***
IL-4	10	-8***	-8***	21	-17***	-22***
IL-5	2	-10**	-3*	3	-20***	-14***
IL-6	17	-20**	-35***	-13	-34*	-52***
IL-7	2	-10***	-1 NS	0	-22***	-21**
IL-8	1	-1 NS	-1 NS	-7	-4 NS	-8 NS
IL-	6	-12***	-17***	13	-18***	-26***

10						
IL-12	8	-7***	-14***	6	-20***	-23***
IL-13	1	-10**	-13**	13	-8***	-20***
IL-17A	7	-9***	-12***	1	-21***	-16**
IL-21	11	-14***	-10***	4	-26***	-23***
IL-23	3	-12***	-12***	-4	-24***	-31***
MIP-1α	5	-5***	-8***	3	-7***	-6**
MIP-1β	3	-6**	-6*	3	-5^{NS}	3^{NS}
TNF-α	5	-7***	-12***	5	-11**	-14**

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

Conclusions: Treatment of RA patients with filgotinib monotherapy resulted in significant reduction in the levels of a broad range of cytokines related to T_H1, T_H2, T_H17 and potentially B cells, as well as innate immunity. This observed anti-inflammatory activity of filgotinib is consistent with its efficacy in RA patients.

References: [1]Kavanaugh A et al. Ann Rheum Dis 2016;0:1-11.doi:10.1136/annrheumdis-2016-210105

Disclosure of Interest: A. Kavanaugh Consultant for: Galapagos, Pfizer, Abbvie, Amgen, Celgene, Janssen, Novartis, Eli Lilly, UCB, 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

DOI: 10.1136/annrheumdis-2017-eular.5814