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THE JAK1 SELECTIVE INHIBITOR FILGOTINIB REGULATES BOTH ENTHESIS AND COLON INFLAMMATION IN A MOUSE MODEL OF PSORIATIC ARTHRITIS

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Background: Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease characterized by the association of musculoskeletal involvement and extra-skeletal symptoms such as psoriasis and Inflammatory Bowel Disease (IBD) with a variable clinical course. Common findings include enthesitis and dactylitis. Current treatments include anti-TNFa and anti-IL-12/IL-23 antibodies with varying success rates but the involvement of several pro-inflammatory cytokines suggests that other targeted therapies may be effective. Notably, the JAKs (a family of 4 non-receptor tyrosine kinases) are crucial for the signaling of many pro-inflammatory cytokines. In this regard, the JAK1-selective inhibitor filgotinib (GLPG0634, GS-6034) demonstrated clinical efficacy in patients with rheumatoid arthritis, a disease that shares some hallmarks with PsA and Crohn's disease, making this molecule a potential therapeutic tool for the treatment of PsA.

Objectives: Filgotinib was evaluated at the dose of 30 mg/kg/d (*per os*) in a mouse model of PsA induced by overexpression of IL-23.

Methods: Overexpression of IL-23 was induced by hydrodynamic delivery of mIL-23 enhanced Episomal Expression Vector (SBI) to male B10.RIII mice[1]. Evolution of inflammation of the paws and fingers was assessed by clinical scoring as well as *in vivo* molecular imaging (Bruker In-Vivo Xtreme imaging system). Enthesis and fingers were collected for expression analysis of inflammatory genes and target-related biomarkers. Neutrophil infiltrate, as well as pSTAT3 positive cells, were analyzed using immunohistochemistry in Achilles' enthesis and subcutaneous area, respectively. Colon was collected for lesion score determination as well as inflammatory and target-related biomarker gene expression.

Results: High levels of IL-23 were maintained during the time-course of the study and were correlated with severity of finger and paw swelling. Localization of the fluorescent signal using ProSense^{TM} imaging was asscociated with inflammation of enthesis and finger reported in PsA. Moderate inflammation of the colon was also observed. Filgotinib significantly improved clinical scoring and tended to prevent neutrophil/granulocyte infiltrate in paw (with significant effect being showed at earlier time point). Filgotinib reversed some up-regulated inflammatory genes in enthesis and/or fingers (CCL20, CXCL1, IL-22, MMP9 and TNFa) and reduced the target-related gene Mx2. Filgotinib significantly counteracted pSTAT3 induction in the subcutaneous area further demonstrating target engagement in the diseased tissue. Finally in line with previous findings[2], Mx2 expression in colon was slightly reversed by filgotinib.

Conclusions: In a mouse model of PsA, filgotinib improved global clinical score and decreased signs of inflammation in hindlimbs. Target engagement both in hindlimbs and colon was also demonstrated. These data support the evaluation of filgotinib in patients with PsA.

References: 1- Sherlock *et al*. 2012 Nature Med 7:1069–1076

2- Van Rompaey *et al*. 2013 J Immunol. 191:3568-3577

Disclosure of Interest: C. Robin-Jagerschmidt Employee of: Galapagos SASU, S. Lavazais Employee of: Galapagos SASU, F. Marsais Employee of: Galapagos SASU, A. Monjardet Employee of: Galapagos SASU, A. Cauvin Employee of: Galapagos SASU, C. Saccomani Employee of: Galapagos SASU, I. Parent Employee of: Galapagos SASU, D. Merciris Employee of: Galapagos SASU, E. Chanudet Employee of: Galapagos SASU, M. Borgonovi Employee of: Galapagos SASU, L. Lepescheux Employee of: Galapagos SASU, M. Auberval Employee of: Galapagos SASU, S. Dupont Employee of: Galapagos SASU, P. Clement-Lacroix Employee of: Galapagos SASU, R. Galien Employee of: Galapagos SASU

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