**Introduction**

Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease characterized by the association of musculoskeletal involvement and extra-skeletal symptoms such as psoriasis, uveitis and inflammatory bowel disease (IBD). The JAKs (a family of 4 non-receptor tyrosine kinases) are crucial for the signaling of many pro-inflammatory cytokines. In that regard, the JAK1-selective inhibitor filgotinib (GLPG0634, GS-6034) demonstrated efficacy in patients with rheumatoid arthritis and Crohn’s disease, conditions sharing some hallmarks with PsA, making this molecule a potential treatment option for PsA.

**Objectives**

The primary objective of this study was to characterize the effects of filgotinib in the IL-23-induced PsA mouse model. In addition to an evaluation of the impact on clinical signs of inflammation, full transcriptome profiling was performed on tissue from the fingers and colon to fully characterize the changes induced by filgotinib.

**Methods**

**In vivo**

Male B10RIII mice underwent a hydrodynamic injection of Ringer’s (sham) or IL23 EEV in Ringer’s into the tail vein (1µg/2.2 mL; i.v.) on day 1. At day 10 after EEV administration, the signs of inflammation were scored according to the procedure described by Sherlock et al.1. Filgotinib at 30 mg/kg was dosed orally (p.o.) from day 10 to day 26, twice daily (BID).

**Imaging**

At day 24, ProSense680 probe was injected (0.8 nmol/10 g; i.p.) 24 hours prior to in vivo imaging, according to the recommendation of the supplier. Granulocyte infiltration was measured using a Bruker In-Vivo Xtreme imaging system (Bruker BioSpin, Billerica, MA, USA) with the following camera settings: 5 sec acquisition time (lEx: 630nm, lEm: 700nm).

**Gene expression**

At day 26, 2 hours after filgotinib administration, the fingers of the rear paws and 1 cm of the distal part of the colon were collected. RNA was extracted and transcriptome analysis was performed using empirical Bayes methods and linear models (limma BioConductor package).

**Results**

**Conclusions**

Systemic expression of IL-23 in mice generated a PsA phenotype that translated to an altered gene expression profile in diseased tissues (colon/fingers). A strong pathology-induced interferon signature was reversed by filgotinib, as was the expression of several inflammation and disease-related genes. These data support the therapeutic potential of filgotinib for the treatment of PsA.

**Results: effect of filgotinib on clinical score and imaging**

Filgotinib 30 mg/kg BID reduces inflammation as of day 16.

**Results: effect of filgotinib on selected genes**

Filgotinib reversed the expression of psoriasis disease mediator (IL-19), inflammation (CD-96) and interferon pathway (OAS-3), genes associated with IL-23 effect.

From the top 50 most differentially expressed genes: filgotinib partially reverses the IL-23-induced PsA in colon and fingers. Negative correlation between IL-23 and filgotinib effects in colon and fingers (Spearman coefficient R=-0.4).

**Results: transcriptomic profiling of colon and fingers, 26 days after IL-23 EEV injection**

Filgotinib mainly impacted the interferon (18%) and inflammation (28%) and interferon (12%) signature in diseased tissues (colon/fingers). A strong pathology-induced interferon signature was reversed by filgotinib, as was the expression of several inflammation and disease-related genes. These data support the therapeutic potential of filgotinib for the treatment of PsA.

**References**


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