Treatment of Rheumatoid Arthritis Patients with the JAK1-Selective Inhibitor GLPG0634 reverses an arthritis-specific Blood Gene Signature to healthy state

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Background

The 4 Janus kinases (JAK1, JAK2, JAK3 and TYK2) are cytoplasmic tyrosine kinases that mediate intracellular signaling of cytokines (e.g. certain interleukins and interferons) and growth factors (e.g. erythropoietin). Filgotinib (GLPG0634) is the first JAK inhibitor that displays a high selectivity for JAK1 versus the 3 other JAK family members in functional assays. It showed a favorable safety and efficacy profile in two 4-week Phase 2a studies in rheumatoid arthritis (RA) patients (Tasset et al., ACR 2013, poster #2381). In order to further characterize GLPG0634, we compared the gene expression profile of circulating leukocytes of healthy volunteers and RA patients before and after 4 weeks of daily treatment with 200 mg of GLPG0634.

Methods

Patients and healthy volunteers

RA patients participated in a Phase 2a Proof of concept study, (randomized, double-blind, placebo-controlled study enrolling 36 patients with insufficient response to MTX). They were orally treated with placebo or 200 mg QD GLPG0634 for 4 weeks. Non-matched healthy volunteers were left untreated.

Blood collection

Blood was directly sampled in PAXgene tubes by venipuncture. In RA patients, it was collected at pre-dose and on the last day of treatment (4 weeks).

Gene expression analysis in human blood

mRNA was extracted, labelled and profiled using Affymetrix U219 micro-arrays. Data analysis was performed in R/BioConductor using linear regression models (limma).

qPCR confirmations

cDNA samples were analyzed by qPCR using Viia7 apparatus.

Conclusions

Disease signature: Heatmap highlighting the differences between transcriptional signature of the RA patients before placebo (yellow code) or GLPG0634 (orange code) treatment and healthy volunteers (green code) of the top-100 best ranked probes.

- A disease expression signature discriminating RA patients from healthy individuals has been identified in whole blood
- The genes identified in this RA disease signature are highly relevant for the disease
- Filgotinib treatment reverts RA disease effects in blood while placebo treatment left the signature virtually unaffected
- The main specific genes affected by filgotinib treatment are associated with metabolic pathways, ECM-receptor signaling, focal adhesion, leukocyte trans endothelial migration and tight junction biology.

Enriched KEGG-pathways in the top-200 most differential probes after GLPG0634 treatment. All p-values (p) are corrected for multiple testing (Benjamini-Hochberg).

<table>
<thead>
<tr>
<th>KEGG Pathway</th>
<th>#Genes</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECM-receptor interaction</td>
<td>3</td>
<td>p=0.040</td>
</tr>
<tr>
<td>Metabolic pathways</td>
<td>11</td>
<td>p=0.060</td>
</tr>
<tr>
<td>RNA transport</td>
<td>4</td>
<td>p=0.040</td>
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<tr>
<td>Focal adhesion</td>
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<td>p=0.040</td>
</tr>
<tr>
<td>Leukocyte trans endothelial migration</td>
<td>3</td>
<td>p=0.040</td>
</tr>
<tr>
<td>N-Glycan biosynthesis</td>
<td>2</td>
<td>p=0.040</td>
</tr>
<tr>
<td>Tight junction</td>
<td>3</td>
<td>p=0.040</td>
</tr>
</tbody>
</table>

Poster available online at www.glpg.com

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