Biological effects of the JAK1 selective inhibitor GLPG0634 on inflammation markers in arthritic mice

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Introduction
Non-selective Janus kinase (JAK) inhibitors have shown long-term efficacy in treating rheumatoid arthritis (RA) however, tolerated doses and thereby efficacy are limited due to JAK2-driven side effects. Selective inhibition of JAK1 may be associated with an improved safety profile while maintaining clinical efficacy. Currently available information for JAK1 selective inhibitors is limited.

GLPG0634 is a JAK inhibitor that displays a high selectivity for JAK1 over JAK2 in human whole blood assays (around 30-fold). GLPG0634 is being developed for the treatment of RA where it displayed encouraging short-term efficacy and a favourable safety profile in two 4-week clinical efficacy. Currently available information for JAK1 selective inhibitors is limited.

Methods
- Oral administration of the selective JAK1 inhibitor GLPG0634 in arthritic mice demonstrates:

1. a selective engagement of the JAK1 target by GLPG0634 in vivo
2. that progression of established arthritis in the CIA model is blocked by selective inhibition of JAK1
3. that GLPG0634 administration inhibits inflammation and confers structural protection at the level of bone and cartilage in a therapeutic CIA model
4. that a single administration of GLPG0634 is sufficient to block CIA-induced inflammatory signalling

Results
- Impact on arthritis: GLPG0634 is as efficacious as etanercept in decreasing disease score
- Impact on cartilage degradation: GLPG0634 is as efficacious as etanercept in limiting cartilage erosion as observed in paw histology (A). MMP3 and MMP13 expression in paw (B) is in line with these findings
- Impact on bone erosion: GLPG0634 is as efficacious as etanercept in limiting bone erosion as observed in paw histology (A). RANKL expression in paws (B) is in line with these findings
- Impact on cell invasion: GLPG0634 is as efficacious as etanercept in limiting T cells and macrophage invasion in paw as observed by IHC in paw (A). Chemotactic agent levels in plasma (B) are in line with IHC data

Conclusions
- Oral administration of the selective JAK1 inhibitor GLPG0634 in arthritic mice demonstrates:
  1. a selective engagement of the JAK1 target by GLPG0634 in vivo
  2. that progression of established arthritis in the CIA model is blocked by selective inhibition of JAK1
  3. that GLPG0634 administration inhibits inflammation and confers structural protection at the level of bone and cartilage in a therapeutic CIA model
  4. that a single administration of GLPG0634 is sufficient to block CIA-induced inflammatory signalling

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