Background: JAK inhibition profile to TOFA, BARI, and UPA against the JAK1/TYK2- (IFNα/pSTAT1), JAK1/2-dependent cytokines (IL-2, -4, and -15), JAK2/2 (GM-CSF)-dependent pathways compared to JAK1/2 (IFNγ/pSTAT1), JAK1/3-dependent cytokines (IL-2, -4, and -15), JAK2/2 (G-CSF/pSTAT3), and JAK2/2 (GM-CSF/pSTAT5)-dependent pathways compared to TOFA and UPA, and in certain cases to BARI (2 mg).

Conclusion: Different JAKi modulate distinct cytokine pathways to varying degrees, and no agent potently and continuously inhibited an individual cytokine signaling pathway throughout the dosing interval. FIL (200 mg) showed a similar activity in average target coverage and time above IC50 to the approved low doses of TOFA (5 mg) and UPA (15 mg); conversely, FIL had reduced mean average inhibition and time above IC50 levels against JAK1/2 (IFNγ/pSTAT1), JAK1/3-dependent cytokines (IL-2, -4, and -15), JAK2/2 (G-CSF/pSTAT3), and JAK2/2 (GM-CSF/pSTAT5)-dependent pathways compared to TOFA and UPA, and in certain cases to BARI (2 mg).

Results: Cellular assays in PBMCs and WB showed dose-dependent inhibition of cytokine-induced pSTATs with all JAKi (correlation between the protein-adjusted IC50 values from PBMCs and IC50 values from WB, r2 = 0.98). Among the most potently inhibited pathways were JAK1/TYK2-dependent cytokine, interferon alpha (IFNα), and the JAK1/2-dependent cytokine, interleukin (IL)-6. FIL and MET had weaker potencies against JAK2/2 TYK2 (G-CSF/pSTAT3), JAK1/2 (IFNγ/pSTAT1), and JAK2/2 (granulocyte-macrophage colony-stimulating factor [GM-CSF]) dependent pathways compared to JAK1/2 TYK2 (IFNα/pSTAT5). FIL and MET showed the greatest selectivity vs the JAK2/2 pathway (GM-CSF/pSTAT3) in monocytes.

The mean concentration-time profiles and time above IC50 over 24 hr for each cytokine/STAT pathway showed that JAK1/2 (IL-6/pSTAT1) and JAK1/TYK2 (IFNγ/pSTAT1) pathways were strongly modulated with all tested JAKi. FIL (200 mg) showed similar activity in average target coverage and time above IC50 to the approved low doses of TOFA (5 mg) and UPA (15 mg); conversely, FIL had reduced mean average inhibition and time above IC50 levels against JAK1/2 (IFNγ/pSTAT1), JAK1/3-dependent cytokines (IL-2, -4, and -15), JAK2/2 (G-CSF/pSTAT3), and JAK2/2 (GM-CSF/pSTAT5)-dependent pathways compared to TOFA and UPA, and in certain cases to BARI (2 mg).

Conclusion: Different JAKi modulate distinct cytokine pathways to varying degrees, and no agent potently and continuously inhibited an individual cytokine signaling pathway throughout the dosing interval. FIL (200 mg) showed a similar inhibition profile to TOFA, BARI, and UPA against the JAK1/TYK2- (IFNα/pSTAT1) or JAK1/2-dependent (IL-6/pSTAT1) responses, consistent with the role of these pathways in clinical efficacy.2 However, FIL displayed a differentiated pharmacologic profile from the other JAKi, showing biologically reduced activity on the JAK1/2 (IFNγ), JAK1/3 (IL-2, -4 and -15), JAK2/2 (G-CSF)-, and JAK2/2 (GM-CSF)-dependent pathways, which play important roles in hematopoiesis and immune functions. These data suggest that FIL (200 mg) may have less impact on a subset of hematopoietic immune functions signaling via JAK2 and JAK3 than those observed at the clinically approved doses of TOFA (5 mg and 10 mg), UPA (15 mg), and BARI (4 mg).

References:


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COMPARISON OF INFLAMMATION DURING METABOLIC CHANGES IN RHEUMATOID AND OSTEOARTHRITIS MOUSE MODELS

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Background: Arthritis is influenced by metabolic changes. Adipokines are bioactive factors produced by adipose tissue with important effects on energy homeostasis and immune responses but are also involved in the pathogenesis of rheumatoid arthritis (RA) and osteoarthritis (OA).

Objectives: To evaluate inflammation during metabolic and adipokine induced changes in experimental models of RA and OA at different time points, an obesity model (high-fat-died, HDF) was therefore combined with an OA (DMM, destabilization of the medial meniscus) and RA (collagen induced arthritis, CIA) mouse model.

Methods: Mice were fed with HDF or ND (normal diet) for 12 (OA) or 6 (RA) weeks prior to arthritis induction. DMM was performed in C57Bl/6 mice and CIA was induced in DBA/1Rj mice. After 4, 6 and 8 (DMM) or after 4, 5 and 7 weeks (CIA) of arthritis induction animals were sacrificed to collect histological and serological data. Clinical scoring for CIA and histological scorings for OA were performed.

Results: Induction of OA and RA was successful in an HDF setting, shown by histological joint destruction. The increased fatty liver score and body weight compared to healthy animals, CRP levels were significantly increased after CIA induction, confirming systemic inflammation. In DMM, the number of CLS

Conclusion: Diet-induced effects were monitored by weight, fatty liver score and crown-like structures (CLS) counts in adipose tissue. To evaluate HDF-induced adipokine levels adiponectin, leptin and visfatin serum concentrations were measured in parallel to the CRP. Local tissue adipokine expression was evaluated by immunohistochemistry.

References: