BARICITINIB IMPROVES JOINT MOBILITY AFTER INJURY IN A RODENT FORCED-AMBULATION MODEL

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Background: Movement-evoked pain and impaired joint mobility are common comorbidities in inflammatory diseases such as Rheumatoid Arthritis (RA) and Osteoarthritis. The Janus kinase (JAK) pathway has been implicated in both inflammation and chronic pain. Clinical data suggests that baricitinib, a selective JAK 1/2 inhibitor, can robustly and rapidly alleviate pain in RA. To this end we developed and tested a therapy that selectively depletes SF+ SF in inflamed joints could decrease their contribution to the arthritis process and thus constitute a viable treatment option. Further focussing of the treatment to only those areas

Methods: Unilateral joint injury was induced in female Sprague Dawley rats (Harlan, Indianapolis, IN, USA) by unilateral intra-articular injection of 20 μg Complete Freund’s Adjuvant (CFA). Using the GaitScan (CleverSys Inc., Reston, VA) treadmill system, a composite gait score comprising range of motion, normalized stance distance, stance/swing ratio, and paw print size was evaluated over 3 days post-injection.5 Rats were treated with vehicle, positive control (40 mg/kg Tramadol), or clinically relevant (based on plasma levels) increasing doses of baricitinib (1, 3, or 10 mg/kg p.o., 2-hrs prior to each test, q.d.). Dorsal root ganglion (DRG) were harvested post-gait evaluation and Total STAT3 (Cell Signaling, #4904) and phospho-STAT3 (Y705) (Cell Signaling, #9131) protein levels were examined via immunoblotting. The p-values were derived from repeated measures ANOVAs.

Results: In rat DRG homogenates, baricitinib significantly decreased phospho-STAT3 (Y705) protein levels in a dose-dependent manner (p<0.01) with a significant effect after a 3 mg/kg dose and a maximal response after a 10 mg/kg in both the ipsilateral (right) and contralateral (left) sides. Total STAT3 protein levels remained unchanged. Similarly, treatment with baricitinib significantly improved composite gait score at the 10 mg/kg dose (p<0.05) by Day 3.

Conclusion: These data indicate that treatment with baricitinib attenuates CFA-induced joint deficits, a surrogate measure of joint pain. This effect correlates with the pharmacodynamic inhibition of JAK-STAT signaling in DRGs. These data support a role for JAK-STAT signaling in pain signaling and provide an opportunity to investigate the potential mechanism of action of baricitinib in joint pain.

REFERENCES


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PHOTODYNAMIC THERAPY TARGETING ACTIVATED FIBROBLASTS INDUCES SYNOVIAL CELL DEATH IN EXPERIMENTAL ARTHRITIS

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Background: Activated synovial fibroblasts (SF) contribute to rheumatoid arthritis (RA) by producing a multitude of cytokines, chemokines and proteases thus aggravating disease. Activated SF can be distinguished from quiescent fibroblasts by their expression of fibroblast activation protein (FAP). Selective depletion of FAP+ SF in inflamed joints could decrease their contribution to the arthritis process and thus constitutes a viable treatment option. Further focussing of the treatment to only those areas affected by the disease can be accomplished by applying targeted photodynamic therapy (PDT). In IPDT a light sensitive molecule, a photosensitizer (PS), is conjugated to a targeting moiety. Upon activation by light this construct produces reactive oxygen species, killing the targeted cells.

Objectives: To develop a photochemotherapeutic strategy that selectively depletes activated SF by targeting FAP in these cells with an