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 comorbidities in inflammatory diseases such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and an anti-TNF antibody. However, in this same model a fusion protein blocker of TNFα (tumor necrosis factor alpha) signaling failed to demonstrate efficacy though inflammation was decreased. The present work investigated the potential of baricitinib, recently approved for treatment of pain in RA, to reduce inflammmagen-induced joint pain and gait impairment in this model of joint inflammation mediated pain.

Objectives: To determine if JAK 1/2 pathway inhibition is effective in treating inflammation-induced joint pain and gait impairment.

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 of range of motion, normalized stance distance, stance/swing ratio, and paw pain size was evaluated over 3 days post-injection. Rats were treated with vehicle, positive control (40 mg/kg Tramadol), or clinically relevant doses of baricitinib (1, 3, or 10 mg/kg p.o., 2-hrs prior to each test, q.d.). Dorsal root ganglion (DRG) were examined via immunoblotting. The p-values were derived from repeated measures ANOVAs.

Results: In rat DRG homogenates, baricitinib significantly decreased phospho-STAT3 (Y705) (Cell Signaling, #9131) protein levels were examined via immunoblotting. The p-values were derived from repeated measures ANOVAs.

Conclusion: These data indicate that treatment with baricitinib attenuates CFA-induced joint deficits, a surrogate measure of joint pain. This effect correlated 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