

Time related effects of non-steroidal anti-inflammatory drugs on Achilles tendinopathy in a murine model

Adam Bitterman, DO, Shuguang Gao, Katie Trella, Jun Li, Jorge Galante, Simon Lee, MD, George Holmes, MD, Johnny Lin, MD, Anna Plaas

Category: Basic Sciences/Biologics

Keywords: Achilles tendon, tendinosis, inflammation, scarring, fibrosis, healing, tendinopathy, ibuprofen

Introduction/Purpose: Tendinopathy has been identified to result from work and sports-related activities, in many patients. Common treatment for such degenerative tendon pathology includes non-steroidal anti-inflammatory drugs (NSAIDs). Although they provide pain relief, their mechanistic effects, on modulating inflammation associated with tendinopathy is poorly understood. Recent reports suggest impaired functional healing of rat rotator cuff tear repairs when treated in the early postoperative period with ibuprofen, while delayed treatment did not affect healing. We have now identified, using a murine model, a cascade of genes associated with innate inflammation, which influence premature fibrotic scarring without repair. The objective of this study was to evaluate the effects of orally administered ibuprofen on inflammation and wound-healing responses after initiation and during progression of Achilles tendinopathy in a murine model.

Methods: All animal experimentation was carried out under IACUC approval. C57BL/6 wild-type male mice (12 wks) received two injections, two days apart, of 100ng rhTGF- β 1 into the midportion of the Achilles tendon. Ibuprofen (IBU) was administered orally as described by Ezell et al⁵, for 7 days either 1 day (Early) or 8 days (Late) after the initiating injury. Experimental groups were 1) Tendinopathy + NO drug, 2) Tendinopathy + IBU Early, 3) Tendinopathy + IBU Late, 4) Naïve mice + IBU Early. Following sacrifice of the mice at 28 days post injury, Achilles tendons were harvested, and RNA was prepared as described by Trella et al⁶, for transcriptomic analyses using wound healing and NfKb target gene platforms (PAMM-121A, PAMM-225ZA Qiagen, Valencia, CA). Tendon histopathology was assessed on paraffin embedded thin sections using standard methods for HE and Safranin O staining.

Results: Both early and late dosing times with ibuprofen prolonged the innate inflammation response genes (e.g., PGE Synthase, Interleukin 1b, Interferon gamma, Cxcl3 chemokine), relative to untreated tendinopathy. Furthermore, early dosing also elevated collagen genes (Collagens 1, 3 and 5), and such a response has been associated with fibrotic scarring. Drug administration to naïve mice showed no significant effects on gene expression in the tendons.

Conclusion: This study represents the first report of the time related effect of ibuprofen on mechanisms involved in healing of tendinopathy. If the drug is administered early after the initiating injury, a prolonged increase in inflammation and potential for scarring in the tendon was observed, whereas later administration resulted in persistent inflammation only. The data suggest that the anti-inflammatory action of such NSAID may occur outside of the tendon (such as the bone marrow) resulting in a dysregulated systemic mechanism that controls the innate (tendon) inflammation and healing pathways.