Fluoroquinolones Impair Tendon-Bone Healing in a Rat Rotator Cuff Repair Model

Alice J. Fox, MSc, Michael Schaeer, MD, Florian Wanivenhaus, MD, Tony Chen, PhD, Erik Attia, BS, Nikolaus B. Binder, MD, PhD, Miguel Otero-Adran, PhD, Susannah Gilbert, MEng, Joseph Nguyen, MPH, Salma Chaudhury, MD PhD, Russell Warren, MD, Scott A. Rodeo, MD.

1Hospital for Special Surgery, New York, NY, USA, 2Hospital for Special, New York, NY, USA.

Disclosures:

Introduction: Fluoroquinolones (FQ) are a family of broad-spectrum antibiotics used in the treatment of a wide range of infections. It is well documented that FQ predispose tendons to tendinopathy and rupture, however, the underlying pathophysiological mechanisms are poorly understood [1]. While multiple studies have explored the cellular and tissue response of FQ-induced tendon injuries, there have been no investigations on the reparative capacity of tendons exposed to FQ. Therefore, the purpose of this study was to investigate the effect of the FQ fleroxacin, on tendon-to-bone healing using an established rodent rotator cuff repair model [2]. Fleroxacin was chosen because of its toxic potential to induce tendinopathy and rupture, thus we hypothesized that fleroxacin-treated animals would show inferior biochemical, histological and biomechanical properties at the healing enthesis compared to controls.

Methods: Ninety-two male Sprague-Dawley rats underwent unilateral detachment of the supraspinatus tendon from the greater tuberosity followed by immediate anatomic repair with transosseous fixation (IACUC approved). Rats were treated with either fleroxacin (900mg/kg/day) or 1X PBS, and were assigned to one of four groups: 1) Pre-Operative (Pre-Op), whereby animals received fleroxacin for 1 week pre-operatively; 2) Pre-and Post-Operative (Pre/Post-Op), whereby animals received fleroxacin for 1 week pre-operatively and for 2 weeks post-operatively; 3) Post-Operative (Post-Op), whereby animals received fleroxacin for 2 weeks post-operatively; and 4) Control, whereby animals received 1X PBS for 1 week pre-operatively and for 2 weeks post-operatively. Animals were euthanized at 2 weeks post-operatively for biochemical (N=5), histological (N=8) or biomechanical analysis (N=10). Quantitative real-time polymerase chain reaction (RTqPCR) was used to evaluate MMP-3, MMP-13 and TIMP-1 mRNA expression levels, using ACTB (β-actin) as a housekeeping gene. The tendon-bone enthesis was assessed by quantitative histomorphometry for metachromasia and collagen fiber orientation. Ultimate-load-to-failure, stiffness, Young’s Modulus, energy-to-failure and mode-of-failure were determined from tensile tests. Statistical comparisons were performed using one-way ANOVA followed by Tukey’s post-hoc test, with p<0.05 considered significant.

Results: mRNA expression: RTqPCR analysis revealed a 30-fold increase in expression of MMP-3, a 7-fold increase in MMP-13 and a 4-fold increase in TIMP-1 in the Pre/Post-Op group compared to the other groups (Figure 1).

Histology: The appearance of the healing enthesis in FQ-treated animals was qualitatively different than controls. The tendons were friable and atrophic. All three FQ-treated groups showed significantly less fibrocartilage and poorly organized collagen at the healing enthesis compared to control animals (Figure 2 and 3).

Biomechanical Testing: There was a significant difference in the mode-of-failure between the experimental and control animals. FQ-treated animals demonstrated an intra-substance failure of the supraspinatus tendon during testing. In contrast, only 1 of 10 control samples failed within the tendon substance. The healing enthesis of the Pre/Post-Op group displayed significantly reduced ultimate load-to-failure compared to the Pre-Op, Post-Op and control groups (Figure 4). Pre/Post-Op animals demonstrated significantly reduced cross-sectional area compared to the Post-Op and control groups. There was also a significant reduction in area between the Pre-Op and control group (Figure 5). There were no significant differences between groups for stiffness, Young’s Modulus or energy-to-failure (data not shown).

Discussion: Fleroxacin treatment negatively influenced repair in this in-vivo acute rotator cuff repair model. Fleroxacin administration pre- and post-operatively was accompanied by increased expression of MMP-3, -13 and TIMP-1. Furthermore, fleroxacin-treated animals displayed reduced fibrocartilage formation and collagen fiber orientation at the tendon-bone enthesis. Differences in ultimate load-to-failure and a reduction in cross-sectional area may have contributed to the shift in mode-of-failure. These findings indicate that there is an active but inadequate repair response that has potential clinical implications for patients with FQ-induced tendinopathy or tendon rupture.

Significance: This study reports a clear association between FQ exposure and impaired healing. Careful consideration should be given to the clinical implications of our findings as the use of this class of antimicrobial agents could have unfavorable effects on the structure and function of musculoskeletal tissues.

Acknowledgments: Figure 1. Animals in the Pre/Post-Op group had significantly increased MMP-3, MMP-13 and TIMP-1
expression levels compared to the other groups (mean ± SEM).

Figure 2. FQ-treated animals had significantly Figure 3. Collagen organization
less fibrocartilage at the healing enthesis was inferior in the FQ-treated groups. groups compared to control animals.

Figure 4. Ultimate load-to-failure (mean ± SEM). Figure 5. Cross Sectional Area (mean ± SEM).
