Magnetization Transfer Detects Changes in Intestinal Fibrosis after Anti-TNFα

S. D. Swanson[1], J. Adler[2], P. Schmiedlin-Ren[3], K. Rahal[3], L. Reingold[3], and E. M. Zimmermann[3]

[1]Department of Radiology, University of Michigan, Ann Arbor, MI, United States, [2]Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, United States, [3]Department of Internal Medicine-Gastroenterology, University of Michigan, Ann Arbor, MI, United States

Introduction: Crohn's disease causes chronic transmural bowel wall inflammation, which often leads to luminal narrowing. Chronic inflammation leads to deposition of collagen in the bowel wall. Magnetization transfer (MT) MRI is sensitive to water interacting with large macromolecules such as collagen. Our previous work demonstrates that MT helps detect the presence of collagen in the bowel wall in an animal model of Crohn's disease (1). Anti-TNF-α has been shown to reduce inflammation in murine (2) and human (3) Crohn's disease. In this work, we study rats treated with rat-specific anti-TNFα to determine if MT can detect differences in the development of fibrosis with and without treatment.

Methods: Adult female pathogen free Lewis strain rats underwent laparotomy. Purified peptidoglycan-polysaccharide (PG-PS) was injected intramurally (12.5 µg rhamnose/gm body weight; 0.05 ml/injection site) into standardized locations in the cecum, distal ileum and Peyer's patches. PG-PS injected rats develop early-phase inflammation at the injection sites in the first 24 hours, followed by a late-phase typified by late-phase inflammation and intense fibrosis beginning at approximately 14 days post-laparotomy. By 21 days post-laparotomy, rats develop bowel wall thickening, intra-abdominal adhesions, and granulomas studded throughout the bowel, liver and spleen. Human Serum Albumin (HSA) injected control animals developed less late-phase inflammation an no fibrosis. Control animals were similarly injected with HSA. Half of each group was treated with a rat-specific anti-TNFα by I.P. injection.

MR images were obtained with aid of a Varian Inova 2.0 T, 31 cm clear bore system. Magnetization transfer (MT) images were obtained with a multi-slice, spin-echo pulse sequence (TR/TE 3000/20 ms) that uses a sinc-shaped RF pulse at 10 kHz (M_{sat}) and 100 kHz (M_0) off-resonance to generate MT or not. The MT ratio (MTR) was calculated in the cecal wall as $100*(1-M_{sat}/M_0)$. Gross gut fibrosis score at the end of the study was determined based on bowel wall thickness, mesenteric thickness, and adhesions. Histologic fibrosis was assessed by pathologists. Tissue collagens were measured by Western blot analysis.

Results: PG-PS rats treated with anti-TNFα (n=15) developed lower gross gut scores than untreated (n=11) PG-PS rats (3.87±3.02 vs. 12.533±3.70, p=6.1E-08) (Fig.1). MTR of anti-TNFα treated rats were significantly lower than untreated rats (17.79±6.24 vs. 27.95±5.80; p=0.0001) (Fig 2.). Gross gut scores correlate with MTR (rho=0.91) (Fig.3). Pro-fibrotic factors were less in anti-TNFα treated rats including procollagen I (2.93±0.67 vs. 9.19±1.09; p=0.000019), and procollagen III (2.19±0.34 vs. 7.06±0.73; p=7.7E-07). There was a trend toward decreased pro-inflammatory cytokines in anti-TNFα treated rats including IL-1 (5.63±1.54 vs. 10.27 ± 1.74; p=0.028), IL6 (23.60 ± 9.42 vs. 45.15±11.46; p=0.079), and TNFα (2.40 ± 0.41 vs. 3.09 ± 0.44; p = 0.13). MTR correlates with concentration of type III collagen (R^2 = 0.39 p < 0.0001 n = 38).

Discussion: We have demonstrated that MT is sensitive to changes in fibrosis that occurs with anti-TNFα treatment. These findings support MT as a non-invasive method for detecting and quantifying intestinal fibrosis.

References: (1) Adler J, et al. "Magnetization Transfer MRI helps detect intestinal fibrosis in an Animal Model of Crohn's disease." *Radiology (*2010) (in press). (2) Marini M, et al. "TNF-α neutralization ameliorates the severity of murine Crohn's-like ileitis by abrogation of intestinal epithelial cell apoptosis." PNAS 100 (14) 8366-8371 (2003). (3) Lichtenstein GR, Olson A, et al. "Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease." Am J Gastroenterol 101(5): 1030-1038 (2006).

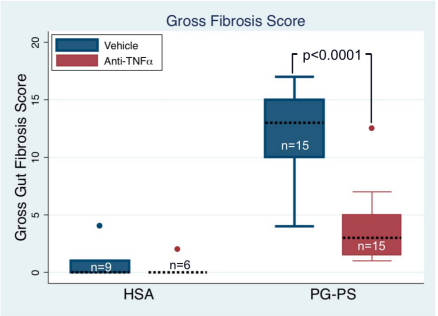

Figure 1. Gross gut Fibrosis for HSA and PG-PS animals with and without anti-TNFα.

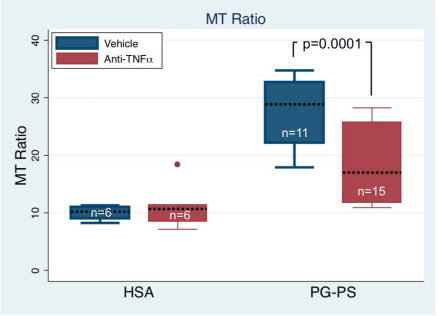

Figure 2. MT ratio for HSA and PG-PS animals with and without anti-TNFα.

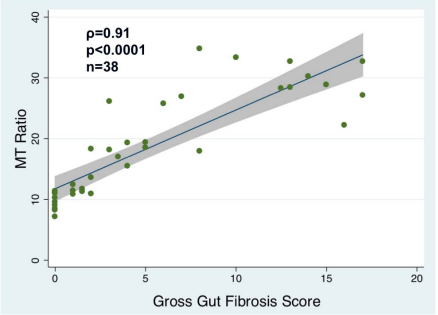

Figure 3. MT Ratio is highly correlated with the gross gut score.

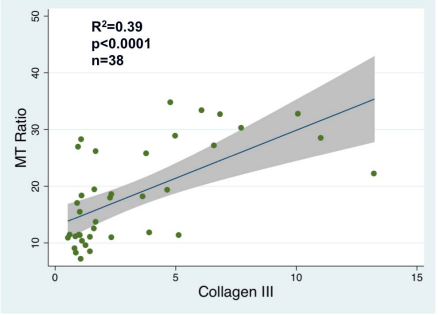

Figure 4. Correlation between MTR and Type III collagen.