

Imaging Liver Fibrosis and Response to Rapamycin Therapy

Christian T. Farrar¹, Bryan C. Fuchs², Helen Day¹, Nicholas Rotile¹, Danielle DePeralta², Arun Subramaniam³, Kenneth K. Tanabe², and Peter Caravan¹
¹Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, United States, ²Surgical Oncology Division, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, ³Sanofi-Aventis, Bridgewater, NJ, United States

Target Audience: Researchers and clinicians who are interested in liver fibrosis and molecular imaging, particularly in the assessment of fibrosis response to therapeutic intervention.

Purpose: Liver fibrosis is a progressive disease in which wound-healing myofibroblasts of the liver respond to injury by promoting replacement of the normal hepatic tissue with a scar-like matrix composed of cross-linked collagen. Late stages of liver fibrosis were previously thought to be irreversible, however, new therapeutic agents are currently being tested that may be able to halt the disease progression or potentially even reverse the course of the disease. However, no methods are currently available for non-invasively assessing disease progression or therapeutic response. Here we demonstrate the use of a collagen-targeted contrast agent EP-3533 for quantitatively imaging liver fibrosis and response to rapamycin therapy on a clinical MR scanner.

Methods: Liver fibrosis was induced in rats by ligation of the common bile duct. Bile duct ligated (BDL) rats were imaged 4, 10, and 18 days following ligation. EP-3533 was prepared as reported previously [1]. Dialyzate fluid (1 ml/0.01 kg) was injected into the abdomen prior to imaging to allow for resolution of the different liver lobes. Rats were imaged on a 1.5 Tesla clinical MRI scanner using a home-built, transmit-receive solenoid coil. Respiratory-gated, 3D inversion recovery (IR) FLASH images were acquired prior to and 45 minutes following i.v. administration of 10 $\mu\text{mol}/\text{kg}$ EP-3533. Images were acquired with inversion delay times of 50, 100, 200, 250, 300, 400 and 1000 ms. Longitudinal relaxation rate (R1) maps were generated from the images using a custom written MATLAB program for voxelwise fitting of the inversion recovery signal intensities as a function of the inversion delay time. Following imaging, animals were sacrificed and liver tissue was subjected to pathologic scoring of fibrosis and analyzed for gadolinium and hydroxyproline content.

Results and Discussion: A representative high-resolution (600 μm isotropic) 3D IR-FLASH MPR image of the rat liver acquired with an inversion delay time of 1000 ms is shown in Figure 1. A statistically significant increase in longitudinal relaxation rate (ΔR1) was observed following EP-3533 injection for the 18 days post BDL group (Figure 2). Similarly, statistically significant increases in Gd (Figure 3) and hydroxyproline ($p<0.01$), a biomarker of liver fibrosis, were observed in *ex vivo* liver tissue from 18 days post BDL rats.

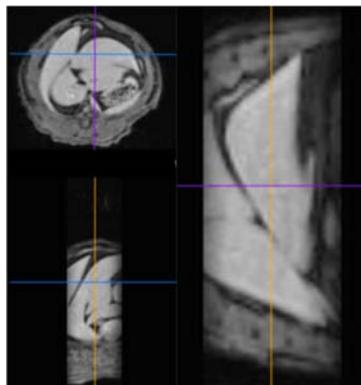


Figure 1: 3D inversion recovery FLASH MPR image of the rat liver acquired with an inversion delay time of 1000 ms.

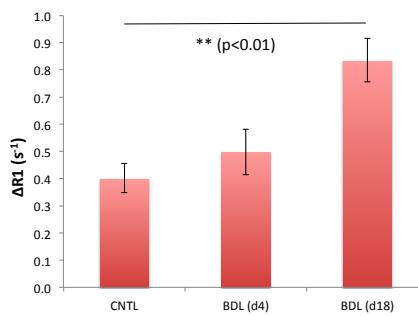


Figure 2: Average change in liver R1 following injection of 10 $\mu\text{mol}/\text{kg}$ EP-3533 for control (CNTL, n=9) and BDL rats 4 (n=9) and 18 (n=8) days post bile duct ligation.

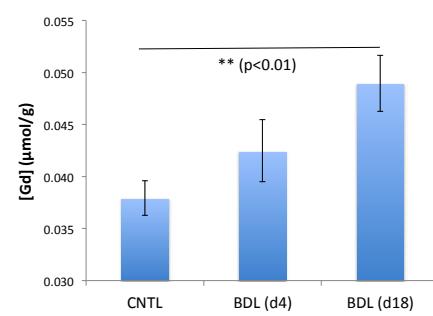


Figure 3: Liver [Gd] measured by inductively coupled plasma (ICP) mass spectrometry in control (CNTL, n=9) and BDL rats 4 (n=9) and 18 (n=8) days post bile duct ligation.

Conclusions: The Gd-based contrast agent EP-3533 can quantitatively monitor liver fibrosis. Studies are currently underway to quantify the longitudinal progression of liver fibrosis in the BDL rat model and to assess the ability of EP-3533 to monitor response to rapamycin therapy.

References:

1. Caravan P, Das B, Dumas S, Epstein FH, Helm PA, et al. (2007) Collagen-targeted MRI contrast agent for molecular imaging of fibrosis. *Angew Chem Int Ed Engl* 46: 8171–8173.