Molecular MR Imaging of Liver Fibrosis with a Collagen-Targeting Gadolinium-Based Contrast Agent

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Introduction

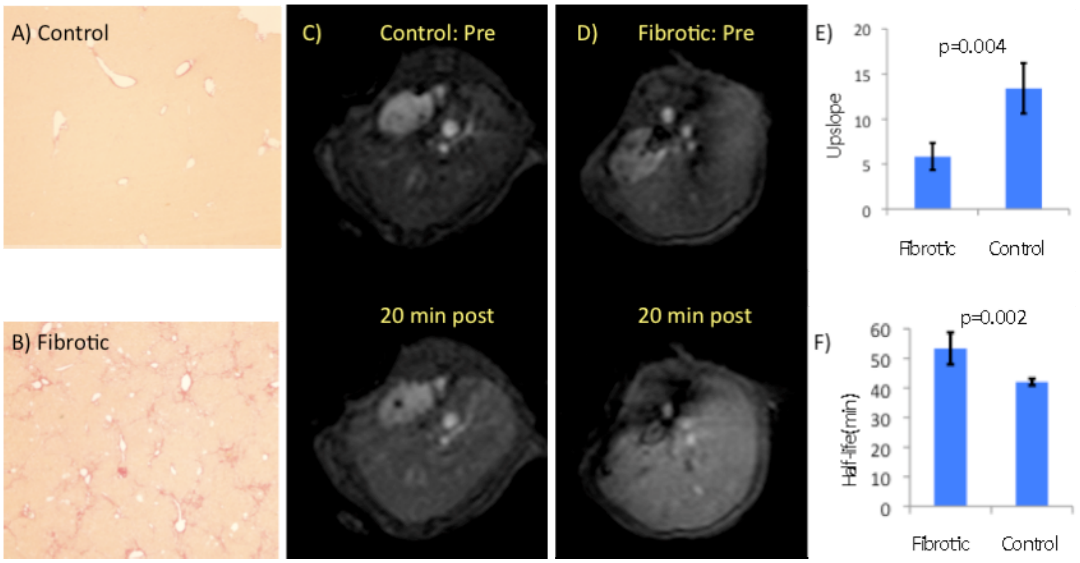
Dramatic increases in the incidence of obesity, diabetes, and the metabolic syndrome are increasing the prevalence of chronic liver diseases. Liver fibrosis occurs in advanced stages of most types of liver injury such as hepatitis C, alcoholic liver disease and nonalcoholic steatohepatitis. Prognosis, surveillance, and treatment decisions in patients with chronic liver disease rely on a precise estimation of the degree of fibrosis. While liver biopsy is the gold standard for assessment of fibrosis it is invasive and has potential complications. Because fibrosis is characterized by excess deposition of type I collagen in the parenchyma, we hypothesize that an imaging agent providing a non-invasive measure of elevated collagen would have broad applications in the early assessment and quantification of fibrosis prior to irreversible cirrhosis and carcinogenesis while potentially monitoring response to therapy. EP-3533 is a type I collagen-targeted Gd-based contrast agent used previously to assess cardiac fibrosis [1,2]. Here, we evaluate EP-3533 as an imaging biomarker of liver fibrosis in a mouse model.

Methods

Strain A/J male mice were administered 0.04 mL of a 40% solution of CCl_4 in olive oil by oral gavage three times a week for 20 weeks (n=6); control mice received only pure olive oil (n=4). Mice were imaged one week after the last CCl_4 dose. Imaging was performed at 4.7 T prior to and immediately following i.v. EP-3533 administration. The rate of contrast uptake into liver was measured using dynamic T1-weighted gradient echo imaging (TR/TE/flip angle=50ms/1.92ms/35°) from 1.5 min pre- to 4.5 min post-injection with 5s temporal resolution. Signal intensity was normalized to percentage of signal at peak uptake and upslopes were determined from the initial signal enhancement versus time curves. T1 was quantified at 6 time points out to 50 min post injection (inversion recovery, TR/TE=3200ms/4ms, 9 inversion times from 40 to 3000 ms). Half-lives of EP-3533 in the liver were estimated from the change in $\Delta R1$ values ($\Delta R1 = 1/T_{1,post} - 1/T_{1,pre}$) assuming mono-exponential decay. Animals were sacrificed 80 minutes after injection and tissue samples were harvested for histology and analysis of gadolinium and hydroxyproline. Sirius red was used for collagen staining.

Results

Histological analysis with Sirius Red stain (Panels A&B) confirmed that after prolonged treatment with CCl_4 the animals develop moderate liver fibrosis (Ishak grade 3-4, Panel B), while control animals showed no fibrosis (Panel A). T1-weighted imaging showed that EP-3533 enhanced both normal and fibrotic liver (Panels C&D) but that enhancement was greater in the fibrotic mice (compare bottom images of Panel C vs Panel D). EP-3533 displays different kinetic characteristics in fibrotic livers versus control animals. The delivery into fibrotic liver was significantly slower, presumably due to poor leakage from blood vessels into intercellular space (Panel E). The half-life of EP-3533 in the liver was significantly longer (Panel F) in fibrotic animals compared to controls.



Conclusions

Molecular MRI using the collagen-targeted, Gd-based contrast agent EP-3533 is able to identify mice with moderate liver fibrosis. Fibrosis can be identified either on the basis of greater T1 enhancement or by means of kinetic measurements. Work is ongoing to determine if liver fibrosis can be accurately staged and quantified using molecular MRI.

References: [1]Caravan et al. Angew. Chem. Int. Ed. 2007, 46:8171. [2]Helm et al. Radiology 2008, 247:788