Noninvasive investigation of iron elimination from the liver following ferumoxytol administration

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Introduction: Ultrasmall superparamagnetic iron oxide (USPIO) particles have a wide range of potential applications in magnetic resonance imaging, and have recently attracted renewed interest following the approval of Feraheme (ferumoxytol) for human use in the USA. Although ferumoxytol is approved only for the treatment of iron deficiency anemia in chronic kidney disease, it can be used off-label as an MRI contrast agent. The high T1 and T2 relaxivities of USPIO particles such as ferumoxytol make them a possible alternative to gadolinium-based contrast agents for patients with renal insufficiency [1], while their unique pharmacokinetics and biodistribution open up new applications not possible with gadolinium. In particular, their uptake by the reticuloendothelial system suggests applications in atherosclerosis [2], lymph node imaging [3] and transplant rejection [4]. One potential disadvantage of USPIO agents, however, is their long elimination time. Iron in the particle core is released within macrophages of the liver, spleen and bone marrow, and absorbed into the intracellular iron storage pool. The goal of this study was to investigate the elimination of iron from the liver following administration of ferumoxytol in healthy human subjects by means of T2* imaging.

Methods: All imaging was performed at 1.5T (Avanto, Siemens). Six healthy subjects without anemia (4 men/2 post-menopausal women, ages 22 – 57) were included, and all gave informed consent to participate under an IRB-approved protocol. Among the exclusion criteria were pregnancy, a history of anaphylactic reaction and iron overload as determined by baseline T2* imaging of the liver. A mean T2* of less than 24ms was used as the criterion for iron deposition [5]. T2* imaging was performed in an axial plane using a multiple gradient echo sequence with fat saturation and the following acquisition parameters: 32 echoes with monopolar readout gradients, minimum TE = 1.3ms and echo spacing = 1.97ms; receiver BW = 840Hz/pix; FOV = 400mm; base resolution = 192; slice thickness = 9mm; TR = 90ms; FA = 15°. In cases of very short T2*, additional data were collected using a customized sequence with a minimum TE of 0.8ms and echo spacing of 0.1ms. These values were achieved by using asymmetric echoes and acquiring successive echoes after separate excitations. Other parameters included: receiver BW = 920Hz/pix; FOV = 400mm; base resolution = 160; slice thickness = 9mm; TR = 8.6ms; FA = 10°. Baseline imaging was performed no more than 32 days prior to administration of ferumoxytol (AMAG Pharmaceuticals, Cambridge, MA), which was purchased through our hospital pharmacy and injected intravenously at dose of 5 mg/kg Fe. T2* imaging was repeated 3 days after administration, which was expected to coincide with peak macrophage uptake. Further scans were performed at 1 month and every 2 months thereafter, for up to 11 months or until T2* > 24ms, signifying no residual iron deposition. Subjects were asked to complete a questionnaire at each visit concerning aspects of diet and lifestyle that may affect iron metabolism. T2* was calculated by fitting the signal intensity as a function of TE to a monoexponential decay using a nonlinear Levenberg-Marquardt algorithm. Maps of R2* (= 1/T2*) were generated by performing the fitting procedure pixel-by-pixel.

Results: No adverse reactions to ferumoxytol were reported. The demographics and results of the questionnaire are summarized in the table below. Figure 1 shows R2* maps from a 28-year old man. Note the dramatic increase in R2* (> 200 s^{-1}) in both the liver and spleen at 3 days post-ferumoxytol. Liver R2* decreases gradually over the following months, but has still not recovered to its baseline value at 11 months. Figure 2 shows mean R2* values for all study participants as a function of time following ferumoxytol administration. Baseline values (R2* = 35.6 ± 4.7 s^{-1}) are plotted at time zero. Note that R2* demonstrates a sharp increase in all subjects at 3 days following ferumoxytol administration. However, the response varies widely, with ΔR2* ranging from 132 s^{-1} in subject 6 to 383 s^{-1} in subject 3. While these subjects had the lowest and highest body mass index (BMI) respectively, the correlation between BMI and ΔR2* at 3 days was not significant (r = 0.69, p = 0.13). The elimination time also differed among study participants; in one subject, R2* had recovered to baseline by 3 months, while in 3 subjects R2* remained above 55 s^{-1} (T2* < 18ms) at 11 months. The relatively fast elimination rate in subject 2 may be due to frequent blood draws, which he undertook for other research studies.

Discussion: The time taken for elimination of iron from the liver after ferumoxytol administration varies greatly among people, and may depend on aspects of diet and lifestyle that affect iron intake and hematopoiesis. However, complete elimination after a 5mg/kg Fe dose can take several months. This should be considered when using ferumoxytol off-label as a contrast agent. Signal on T2- and diffusion-weighted images will also be affected in patients taking ferumoxytol.

subj	age/sex	weight/height	BMI	Regular meat consumption	Oral iron supplements	Exercise [intensity/ time per week]	Blood draws since previous scan*
1	52 / F	63.5 kg/153 cm	27.1	yes	none	light/2hrs	-/1/1/1/-/-/-/-
2	41 / M	80.3 kg/160 cm	31.4	yes	none	none	3/0/2/2/2/2/-/-
3	57 / F	97.5 kg/168 cm	34.6	yes	16mg/day	none	-/1/1/1/0/1/0/1
4	25 / M	100.2 kg/176 cm	32.5	yes	none	none	0/0/0/0/0/0/1/1
5	28 / M	79.4 kg/178 cm	25.1	yes	none	moderate/3hrs	0/0/0/0/0/0/0/0
6	22 / M	71.7 kg/179 cm	22.5	no (vegan)	none	moderate/4.5hrs	0/0/0/0/0/0/0/-

*number since previous scan (or over prior 2 months) at baseline/3D/1M/3M/5M/7M/9M/11M, where D=day, M=month. '-'= not applicable or not available

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References:
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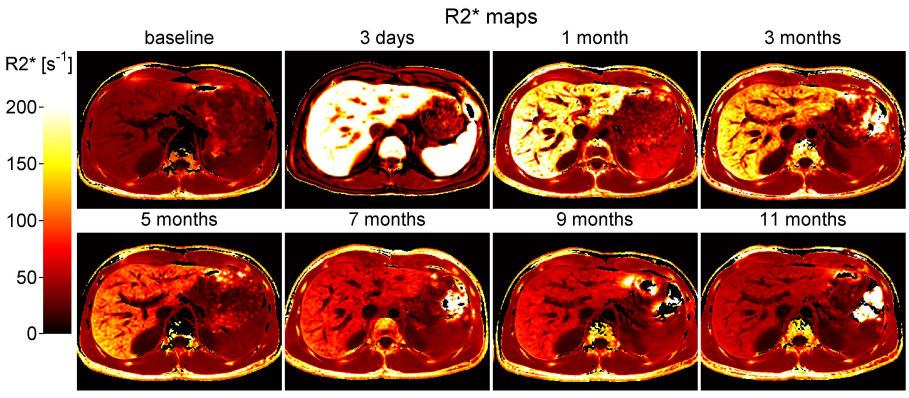

Figure 1: R2* maps from subject 5 at all time points. The color scale (left) ranges from 0 s^{-1} – 200 s^{-1}. Note the large R2* increase in the liver and spleen at 3 days post-ferumoxytol. Liver R2* decreases gradually over the following months, but has still not recovered to its baseline value at 11 months.

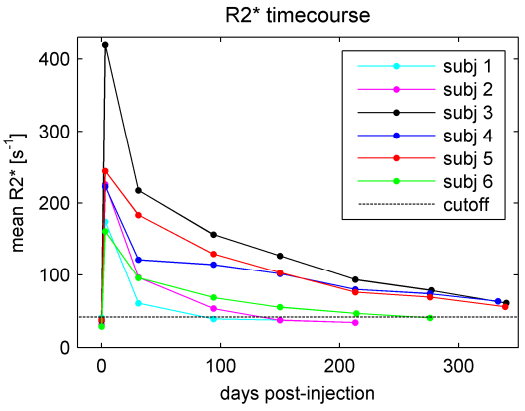

Figure 2: Mean R2* values in the liver as a function of time after ferumoxytol administration. The horizontal line marks the cutoff for iron deposition (T2* = 24ms , i.e. R2* = 41.7 s^{-1}).