Imaging of Osteonecrosis with Ferumoxytol-Enhanced MRI

NCT02893293

April 11, 2023

1. PURPOSE OF THE STUDY

a. Brief Summary

The overarching goal of our project is to establish a novel, non-invasive, immediately clinically applicable imaging test for the diagnosis of bone tumors, including primary malignant bone tumors, metastases, as well as benign bone lesions, osteonecrosis and infection/non-cancer inflammatory processes. The purpose of this project was to evaluate imaging characteristics of osteonecrosis before and after decompression surgery with ferumoxytol-enhanced MRI. Our approach relies on the FDA-approved iron supplement drug ferumoxytol (Feraheme), which is used in patients for intravenous treatment of iron deficiency. Ferumoxytol is composed of iron oxide nanoparticles, which provide a strong T1- and T2-signal on magnetic resonance (MR) images and, thus, can be used as an MR contrast agent. Based on our extensive experience with pre-clinical and clinical imaging applications of iron oxide nanoparticles, we hypothesize that MR images after intravenous injection of ferumoxytol will improve lesion detection and characterization compared to conventional unenhanced and Gd-enhanced MRI scans.

b. Objectives

1. We hypothesize that MR images after intravenous injection of ferumoxytol will improve the detection of osteonecrosis lesions compared to standard MRI scans.
2. We hypothesize that ferumoxytol-T2-enhancement of osteonecrotic bone lesions on MR images correlates with the quantity and distribution of healthy bone marrow cells in the lesion.
3. We hypothesize that ferumoxytol-enhanced MRI will improve evaluation of therapy success of osteonecrosis after decompression surgery.

c. Rationale for Research in Humans

In vivo studies in human patients are needed because the biodistribution of ferumoxytol nanoparticles is different in humans compared to animals. We did and are performing additional studies in mouse models in order to minimize and optimize studies in human patients. MR signal effects of ferumoxytol are dependent on its ability to interact with human bone marrow cells and other target tissues. To assess the applicability of the iron supplement ferumoxytol as a contrast agent in patients, we must investigate humans.

2. STUDY PROCEDURES

a. Procedures

Screening will occur during a regular clinic visit. Each participant will undergo an MRI after a single intravenous injection of ferumoxytol at a dose of 5 mg Fe/kg body weight. Precontrast images will be added when feasible. Postcontrast images will be obtained directly after and/or 1-2 days after ferumoxytol administration. In patients with osteonecrosis who undergo a surgical decompression procedure with implantation of bone marrow derived cells into the osteonecrosis, a ferumoxytol-enhanced MRI will be performed before surgery and follow up MR scans will be obtained at 1-6 months after the surgery. When available, routinely obtained biopsy and/or surgical resection samples of bone lesions will be examined by our collaborating pathologist for presence of mesenchymal stromal cells, macrophages and possibly iron content in samples that happen to be obtained shortly after the ferumoxytol injection.

b. Procedure Risks

MRI is a non-significant risk exam, as defined by the FDA and IRB guidelines. We obtained an IND from the FDA to conduct these studies. Ferumoxytol-MRI does not involve any radiation exposure and provides information about the cell composition of bone lesions that is not attainable with standard MRI. The iron supplement ferumoxytol is FDA-approved for treatment of iron deficiencies in patients with renal failure. However, the FDA issued a black box warning due to rare, but potentially severe allergic reactions to this agent. Therefore, we follow the FDA-recommended administration protocol and closely monitor patients for potential adverse events. Taking into consideration Dr. Daldrup's extensive experience with this and other, similar nanoparticle-based contrast agents, risk to participants is considered to exceed the potentially highly beneficial diagnostic in formation. With the proposed low enrollment rates and careful exclusion of patients with history of severe allergy to other drugs, we risk to encounter an SAE was low. We carefully monitored patients over at least 1 hour after ferumoxytol administration to detect any UAEs early and treat them appropriately. Since we obtained follow up imaging studies, we used these encounters to follow up on any late effects.

c. Use of Deception in the Study

No deception, N/A

d. Use of Audio and Video Recordings

No recording, N/A

e. Alternative Procedures or Courses of Treatment

The current alternative diagnostic methods are: biopsy, which is invasive, painful, and frequently inadequate; Conventional MRI without an iron nanoparticle contrast, which cannot distinguish healthy and necrotic cells in osteonecrosis; PET/CT/Xray, which add exposure to ionizing radiation. The current standard of imaging is an MRI; the addition of an iron nanoparticle contrast agent is expected to make this test more sensitive and

specific. No standard treatment will be withheld, and the standard of care diagnostic test is included in our research.

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Our study is diagnostic only and will not limit the participants' treatment options. The conduct of our research should actually improve the speed with which the participants receive the most appropriate therapy, as we expect to be able to distinguish much more quickly between the differentials for the symptoms the patients experience.

g. Study Endpoint(s)

Endpoint of these examinations is to define distinctive MR signal characteristics of osteonecrosis lesions. Secondary endpoint is to define specific ferumoxytol-MR imaging features that indicate treatment response to decompression surgery and stem cell transplant.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Our group has worked on MR imaging techniques with iron oxide nanoparticles since 1995. We and others have found that intravenously injected ultra small superparamagnetic iron oxide nanoparticles (USPIO) with diameters in the order of 20-50 nm cause a long lasting, enhancement on MR images. Mononuclear cells in the bone marrow, including macrophages and mesenchymal stromal cells, phagocytose USPIO which leads to a significant negative (dark) signal effect on T2-weighted MR images (1-4). This can be used for improved delineation of bone lesions and for in vivo tracking of macrophages and stem cells (1, 4). In pathologies with an increased microvascular permeability, USPIO extravasate into the interstitium and cause a T1-effect of the target tissue, which is strongly dependent on the proton content of the interstitial space (among other technical factors). We have thoroughly investigated various factors that lead to an optimized tissue T1-enhancement of USPIO. We have shown that malignant lesions in the bone marrow of patients show nearly no USPIO T1-enhancement, presumably due to their high cellularity, small intercellular space and low proton content. Inflammations, on the other hand, show a strong T1-enhancement, presumably due to the edematous, proton rich environment. These data suggest that tumors and inflammations may demonstrate differences in T1-enhancement. USPIO in the interstitium are subsequently slowly phagocytosed by macrophages and/or mesenchymal stromal cells, where they primarily cause a negative (dark) signal effect on T2-weighted MR images (11,13,18,19,24). Focal bone lesions in organs of the RES (reticulo-endothelial system) contain no or very few macrophages, thus they phagocytose few USPIO, and stand out as bright lesions. However, macrophage rich inflammations cause a marked signal loss on delayed T2-weighted MR images. Thus, we have evidence from a variety of pre-clinical and clinical investigations, that bone lesions may show distinct T2-enhancement patterns on MRI.

Of note, I – the PI – have applied USPIO as MR contrast agents preclinical studies as well as in phase II and III clinical trials in adult patients (9-26). These contrast agents are

overall well tolerated and show excellent safety profiles in the majority of patients. The delivered iron dose via a typical ferumoxytol administration is in the order of 150-500 mg iron oxides (note that these are coated iron particles, not free iron), which is equivalent to or lower than the iron dose administered with one blood transfusion. USPIO are slowly metabolized in the liver and not excreted via the kidneys. Thus, they are safe to use in patients with renal insufficiencies and are not associated with any risk of nephrogenic sclerosis (a potential adverse event after injections of certain gadolinium chelates). Anaphylaxis or anaphylactoid reactions were reported in 0.2% of subjects, which is in the order of or lower compared to other MR contrast agents.

References:

(1) Khurana A, Nejadnik H, Gawande R, Lin G, Lee S, Messing S, Castaneda R, Derugin N, Pisani L, Lue TF, Daldrup-Link HE. Intravenous ferumoxytol allows non-invasive MR imaging monitoring of macrophage migration into stem cell transplants. Radiology 264(3):803-11, 2012, PMCID: 3426856

(2) Nejadnik H, Henning TD, Castaneda RT, Boddington S, Taubert S, Jha P, Tavri S, Golovko D, Ackerman L, Meier R, Daldrup-Link HE: Somatic differentiation and MR imaging of magnetically labeled human embryonic stem cells. Cell Transplantation 21(12):2555-67, 2012

(3) Khurana A, Chapelin F, Lenkov O, Beck G, Donig J, Nejadnik H, Derugin N, Chan CF, Gaur A, Sennino B, McDonald D, Kempen P, Tikhomirov G, Rao J, Messing S, Daldrup-Link H. Iron Administration before stem cell harvest enables MRI tracking after transplantation. Radiology 269(1):186-97, 2013

(4) Klenk C, Gawande R, Uslu L, Khurana A, Qiu D, Quon A, Donig J, Rosenberg J, Luna- Fineman S, Moseley M, Daldrup-Link HE. Ionising radiation-free whole body MRI versus 18F- FDG PET/CT scans for children and young adults with cancer: A prospective, non-randomized, single-centre study. Lancet Oncology 15(3):275-85, 2014

(5) Pai AB, Nielsen JC, Kausz A, Miller P, Owen JS. Plasma pharmacokinetics of two consecutive doses of ferumoxytol in healthy subjects. Clin Pharmacol Ther. 2010;88(2):237-42

(6) Lu M, Cohen MH, Rieves D, Pazdur R. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. Am J Hematol. 2010;85(5):315-9

(7) Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, Pereira BJ. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. Clin J Am Soc Nephrol. 2009; 4(2):386-93

(8) Schwenk MH. Ferumoxytol: a new intravenous iron preparation for the treatment of iron deficiency anemia in patients with chronic kidney disease. Pharmacotherapy. 2010;30(1):70-9

(9) Simon GH, von Vopelius-Feldt J, Fu Y, Schlegel J, Piontek G, Wendland MF, Mei-Hsiu C, Daldrup-Link HE: Ultrasmall superparamagnetic iron oxide- enhanced magnetic resonance imaging of antigen-induced arthritis: a comparative study between SHU555C, Ferumoxtran-10 and Ferumoxytol. Investigative Radiology 2006; 41(1):45-51

(11) Reimer P, Rummeny EJ, Daldrup HE, Tombach B, Berns T, Balzer T, Peters PE: Clinical Results with Resovist: A Phase 2 Clinical Trial. Radiology 1995; 195: 489- 496

(12) Daldrup HE, Link TM, Blasius S, Könemann S, Jürgens H, Rummeny EJ: Monitoring Radiation-Induced Changes in Bone Marrow Histopathology with Ultra-

Small Superparamagnetic Iron Oxide (USPIO) Enhanced MRI. J Magn Reson Imaging 1999, 9: 643- 652
(13) Daldrup-Link HE, Rummeny EJ, Ihßen B, Kienast K, Link TM: Iron oxide enhanced MR imaging of bone marrow in patients with non- Hodgkin`s lymphoma: differentiation of tumor infiltration and hypercellular bone marrow. Europ Radiol 2001; 11: 1276-1284
(14) Daldrup-Link HE, Rydland J, Helbich T, Turetschek K, Haraldseth O, Link TM, Brasch RC, Shames D, Rummeny EJ: Quantitative MRI- Estimates of breast tumor microvascular permeabilities to the macromolecular contrast agent Feruglose (Clariscan) correlate with histologic tumor grade: Initial Phase II Multicenter Trial. Radiology 2003; 229(3): 885-92
(15) Metz S, Bonaterra G, Rudelius M, Settles M, Rummeny EJ, Daldrup- Link HE: Capacity of Human Monocytes to phagocytose approved iron oxide MR contrast agents. Eur Radiol 2004; 14(10):1851-8
(16) Daldrup-Link HE, Rudelius M, Piontek G, Metz S, Bräuer R, Debus G, Corot C, Schlegel J, Link TM, Peschel C, Rummeny EJ, Oostendorp RAJ: Migration of iron oxide labeled human hematopoietic progenitor cells in a xenotransplant model: in vivo monitoring using clinical magnetic resonance imaging equipment. Radiology 2005; 234(1): 197-205
(17) Daldrup-Link HE, Meier R, Rudelius M, Piontek G, Piert M, Metz S, Settles S, Uherek C, Schlegel J, Rummeny EJ: In-vivo Tracking of genetically engineered anti-HER2/neu directed Natural Killer to HER2/neu positive Mammary Tumors with Magnetic Resonance Imaging. Eur Radiol 2005; 15(1): 4-13
(18) Simon GH, von Vopelius-Feldt J, Wendland M, Schlegel J, Mei- Hsiu C, Daldrup-Link HE: Ultrasmall superparamagnetic iron oxide enhanced MR imaging of normal bone marrow in rodents. Academic Radiology 2005; 12(9):1190-7
(19) Simon GH, von Vopelius-Feldt J, Wendland M, Fu Y, Piontek G, Schlegel J, Chen, MH, Daldrup-Link HE: MRI of arthritis: Comparison of ultrasmall superparamagnetic iron oxide vs. Gd-DTPA. Journal of Magnetic Resonance Imaging 2006; 23(5):720-7
(20) Metz S, Lohr S, Settles S, Beer A, Woertler M, Rummeny EJ, Daldrup-Link HE: Ferumoxtran-10 enhanced MR imaging of the bone marrow before and after conditioning therapy in patients with Non Hodgkins Lymphoma. Eur Radiol. 2006; 16(3):598-607, 2006
(21) Simon GH, Bauer J, Saborowski O, Fu Y, Corot C, Wendland MF, Daldrup-Link HE: T1 and T2 relaxivity of intracellular and extracellular USPIO at 1.5T and 3T clinical MR scanning. Eur Radiol. 2006; 16(3):738-45
(22) Henning TD, Wendland MF, Golovko D, Sutton EJ, Sennino B, Malek F, Bauer JS, McDonald DM, Daldrup-Link HE: Relaxation effects of ferucarbotran-labeled mesenchymal stem cells at 1.5T and 3T: discrimination of viable from lysed cells. Magn Reson Med 2009; 62(2):325-332
(23) Golovko D, Henning T, Bauer JS, Settles M, Frenzel T, Mayerhofer A, Rummeny E, Daldrup-Link HE: Accelerated stem cell labeling with ferucarbotran and protamine. Eur Radiol. 2010; 20(3): 640-8
(24) Meier R, Henning TD, Boddington S, Tavri S, Arora S, Corot C, Daldrup-Link HE: Breast cancers: MR imaging of folate receptor expression with the folate- specific nanoparticle P1133. Radiology 255(2):527-35

(25)Daldrup-Link HE, Golovko D, Ruffell B, Denardo DG, Castaneda R, Ansari C, Rao J, Tikhomirov GA, Wendland MF, Corot C, Coussens LM. MRI of tumor-associated macrophages with clinically applicable iron oxide nanoparticles.
(26) Daldrup-Link H, Coussens LM. MR imaging of tumor-associated macrophages. Oncoimmunology2012 Jul 1;1(4):507-9.

b. Findings from Past Animal Experiments

Use of an iron nanoparticle contrast agent was studied in imaging of an arthritis model in rats. This directly contributed to the proposed research.

(21) Simon GH, Bauer J, Saborowski O, Fu Y, Corot C, Wendland MF, Daldrup-Link HE: T1 and T2 relaxivity of intracellular and extracellular USPIO at 1.5T and 3T clinical MR scanning. Eur Radiol. 2006; 16(3):738-45
(22) Henning TD, Wendland MF, Golovko D, Sutton EJ, Sennino B, Malek F, Bauer JS, McDonald DM, Daldrup-Link HE: Relaxation effects of ferucarbotran-labeled mesenchymal stem cells at 1.5T and 3T: discrimination of viable from lysed cells. Magn Reson Med 2009; 62(2):325-332
(23) Golovko D, Henning T, Bauer JS, Settles M, Frenzel T, Mayerhofer A, Rummeny E, Daldrup-Link HE: Accelerated stem cell labeling with ferucarbotran and protamine. Eur Radiol. 2010; 20(3): 640-8
(24)Daldrup-Link HE, Golovko D, Ruffell B, Denardo DG, Castaneda R, Ansari C, Rao J, Tikhomirov GA, Wendland MF, Corot C, Coussens LM. MRI of tumor-associated macrophages with clinically applicable iron oxide nanoparticles.

4. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Investigational Drugs, Biologics, Reagents, or Chemicals

Investigational Product 1	
Name:	Feraheme™
Dosage:	5 mg Fe/kg
Administration Route:	Intravenous
Manufacturer	AMAG
IND#	111,154

b. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	NA
Dosage:	NA
Administration Route	NA
New and different use? (Y/N)	NA

5. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS

N/A

6. PARTICIPANT POPULATION

a. Planned Enrollment

(i) Target is 20 participants: 10 patients with osteonecrosis receiving ferumoxytol; 10 patients with osteonecrosis not receiving ferumoxytol
(ii) single site study; 20.
(iii) pediatric and young adult patients (8 - 40 years), male or female subjects, referred to the cancer center for assessment of an osteonecrosis lesion in the bone.
iv) control pediatric and young adult patients (8 - 40 years), male or female subjects, with osteonecrosis who receive an MRI without ferumoxytol
Inclusion criteria: Osteonecrosis
Age, Gender, and Ethnic Background:
8 to 40 years of age
any gender
any ethnicity

b. Vulnerable Populations

As avoiding ionizing radiation is an increasing concern in the medical field, and as ionizing radiation exams are not particularly effective in distinguishing between the two conditions, developing a safe and effective diagnostic exam for the pediatric population is highly desirable.

c. Rationale for Exclusion of Certain Populations

N/A

d. Stanford Populations

N/A. While we will not avoid recruiting these populations, we will not specifically seek them out; and they would only be considered for the research if they undergo the same screening process as other participants.

e. Healthy Volunteers

None, N/A

f. Recruitment Details

All potential participants will be patients seen through regular referral methods in the pediatric oncology clinic and will be offered participation if it seems appropriate. If the patient and/or parents are interested in this new experimental imaging procedure, a meeting with a pediatric radiologist from the study team will be arranged or the phone details will be provided which allows the radiologist to set up an appointment with the patient and/or parents via phone or in person. The study investigator will then explain and discuss the details of the experimental MR imaging study procedure with the patient and/or parents and discuss the possibility of enrollment of the child into the study. Recruitment will be invitation only.

g. Eligibility Criteria

i. Inclusion Criteria

8-40 years of age, suspected or confirmed diagnosis of osteonecrosis

ii. Exclusion Criteria

contraindication to MRI (metal implants), need for sedation or anesthesia, claustrophobia.
Hemosiderosis/ hemochromatosis as defined by decreased T2-signal of liver will exclude patients from arm 1 (ferumoxytol-MRI). Patients with hemosiderosis/hemochromatosis can still be included in the osteonecrosis study and would undergo MRI evaluation without ferumoyxtol (control group).

h. Screening Procedures

During the course of a normal clinic visit, collaborating pediatric oncologists who note a patient who meets the inclusion/exclusion criteria, will inform them about the opportunity to enroll in the study. If the patient and/or parents are interested, a meeting with a pediatric radiologist from the study team will be arranged or the patient's name, phone details and MRN of the patient will be provided to allow the radiologist to set up an appointment with the patient and/or parents. We have applied for a limited Waiver of Authorization for Recruitment.

i. Participation in Multiple Protocols

During the enrollment process, patients will be asked if they are enrolled in any other studies, and a question will be on the top of the first page of the consent form. Should the patient be enrolled in another study, they will be advised to notify the PI for the other study that they are participating in our imaging study, and they will be encouraged to have the other PI contact our staff. We do not expect our study to impact any other results, as the MRI is a non-invasive imaging study; but as it involves a metabolically active drug (iron supplement), we will do our best to communicate clearly with the patients and any other PIs. Of note, the ferumoxytol dose administered for MRI (5 mg/kg) is far below the usual dose for the treatment of iron deficiency (2 x 510 mg) and does not affect the Hb levels of the patients. Should questions remain about the advisability of participation in our study, the potential participant will be excluded.

j. Payments to Participants

No payment, N/A

k. Costs to Participants

No costs will be charged to the participant. We expect to pay scanning costs from an NIH grant and the PI's research startup funds, including the contrast agent costs.

l. Planned Duration of the Study

The revised anticipated study duration is until 2026. (i) screening should take 15-30 minutes; (ii) active participation involves two MRI scans for a total of approximately 2-3 hours; (iii) follow up MRI(s) within 1-6 months after decompression surgery will be evaluated to determine clinical outcomes (iv) data analysis will continue until publication in approximately 12 months from initiation.

7. RISKS

a. Potential Risks

i. Investigational devices

N/A

ii. Investigational drugs

We applied for an IND with the FDA for off-label administration of the FDA-approved iron supplement ferumoxytol as a contrast agent (IND 111 154)

iii. Commercially available drugs, biologics, reagents or chemicals

Dr. Daldrup has applied USPIO as MR contrast agents in phase II and III clinical trials in adult patients. These contrast agents are generally well tolerated and show excellent safety profiles. The delivered iron dose via a typical ferumoxytol administration is in the order of 150-500 mg iron oxides (note that these are coated iron particles, not free iron), which is equivalent to or lower than the iron dose administered with one blood transfusion. USPIO are slowly metabolized in the liver and not excreted via the kidneys. Thus, they are safe to use in patients with renal insufficiencies and are not associated with any risk of nephrogenic sclerosis (a potential adverse event after injections of certain gadolinium chelates). The FDA recently issued a box warning about rare but potentially fatal allergic reactions to ferumoxytol. Anaphylaxis or anaphylactoid reactions were reported in 0.2% of subjects, which is in the order of other MR contrast agents. So far, we did not observe any allergic reaction in our patient population.

iv. Procedures

MRI w & w/o contrast
f/u MRI w/o contrast
Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MRI scanner uses a very strong magnet that will attract some metals and affect some electronic devices.
In some cases, having those devices means the participant should be excluded.
Additionally, when contrast is injected, as with any intravenous injection, there are risks of bruising, bleeding, or infection from the venipuncture; and allergic reaction to the injected contrast.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

N/A

vii. Psychological well-being

Some small risk of a patient experiencing claustrophobia. This is an infrequent but regular occurrence in any MRI facility. Every effort is made to minimize this risk and the research and clinical staff are well trained to act appropriately.

viii. Economic well-being

N/A

ix. Social well-being

N/A

x. Overall evaluation of risk

Low

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b. International Research Risk Procedures

N/A

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c. Procedures to Minimize Risk

An MRI screening form will be completed prior to participation. Any potential contraindication to MRI revealed by the comprehensive screening form will result in participant exclusion. The research team will use the clinical systems and the REDCap database for data management. REDCap is maintained by Clinical Informatics at Stanford University as a HIPAA compliant, secure, encrypted database for research purposes. Data exported by the researchers from these secure systems will only be exported in a deidentified form to minimize risks to confidentiality.

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d. Study Conclusion

Endpoint of these examinations is to define distinctive MR signal characteristics of malignant tumors and infection/inflammatory processes, which will be immediately applicable in a clinical setting. The scans occur in the clinical setting and make use of the normal clinical procedures and precautions, including the availability of medical emergency response teams and constant monitoring by medical personnel.

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e. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

Of note, Dr. Daldrup-Link has applied iron oxide nanoparticles as MR contrast agents in phase II and III clinical trials in adult patients. These contrast agents are very well tolerated and show excellent safety profiles. The delivered iron dose via a typical ferumoxytol administration is in the order of 150-500 mg iron oxides (note that these are coated iron particles, not free iron), which is equivalent to or lower than the iron dose administered with one blood transfusion. Iron oxide nanoparticles are

slowly metabolized in the liver and not excreted via the kidneys. Thus, they are safe to use in patients with renal insufficiencies and are not associated with any risk of nephrogenic sclerosis (a potential adverse event after injections of certain gadolinium chelates). Anaphylaxis or anaphylactoid reactions were reported in 0.2% of subjects, which is in the order of or lower compared to other MR contrast agents (see FDA report: Lu M, Cohen MH, Rieves D, Pazdur R. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. Am J Hematol. 2010;85(5):315-9). In the unlikely event of an anaphylactoid reaction, appropriate actions will be taken as with any other contrast agent reaction and the event will be reported to the IRB.

ii. Person(s) responsible for Data and Safety Monitoring

The Stanford Cancer Center Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities approximately once per year to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

iii. Frequency of DSMB meetings

AEs will be reviewed at every research team meeting, or at least once a month, whichever is more frequent.

iv. Specific triggers or stopping rules

v. Any signs of an anaphylactoid reaction, such as rash, urticaria, nausea, cough, breathing difficulty will lead to discontinuation of contrast administration and symptomatic treatment. DSMB Reporting

vi. The ME will forward written reports to the appropriate entities via email. Will the Protocol Director be the only monitoring entity? (Y/N)

N

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

Y

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f. Risks to Special Populations

g. Risk to Children

The research presents more than minimal risk to children, but holds out the prospect of direct benefit for the individual subject or is likely to contribute to the subject's well-being.

MRI is recognized as a non-significant risk, when used on-label, as in this research. Additionally, the contrast agent is an FDA approved medicine being used off-label, and has been assessed as having significantly similar or lower risk to existing on-label contrast agents used in similar applications. As off-label use of this contrast agent is expected to quickly and clearly illuminate an otherwise difficult diagnostic question (presence of osteonecrosis, success of osteonecrosis surgery) with low risk, no ionizing radiation, no invasive procedures (such as bone biopsy), the study team assesses this research as research involving marginally greater than minimal risk with prospect of direct benefit to the participant.

8. BENEFITS

We expect to be able to accurately delineate and differentiate bone lesions by assessing the difference in uptake and retention of the contrast agent on MRI scans. As this is a significant improvement over the existing standard of care, participants may benefit by improved diagnosis of an osteonecrosis. In patients who already have a specific diagnosis of osteonecrosis, confirmation of the existing diagnosis and better assessment of treatment effects are potential benefits. Overall, ferumoxytol can limit potentially painful and unnecessary biopsies, provide quicker and more accurate diagnoses, quicker access response to therapy, and thereby, reduce morbidity and mortality. In patients with osteonecrosis, the information obtained from ferumoxytol-enhanced MRI scans can improve prediction of successful treatment outcomes.

9. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.

10. STATISTICAL PLAN

All experiments were analyzed using R version 3.4.4. The number of patients per experimental group were determined by power analyses. Signal-to-noise ratios (SNR) and T2 relaxation times were pairwise compared between osteonecrosis lesions with and ferumoxytol administration, and between decompression track areas with and without visible iron-labeled cells, using a mixed-effects model including a random effect term accounting for correlation among the measures within a same patient. A Fisher exact test was applied for comparison of clinical outcomes of osteonecrosis with and without ferumoxytol enhancement. In addition, differences in time to progression of osteonecrosis from surgery between bone lesions that did or did not enhance with ferumoxytol were assessed by log-rank tests. Because of the small sample size and exploring purpose of this study, a $P < 0.05$ without adjustment for multiple comparisons was considered to indicate significant differences between experimental groups.