
 Mount Sinai	Protocol Title:	Detection of Liver Fibrosis Using IVIM Diffusion and DCE MRI in HCV
	Principal Investigator Name/Contact Info:	Bachir Taouli, MD
	Primary Contact Name/Contact Info	Nelson Chen 212-824-8476 nelson.chen@mountsinai.org
	Date Revised:	9/16/2016
	Study Number:	GCO09-1187

Detection of Liver Fibrosis Using IVIM Diffusion and DCE MRI in HCV

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MSSM Protocol Template HRP-503a

Instructions:

1. Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.
2. For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document. **Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.**
3. If you reference page numbers, attach those pages to this protocol.
4. When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.

Brief Summary of Research (250-400 words):

1) Objectives:


Research Question:

MAIN HYPOTHESES

1. IVIM, DCE-MRI and MRE metrics can non invasively discriminate severe fibrosis/cirrhosis (F3-F4), from no fibrosis (F0) and intermediate fibrosis (F1-F2). To test our hypothesis, we will prospectively determine in a cohort of 100 subjects (including 80 with chronic liver disease and 20 controls) whether IVIM DW-MRI, DCE-MRI and MRE parameters are valid markers of liver fibrosis, using histopathology from liver biopsy or explant as the reference.
2. MRI has equivalent performance to ultrasound elastography [including TE (transient elastography, Fibroscan) and ARFI (Acoustic Radiation Force Impulse imaging, Siemens) and serum markers for staging liver fibrosis, with the advantage of being more comprehensive and by providing whole liver coverage.

SECONDARY HYPOTHESES

3. A blood pool contrast agent such as gadofoset trisodium has better precision and accuracy in discriminating different degrees of liver fibrosis, compared to extra-cellular gadolinium agents such as Gd-BOPT.
4. Arterial spin labeling (ASL) can provide perfusion metrics used to discriminate different degrees of liver fibrosis.
5. There is a change in portal flow, hepatic perfusion fraction measured with IVIM DW-MRI and in hepatic/splenic stiffness measured with MRE from fasting to non fasting state.

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2) Background


There is an expected increased incidence of chronic hepatitis C virus infection (HCV) in the United States within the next years, with subsequent increased risks of liver damage, including fibrosis and cirrhosis, which may eventually lead to hepatocellular carcinoma and end-stage liver disease requiring liver transplantation. This disease is/will be the source of enormous health care costs and morbidity/mortality. Most hepatologists still rely on liver biopsy findings in patients newly diagnosed with HCV, which enables the assessment of liver damage (fibrosis and inflammation). Liver biopsy has limitations, including cost, invasiveness, poor patient acceptance, limited sampling, inter-observer variability and is difficult to repeat. Non invasive tests to capture the extent of liver damage at a larger scale are urgently needed. These will gain more acceptance among patients and hepatologists. In this proposal, we would like to test and validate non invasive magnetic resonance imaging (MRI) methods based on advanced diffusion (intravoxel incoherent motion diffusion MRI: IVIM DW-MRI) and dynamic contrast-enhanced MRI (DCE-MRI) for the detection of fibrosis and cirrhosis in HCV patients. Based on our recent preliminary data, we believe that the combination of IVIM DW- and DCE-MRI has potential for detection of fibrosis and cirrhosis with excellent accuracy, while enabling coverage of the whole liver. In order to improve the diagnostic performance of MRI, we would like to build and validate a predictive model based on advanced functional MRI metrics (diffusion and perfusion). If validated, this novel non invasive algorithm will not only decrease the number of liver biopsies, but also enable earlier diagnosis of liver fibrosis when antiviral treatment is more effective, and enable a comprehensive evaluation of the liver (to assess for cirrhosis, portal hypertension and hepatocellular cancer). This could significantly reduce the cost of care, could become a useful tool for testing new antifibrogenic and antiviral drugs in HCV, and could be used to follow patients for detection of progression to cirrhosis. This will be a highly significant progress in liver diseases given the increased burden of HCV in this country, and would benefit a large number of Americans over the next decade.

Purpose of study:

- 1) Determine the prospective diagnostic performance of DW-MRI, DCE-MRI and MRE for staging liver fibrosis in patients with chronic liver disease in comparison to controls.
- 2) Compare the diagnostic performance of MRI vs. transient elastography (TE) and acoustic radiation force impulse (ARFI) imaging and serum markers for non invasive detection of liver fibrosis in patients with chronic liver disease in comparison to controls.

Secondary Objectives:

- 1) Assess the role of a breath-hold/free-breathing phase contrast MR imaging sequence to assess portal vein and hepatic artery velocity and flow.
- 2) Assess the role of hepatic and splenic stiffness measured with MRE as surrogate measures of portal hypertension (measured with portal pressures, which will be clinically indicated).

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- 3) Assess the role of a FDA approved blood pool gadolinium contrast agent, Gadoxdate disodium (Eovist), Lantheus) for the measurement of liver MR Perfusion, compared to extra-cellular contrast agents.
- 4) Assess the role of arterial spin labeling (a non contrast technique) for measurement of hepatic perfusion.

3) Setting of the Human Research

Mount Sinai Medical Center - Department of Radiology/Translational and Molecular Imaging Institute (TMII)

4) Resources Available to Conduct the Human Research

We have the equipment (MRI scanners, Fibroscan and ARFI) and we are in an open dialogue with the staff of Liver disease and liver transplant to be able to recruit the subjects needed to complete this study.

5) Study Design


a) Recruitment Methods

Subjects with liver disease will be identified and recruited for the study by their physicians in the Liver Transplant and/or Liver Disease team. This selection will come from the physicians' recommendation, which is familiar with their patient's history. The referring physicians will not be considered co-investigators except Dr. Friedman and Dr. Dieterich. Dr. Friedman and Dr. Dieterich are both Co-investigators on this project. They will tell the other physicians in Liver Transplant and Liver Disease about the study and help to enroll patients.

Other sources of potential subjects are the KCC ambulatory procedure list and the Mount Sinai Liver Transplant list provided by the Liver Transplant/Liver Disease Department. Subjects with liver disease who underwent liver biopsy at Mount Sinai will be identified by Dr. Fiel from the Pathology Department. Dr. Fiel is a Co-investigator on this study and provides the study team with a quarterly Pathology list.

The treating physician will be the first to notify potential subjects about the study. If subjects consent to be contacted the Research Coordinator will call them to explain the study and to ask if they are willing to be part of this study. No potential subject will be contacted by the study team without subject's prior consent. The study coordinator will review all listings and the patient's medical records to check for their eligibility according to the inclusion/exclusion criteria and contraindications for MRI. A HIPAA waiver of authorization will be requested for the study.

An announcement within the MSSM Broadcast emails will be used for recruitment.

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ResearchMatch will also be used as a method for identifying and contacting potential subjects. The study specific announcement is included with this submission.

b) Inclusion and Exclusion Criteria

Inclusion criteria

Study group

- 1) Chronic liver disease (including viral hepatitis, alcoholic hepatitis, non alcoholic steatohepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, etc.)
 - 2) 18 years of age and older
 - 3) Patient is able to give informed consent for this study and agrees to provide a blood sample
- Patients preferably (but not necessarily) underwent/will undergo:
- 4) Liver biopsy (percutaneous or transjugular or surgical) performed within 6 months, as part of routine clinical care and/or
 - 5) Liver transplant or liver resection performed as part of routine clinical care and/or
 - 6) Medical therapy for portal hypertension or TIPS placement as part of routine clinical care and/or

Antiviral therapy for HCV infection.

Control group


- 1) Patients without history of liver disease and healthy volunteers
- 2) 18 years of age and older
- 3) Subject is able to give informed consent for this study and agrees to provide a blood sample

Exclusion criteria

1. Age less than 18 years
2. Unable or unwilling to give informed consent
3. Contra-indications to MRI
 - a. Electrical implants such as cardiac pacemakers or perfusion pumps
 - b. Ferromagnetic implants such as aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, tattoos near the eye, or steel implants
 - c. Ferromagnetic objects such as jewelry or metal clips in clothing
 - d. Pregnant subjects
 - e. Pre-existing medical conditions including a likelihood of developing seizures or claustrophobic reactions.

As with all subjects referred for MRI, each subject is screened for possible contraindications with a routine questionnaire.

Subjects with GFR <30 will not undergo DCE-MRI with Gadolinium contrast. For subjects with GFR <30, we will still consider enrolling them for a non-contrast MR protocol, including non-contrast sequences, FibroScan and/or ARFI and blood tests. Subjects with GFR between 30 and

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60 will receive only either a half dose Multihance or Gadoxedate disodium (Eovist), and will not have repeat DCE-MRI studies with Gadolinium contrast. Only subjects with GFR ≥ 60 will be proposed to return for repeat DCE-MRI studies with Gadolinium contrast. Subjects with GFR < 60 will be considered to return for repeat non-contrast MRI-studies.

We will consider injecting gadolinium contrast in healthy volunteers, for the purpose of DCE-MRI image optimization.

c) Number of Subjects

250

d) Study Timelines

6 years

e) Study Endpoints

Liver fibrosis detection and staging

f) Procedures Involved in the Human Research

Visit 1

Blood test – GFR measurement to be done to evaluate renal insufficiency, liver serum markers, and pregnancy if applicable will be done for research - takes about 10 minutes. DW-MRI and DCE-MRI (MRI with intravenous contrast only if GFR > 30) is standard of care and added MRE which is research will be 5 extra minutes (the entire MRI will take about 45 minutes)

Fibroscan and/or ARFI to determine liver stiffness will be done for research - takes about 10-20 minutes.


Visit 1 should take about 60-90 minutes.

Patients under medical treatment for portal hypertension or TIPS procedure are considered to be scheduled for visit 1 before they start their portal hypertension treatment or get TIPS placement.

Visit 2

DW-MRI and DCE-MRI (MRI with intravenous contrast only if GFR > 60) with MRE sequences is done for research and done for reproducibility and will take another 45 minutes to complete to the first 30 subjects. This visit will take place within a week after visit 1.

This visit may have another blood test and another Fibroscan and/or ARFI so the entire visit should take about 60-90 minutes.

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Patients under medical treatment for portal hypertension or TIPS procedure are considered to be scheduled for visit 2 after they started their portal hypertension treatment or got TIPS placement to look at changes in hepatic flow and liver stiffness.

Patients starting antiviral therapy for HCV will be evaluated before they start the therapy, and will be repeated 3 to 6 months after the end of therapy.

We would like to perform the following sub-studies: All subjects will receive by default Gd-BOPTA (Multihance, Bracco) enhanced MRI (half dose at 0.05 mmol/Kg for the perfusion study) at 1.5T or 3T. In addition, the subjects may receive one of the following options:

Option 1: 1.5T MRI using (Gadoxetate disodium (Eovist)) will be performed in up to 10 subjects.

- Sub-arm 1: In up to 5 subjects receiving Gadoxetate disodium (Eovist), the studies will be repeated twice at least 24h apart to measure reproducibility of DCE-MRI using Gadoxetate disodium (Eovist)

Option 2: 3T MRI using Gd-BOPTA (same dose as above), will be performed in up to 10 subjects. These could be different or same subjects as in option 1.

MR Elastography: Will be performed in all patients before contrast injection, using a 1.5 and/or 3T system (Siemens). The patient will be asked to perform multiple breath-holds during the image acquisition.

Option 3: Compare image quality and liver perfusion quantification between Cartesian and radial DCE-MRI acquisitions in a small subset of subjects (n=15), using the same contrast dose and MR system.

The liver explant analysis will be performed as part of routine clinical care. In addition, the following will be assessed: degree of biliary differentiation (by measuring semiquantitatively cytokeratin-19 expression).

Extra MRI sequences of the abdomen will be done for research.


Fibroscan and/or ARFI to determine liver stiffness will be done for research.

A blood test will be done to evaluate renal insufficiency, only if no recent EGFR value (not older than 6 weeks) is available in the medical record for contrast administration determination.

A blood test will be done to evaluate liver serum markers for research purposes.

A pregnancy test, if pregnancy cannot be excluded by women of child-bearing potential, will be performed prior to any scan to determine eligibility for study participation.

g) Specimen Banking

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N/A

h) Data Management and Confidentiality

All research data will be stored separately from direct identifiers (e.g. name, address, DOB, MRN, SSN) that can link the data to a person's identity. Research data files will be stored using a unique "code" instead. The "linking code file" will be maintained separately in Dr. Taouli's office.

The file that links the code to the person's identity (direct identifiers) will be maintained electronically and in an encrypted file on a departmental network drive in Dr. Taouli's office.

All research data files will be stored electronically in encrypted files. Access to the data files will be through restricted view set up by Radiology IT and password protected. The data will be stored for 7 years.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

N/A Minimal risk

j) Withdrawal of Subjects

Subjects may withdraw at any time from the study with no penalty. This will not affect their ability to receive medical care. If a subject withdraws from the study, they must contact the PI in writing. The subject's data may still be used after they have withdrawn authorization.


The study doctor, the sponsor or the institution may stop the subject's involvement in this study at any time without his/her consent. This may be because the study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in the subject's best interest, or for any other reason. If specimens or data have been stored as part of the study, they too can be destroyed without the subject's consent.

6) Risks to Subjects

Approximately two percent (2%) of participants experience some side effects with the use of gadolinium; however, they are mostly mild (nausea, headache, hives, temporary low blood pressure).

Risks Associated With Intravenous Catheter Placement:

Likely:

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- Minor discomfort;
- Pain in the injection site.

Less Likely:

- Bleeding;
- Infection;
- Bruising.

Risks Associated With MRI:

- Anxiety/stress;
- Claustrophobia;
- Discomfort.

Because of the powerful magnetic force of the MRI scanner, a subject may not be able to participate in the study if he/she has:

- Metallic or other surgical implants (for example: pacemaker, heart valves, aneurysm clips, metal plates or pins and some orthopedic prostheses);
- Metal pieces in your eye(s) or other body part(s); or
- Difficulty lying still or inability to lie on your stomach
- Claustrophobia
- Anxiety/stress.

Risks Associated with Gadolinium

Less likely

- Headaches;
- Nausea.

Less likely, but serious


- Allergic reaction.

Very rare, but serious

- Nephrogenic systemic fibrosis (NSF)/Nephrogenic Fibrosing Dermopathy (NFD). NSF is a condition associated with the gadolinium contrast agent when there is severe kidney disease. Symptoms include tightening or scarring of the skin and organ failure. In some cases, it can be deadly. NSF has not been seen in patients with normal working kidneys or mild problems in kidney function.

Reproductive Risk

If a subject is pregnant or nursing or plans to become pregnant during the course of the study, he/she cannot take part in this research study. We do not know the effects on the fetus, breastfeeding baby, or mother-to-be, and this study may cause harm. A subject should not become pregnant or breastfeed, while on this study. To ensure the safety of subjects, pregnancy

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tests, if pregnancy cannot be excluded by the participant, will be performed prior to any scan for women of child-bearing potential.

All procedures will be explained thoroughly to each subject before they are scanned. The subject will be given an option to listen to music during the scan to help calm their fears and lessen the noise of the MRI scanner. All subjects will be given a call button to push if they need to speak to the technician if they feel anxious.

The loss of confidentiality or privacy is possible, but all scans will be coded with a study ID number and all names, DOB and all other similar data will be removed. The code will be kept in a separate secure location. Every attempt will be made that confidentiality or /privacy will be maintained.

7) Provisions for Research Related Injury

In the event of injury resulting from a subject's participation in this study, the facilities at Mount Sinai Hospital and professional attention will be made available to the subject at his/her expense. Financial compensation from Mount Sinai will not be provided.


8) Potential Benefits to Subjects

The subjects may not receive any direct benefit from participation in this research study. Others may not benefit either. However, possible benefits to others include decreasing the numbers of invasive biopsies, which will potentially enable earlier diagnosis of liver damage.

9) Provisions to Protect the Privacy Interests of Subjects

Every effort will be made by the investigators and study coordinators to keep all the information in this study strictly private, including subjects' personal information, from the time participants are identified for recruitment until they complete study participation. This includes communication when scheduling appointments, leaving phone messages and follow-up contact. Records of participation, progress and images taken while on the study will be kept secure at Mount Sinai and in a computer file at the sponsor's headquarters. All data sent to the sponsor over the internet will be coded.

All efforts will be made to make the subjects feel at ease with the research situations. They will have the opportunity to ask questions and will have ample time to review and think about any questions, examinations and procedures in the study. Research procedures will be explained in simple, clear, concise language. Members of the research team will be appropriately able to approach prospective participants about the study because the potential subjects may be eligible for enrollment, their physicians have referred them for potential enrollment, and the research team is knowledgeable about study guidelines and protocol.

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10) Economic Impact on Subjects

The subject will incur no extra costs, the scans that are part of the standard of care will be submitted to their insurance and other scan time or scans that are part of the study will be paid for by the study sponsor.

11) Payment to Subjects

Subjects will be compensated \$40 for each completed scan (up to four, potentially), for travel related expenses. Subjects who do not incur travel related expenses in order to participate do not qualify for compensation.

12) Consent Process

Subjects will be given the consent form by their physician to read and take home to think about and then call the research team to make an appointment if they would like to be part of the study. They will be given the opportunity to review the consent document at home, discuss it with whomever they like, think about the information that has been presented to them and be able to make an informed decision, without being concerned or be in any kind of anxiety provoking situation as to whether they wish to participate.

Patients being called by the Research Coordinator will be given the opportunity to ask any questions or mention any concerns about the study and to call back with their decision or any further questions. They will be given time to think about the information that has been presented to them over the phone and they will be offered to receive the consent form prior to a decision whether to take part or not.


All subjects will be consented in Radiology Department before they undergo the MRI examination after they have been given time to review and consider being part of the study. Consent will be obtained by only the members of the study team who have been trained properly and not by referring physicians who are not part of the study team. The subject will be provided with a copy of the signed consent form.

13) Process to Document Consent in Writing

We will make the subjects chart with the date that each subject is consented.

14) Vulnerable Populations

Economically or socially disadvantaged persons are eligible for the study if the Principal investigator believes that they will be good candidate. The study will be carefully explained and discussed with the patient. Any questions that the patient has will be explained thoroughly to both the satisfaction of the principle investigator as well as the patient. We do not wish to enroll

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any person who is does not fully understand what is involved in this study, nor do we wish to improperly influence any participant.

In order to protect the rights and welfare of subjects, we will **not** preferentially enroll vulnerable subjects. In order to protect the rights and welfare of subjects, we will provide information to the subjects that they can fully understand, and similarly write the consent document in a simple manner and language that someone with sixth grade language could comprehend.

Pregnant subjects are excluded from participation in this study because of the possible effect of gadolinium to the fetus.

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

The results of the research portion of MRI (including the MR Elastography), the FibroScan, the ARFI and blood tests (part of the research portion) results will not be given to the subject. However, during the participation in this study, the subjects will have access to any study information that is part of their medical record. The investigator is not required to release research information that is not part of the medical record. Results of the MRI scans will be accessible in the Mount Sinai electronic medical record.


18) IRB Review History

This study was last approved by the IRB on 02/20/2014.

19) Control of Drugs, Biologics, or Devices

Note: The IDS has its own forms that must be completed and a review process that must be followed before the IDS representative will sign off on Appendix B for submission to the PPHS.

The drugs are just the contrast agents used and are stored within the department.

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