Research Proposal
LU 206338
Evaluation of Gadoterate in Patients with Renal Dysfunction
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Background and Significance

Magnetic Resonance Imaging (MRI) has become an indispensable tool in disease diagnosis and patient management. Imaging with MRI yields the highest quality tissue characterization in most regions of the body, and does so without the potential harmful effects of ionizing radiation. A discussion of MRI technology is beyond the scope of this proposal, but, briefly, MRI utilizes both fixed and dynamic magnetic fields to excite the body's water molecules and extract images of the local tissue environment. Gadolinium (Gd) is a naturally-occurring element which is paramagnetic – meaning it can change the local magnetic field. Therefore, tissue infused with a chemical agent containing Gadolinium will appear more prominent on an MR image. Gadolinium-based intravenous contrast agents (GBCA) are therefore widely used for enhancement of anatomic structures during magnetic resonance imaging (MRI) examinations. These agents allow more detailed and complete characterization of anatomy and disease processes. For example, the degree of viability within a treated tumor can be evaluated based upon residual Gadolinium enhancement within the lesion, or a fluid collection can be characterized as infected if it has enhancement around its periphery. However, GBCAs have been implicated in varying degrees of nephrotoxicity and, very seldomly, in a skin and organ fibrotic disorder called Nephrogenic Systemic Fibrosis (NSF) [1-7]. This condition is theorized to result from toxicity related to free Gadolinium (free Gd is toxic) that has become dissociated from its bound state in the larger contrast molecule. Decreased renal function theoretically results in longer circulation of the GBCA and thus a greater likelihood of Gd dissociating and accumulating in tissues. The American College of Radiology therefore advises caution when using Gadolinium in patients with estimated glomerular filtration rates (GFR – a standard calculation of kidney function that estimates how much flow is filtrated through the kidney, based upon serum creatinine concentration, age, weight, and race) less than 60 ml/min and advises no routine use in GFR < 30 ml/min [7].

Gadoterate (Dotarem ™) is a particular Gadolinium agent that has been widely used in Europe for over 24 years and has recently become commercially available in the U.S. Its chemical formulation confers significantly greater stability to the bound state of Gadolinium, compared with other GBCAs (Figure 1) [8-10]. Furthermore, experience based upon widespread clinical use in Europe, as well as data yielded by several smaller studies, strongly indicate that Gadoterate is safe in patients with GFR < 60 and even in patients with GFR < 30 [11-15]. Of note, there have been no cases of NSF in over 43 million administrations in Europe [14], and a German post-marketing analysis of more than 84,000 patients demonstrated no adverse renal events (general adverse events were < 0.3%) despite over 750 patients defined as having a risk factor of chronic renal disease [12]. And, a study of over 500 dialysis patients revealed no cases of NSF after 6 months [15]. It is also important to highlight that even in populations with reduced GFR and end stage renal disease (ESRD) who received serial high-doses of significantly less-stable Gadolinium contrast agents, only a 3-4% rate of NSF has been reported [7,16]. The risk of using a more stable GBCA within strict dosing guidelines is much less. (More generally, there have been an estimated 200 million Gadolinium administrations, with fewer than 1000 cases of NSF). While the risk

of contrast administration can never be entirely ignored, it is important to be cognizant of these conclusions when considering the suboptimal clinical care often afforded patients who do not receive Gadolinium contrast exams. For example, definitive diagnosis of hepatocellular carcinoma in a patient with cirrhosis, or of renal cell carcinoma in a patient with uncharacterized renal lesions, is all but limited to contrast-enhanced imaging, and manifests in dramatically disparate therapy compared with less definitive diagnosis (therapy initiation vs. serial follow-up imaging or invasive biopsy). Therefore, the benefits of having a GBCA on formulary, with which Gadolinium-enhanced MRI exams could be performed on any patient, regardless of GFR, would be significant to patient-care. The potential scale is significant due to the number of patients that fall into this category in our institution's catchment population as well as across the U.S. [17]. However, widespread misunderstanding of the chemical and clinical data has instilled fear of both medical and legal complications and has precluded current radiology practices from using GBCAs in patients with GFR<30. Currently, we estimate in excess of 800 exams that are annually performed at our institution without Gadolinum enhancement – and thus suboptimally - due to GFR restrictions. Our goal is to therefore gather robust single-site pilot data at Loyola University Medical Center and then proceed to a larger multi-site trial demonstrating the safety and utility of Gadoterate in this particular patient population.

Hypothesis and Study Aims

Hypothesis 1: Use of Gadoterate in a population of patients with GFR<30 will not result in statistically-significant numbers of adverse renal events, defined by decreased GFR and/or NSF.

Hypothesis 2: Use of Gadoterate in a population of patients with GFR<30 will result in more definitive radiologic interpretations and improved clinical care compared with those associated with non-contrast images only. Metrics of evaluation include improved timeliness and quality of disease treatment, as well as fewer follow-up imaging studies with greater specificity (see below).

Specific Aim 1: Establish Gadoterate-based MRI protocols for GFR<30 patients, and establish database (and analytic models) of pre and post-exam laboratory data as well as relevant demographic data.

Specific Aim 2: Establish database of comparative radiologic findings, clinical care decisions, therapy outcomes, and downstream imaging costs, for radiology interpretations based upon unenhanced vs. Gadoterate-enhanced MRI images.

Study Design

The study design is straightforward, and will consist of 2 equal-sized cohorts of patients, all of whom have GFR of < 30 ml/min, but are not on dialysis, and all of whom are being sent for an MRI examination in the course of routine clinical evaluation of one of the following indications: suspected or known head/neck/brain mass, hepatic mass, renal mass, pancreatic mass, or prostate mass, as well as evaluation of carotid or abdominopelvic vasculature. These relatively few indications constitute the vast majority of indications for contrast MRI in our health system, similar to most institutions. As such, there will be significant statistical representation of these indications in each cohort. At the same time, limiting the study to these indications will allow greater organizational structure, with more focused points of enrollment. Note that each of the corresponding clinical departments has expressed significant interest in participation; patients will be enrolled over a two year period from the hepatology, surgery, urology, neurology, and neurosurgical services at Loyola. Following IRB approval and informed consent, patients in the first group will receive MRI exams with no Gadolinium contrast, while the other group will receive standard pre-contrast *and* Gadoterate-enhanced acquisitions (0.2 mL/kg). MRI protocols utilized in the study will be comprised of the standard Body protocols (routine abdomen, liver-pancreas, renal, prostate,

angiography) as well as the standard Neurologic exam protocols (routine brain, orbital, brainstem, neck, angiography).

Ineligibility criteria will include pregnancy, lactation, planned initiation of chemotherapy or surgery within 72 hours of the MRI exam, hemodynamic instability or acute coronary syndrome, history of nephrotoxic medication within 2 weeks of the exam (Amphotericin B, Lithium, Pentamidine, Aminoglycosides, Acyclocvir, Gancyclovir, or Foscavir), and age less than 18 years.

Aim 1:

Each patient's GFR will be recorded prior to the exams and 48-72 hours after scanning. In addition, each patient will be contacted at baseline as well as 6 weeks, 3 months, and 6 months post-scan to comprehensively evaluate for any symptoms or signs of NSF (see attached sheet) [19]. If at any point a patient's follow-up interviews indicate they might be experiencing symptoms of NSF, or if their post-MRI research blood draw indicates deteriorating renal function, the study PI will be notified and the patient will be referred for further medical evaluation, if necessary. All relevant demographics, such as hypertension, diabetes, coronary artery disease, and liver disease, will be recorded. The data will be analyzed, using standard statistical methods, for any significant and disparate variations in renal function.

Aim 2:

Each MRI exam will be independently interpreted by 2 participating sub-specialty-trained (either neuro or body) radiologists. To limit bias, the readers will initially be blinded to history and prior exams and their respective interpretations recorded in the research database (history and prior exams will subsequently be provided, as usual, for the final interpretations used in clinical care). The interpretations and inter-reader correlation will be recorded for each exam. Via Loyola electronic medical record (EMR) we will record the chronology of all subsequent related diagnoses, imaging studies, pathology results, therapies, and related costs (defined as gross hospital charge), within the study period (1-2 years) and for one year afterward. These data will be analyzed to compare differential outcomes between the non-contrast and contrast cohorts.

To further explore the concept of Gadoterate-based differential outcomes, two separate interpretations for each Gadoterate-enhanced MRI will be recorded in the research database: an interpretation based upon only the non-contrast images and the full interpretation of the whole exam (non-contrast + contrast images). We will subsequently record the *predicted* outcome data, as described above (diagnoses, subsequent imaging studies, pathology results, therapies, and projected related costs), that would be associated with the more limited interpretation of the non-contrast images. Comparison to the actual outcomes of that patient will subsequently be analyzed. This is both feasible and straightforward since the vast majority of the clinical MRI indications in this study have a well-defined diagnostic/therapeutic pathway – i.e. a solitary liver lesion demonstrated to be malignant by contrast MRI would result in chemo-embolization, whereas an indeterminate result based on non-contrast would lead to a liver biopsy [18]. Another example: Cystic renal lesions which cannot be completely characterized without contrast are typically followed with serial imaging exams to check for growth, whereas demonstration of a simple cyst by contrast-enhanced exam will typically result in no further imaging.

Statistics:

Previously-tested GBCAs in chronic kidney failure patients have resulted in 10-25% rates of decreased GFR, depending upon the study, with most investigations recording rates in the range of ~15% [5]. Based upon various data thus far (noted above), the rate is expected to be no more than 5% using Gadoterate;

therefore if we wish to detect a significantly lower rate of renal complications with a power of 90% and a 5% significance, then a sample size of approximately 136 patients receiving Gadoterate is properly powered to address Aim 1. The non-Gadoterate control arm does not need to be as large for analysis of Aim 1, however, it will consist of 136 patients as well, to properly power analysis of Aim 2. This number is expected to be more than sufficient considering that significant interpretive and outcome differentials are anticipated at a far greater rate than 5%, between the non-contrast image and contrast image evaluations.

Study Procedures

Subject selection

Inclusion Criteria: GFR less than 30 ml/min, but not on dialysis, with indications for MRI as described above. GFR will be calculated in the same fashion as in current use in our department:

$$\text{eGFR} = \frac{(140 - Age) \times Mass\ (kg) \times (0.85\ if\ female)}{72 \times serum\ creatinine\ \left(\frac{mg}{dL}\right)}$$

Exclusion Criteria: Pregnant and lactating females; planned initiation of chemotherapy or surgery within 72 hours of the MRI exam; hemodynamic instability or acute coronary syndrome; history of the following nephrotoxic medications within 2 weeks of the exam: Amphotericin B, Lithium, Pentamidine, Aminoglycosides, Acyclocvir, Gancyclovir, or Foscavir; age less than 18 years.

Note that many patients within the inclusion criteria may have pre-existing conditions which could, theoretically, cause a GFR decrease unrelated to the Gadoterate in the 48-72 hour post-injection window; however, such cases will be statistically represented in both cohorts and, as such, are not expected to affect the comparisons between the two populations due to the sufficient statistical power of the study.

Recruitment

Patient recruitment will occur via two complementary mechanisms: In the clinician office when the study is ordered and via the research nurse and/or study coordinator. It is expected that a significant component of patients will be recruited into the study by the clinicians in the participating departments. Education of clinicians in these departments is ongoing at this time and all have been enthusiastic about participating. In addition, the nurse coordinator will review the radiology informatics system, on a daily basis, to identify all eligible patients for whom non-contrast MRIs have been ordered due to GFR concerns. In such cases the nurse coordinator will contact the study PI to determine eligibility. If the patient meets eligibility criteria, the study PI will confirm with the patient's ordering physician. The patient will be contacted and the study PI, sub-investigator, or other appropriate study staff will explain the study, with its risks and benefits, to the patient at least 8 hours prior to the MRI exam. The study PI or sub-investigator will contact the ordering physician prior to the date of the exam to obtain an updated order allowing for contrast MRI. Signature of the consent form itself will then be available for the patient at the time of the exam. In either of these scenarios a patient who does not want Gadoterate contrast will receive the usual non-contrast MRI.

In reviewing the radiology informatics system, the coordinator may identify a patient who meets eligibility criteria and whose GFR has already been obtained through standard care, but who already had a standard MRI completed without contrast within the past 24 hours. If this occurs, the PI will be notified to determine if it is appropriate to contact the patient and obtain consent post-MRI. If the patient consents

to the study, they would be placed into the control (non-contrast) group and undergo the remaining study activities of post-MRI blood draw and questionnaires at baseline, 6 weeks, 3 months and 6 months.

Consent

A discussion of the study, including discussion of risks and benefits, will be conducted by the study staff (PI, sub-investigator, research nurse, or study coordinator) with the patient at least 8 hours prior to the exam (except, as noted above, in the event a patient is identified post-exam). The consent form can then be signed at the time of the exam. Consent will be obtained following our institution's policies and procedures. Patient eligibility will be confirmed prior to study enrollment.

If a patient is unable to give informed consent due to cognitive dysfunction (for example, stroke, trauma, or encephalopathy from liver failure), their guardian, spouse, parent, or the individual holding power of attorney for their healthcare will be approached to consent for the patient. If the patient regains his or her ability to make decisions, he or she will be informed about the study and asked for a decision about continued participation. In the event the patient does not regain his or her ability to make decisions at the time the questionnaires are administered, the individual who consented on behalf of the patient will be asked to answer the symptom questionnaires on the patient's behalf.

Recruitment materials

No advertising will be provided. Written material will consist of the ICD. $25 will be provided to patients as compensation for their 2-3 day return visit (blood-draw) and $5 for parking.

Selection

It is expected that a significant percentage of patients fulfilling the eligibility criteria will nevertheless choose to decline receiving Gadoterate and receive the default non-contrast exam. These patients will be asked to take part as the non-contrast arm of the study.

Gadoterate

Gadoterate will be the only contrast agent used. There is no placebo and no blinding is needed. Gadoterate will be provided by Guerbet pharmaceuticals and will be stored in the identical fashion that all Gadolinium agents are stored in the department (see attached package insert). Gadoterate will be administered according to its standard weight-based protocol, 0.2 mL/kg [8].

Administrative Organization

This will be a single site study conducted at Loyola University Medical Center. Patient recruitment and participation from the referring clinicians in the hepatology, neurosurgery, neurology, neurosurgery, and urology divisions will be coordinated by an MRI nurse coordinator, who will devote 10% time to this project. In addition, all blood draws and patient follow up will be coordinated by the nurse coordinator. All imaging will be conducted on-site. The standard LUMC laboratory locations and procedures will be used to calculate GFR from the patients' serum.

The clinical research office (CRO) will assist with statistical data analysis.

Safety and Monitoring

As with any intravenous contrast agent, numerous nonspecific adverse (mostly allergic-type) reactions are possible, though rare (see attached package insert), for Gadoterate, and no more common than in any other agent in clinical use. The most serious adverse event is difficulty breathing. Patient safety related to

such events will be monitored by direct technician and nurse supervision at the time of the exam and in the immediate period following – this is standard department protocol for all contrast MRI exams.

The main additional serious adverse reaction is the one being specifically monitored in this study - renal toxicity. Monitoring of this will be done by 48-72 hour post-exam serum creatinine evaluation, as described above. In addition, long-term toxicity in the form of NSF will be evaluated by detailed phone follow-up, designed to identify any potential signs of NSF (see Figure 2). In the event of a positive response to 3 or more of the questions in the questionnaire, the patient will be assisted in scheduling a Dermatology appointment at LUMC.

The PI (Ari Goldberg) and the nurse coordinator will be responsible for tracking and assessing any adverse events.

Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others:

Any adverse events, as described above or unanticipated, involving risk to participants, will be promptly submitted to the IRB in accordance with established guidelines.

In addition, all data related to renal function and NSF will be routinely reviewed by the PI every 3 months.

Analysis

Image analysis: As described above, each MRI exam will be independently interpreted by 2 participating sub-specialty-trained (either neuro or body) radiologists, with the readers blinded to history and prior exams. For both contrast and non-contrast exams, the images will be viewed in the standard clinical fashion (Intellispace PACS system). For the contrast exams, the interpreting radiologists will first render an evaluation based upon *only* the non-contrast images - these interpretations will be recorded only within the research database. As described earlier, this will enable evaluation of the added advantages of the contrast agent. The overall contrast-exam interpretations, as well as the interpretations of the non-contrast exams, will be recorded in both the research database as well as dictated into the EMR, since these studies will be ordered as part of clinical care. The CRO will assist in analyzing trends of inter-reader correlation and variability.

Outcomes analysis: We will analyze the differential outcomes, between the two cohorts, as well as between the projected and actual outcomes within the contrast cohort, in these specific categories: diagnoses, number and types of subsequent imaging studies, pathology results, therapies, and related costs (defined as gross hospital charge), within the study period and extending 1 year afterward. The CRO will assist in analyzing variation within these metrics between the non-contrast vs. contrast cohorts. The CRO will also assist in analysis of variation between the projected outcomes and actual outcomes within the contrast cohort.

Risks vs Benefits

The risks particular to involving this patient population (GFR < 30 ml/min) in this trial are decreased renal function, including the possibility of the need for permanent dialysis, and NSF. However, extensive clinical experience and literature clearly support the fact that the chance of significant renal dysfunction is small and the chance of NSF is quite remote. On the other hand, the addition of Gadolinium contrast to an MRI exam is often of critical importance for determining accurate anatomic relationships, differentiating benign from malignant lesions or infected tissue from normal tissue, and determining resolving vs.

worsening disease. Patients who are ill and who therefore often need these important determinations from their MRI studies are often the ones unable to have Gadolinium contrast due to GFR concerns. Thus, while the risk is real, the benefits are clear and of immediate impact in numerous clinical situations. It is anticipated that patients involved in this study will be the recipients of such benefits. More generally, establishment of safe contrast-MRI protocols in this general population will contribute to advancement in the standard of care by which MRI is utilized for them, with these benefits potentially realized on a much more significant scale.

References

[1] Thomsen HS: Nephrogenic systemic fibrosis: A serious late adverse reaction to gadodiamide. Eur Radiol 16: 2619–2621, 2006
[2] Sam AD, Morasch MD, Collins J, Song G, Chen R, Pereles FS: Safety of gadolinium contrast angiography in patients with chronic renal insufficiency. J Vasc Surg 38: 313–318, 2003
[3] Marckmann P, Skov L, Rossen, Dupont A, Damholt MB, Heaf JG, Thomsen HS: Nephrogenic systemic fibrosis: Suspected etiological role of gadodiamide used for contrastenhanced magnetic resonance imaging. J Am Soc Nephrol 17: 2359–2362, 2006
[4] Update on Magnetic Resonance Imaging (MRI) Contrast Agents Containing Gadolinium and Nephrogenic Fibrosing Dermopathy, 2006. Available at: http://www.fda.gov/cder/ drug/advisory/gadolinium_agents_20061222.htm. Accessed November 1, 2008
[5] Parazella M, Current Status of Gadolinium Toxicity in Patients with Kidney Disease; Clin J Am Soc Nephrol 4: 461–469, 2009.
[6] Janus et al. Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: Results of the FINEST study, Eur Journal Radiol. 2010; 73:357-359.
[7] ACR committee on Drugs and Contrast Media, ACR Manual on Contrast Media, Version 9, 2013
[8] DOTAREM [package insert], Bloomington, IN: Guerbet LLC; 2013
[9] Port M et al. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review Biometals, 21, 469-490, 2008
[10] Laurent et al. Comparative study of the physiochemical properties of six clinical low molecular weight gadolinium contrast agents. Contrast Media Mol Imaging. 2006; 1(3): 128-137.
[11] Deray et al. Safety of meglumine gadoterate(Gd-DOTA)-enhanced MRI compared to unenehanced MRI in patients with chronic kidney disease (RESCUE study). Eur Radiology. 2013;23:1250-1259.
[12] Maurer et al. Tolerability and diagnostic value of gadoterate acid in the genral population and in patients with risk factors; Results in more than 84,000 patients. Eur Radioplogy. 2012; 81:885-890.
[13] Herborn et al. Clinical safety and Diagnostic Value of the Gadolinium Chelate Gadoterate Meglumine (Gd-DOTA). Invest Radiol. 2007;42(1): 58-62
[14] Guerbet data
[15] Amet S et al. Prevalence of Nephrogenic Systemic Fibrosis (NSF) in dialysis patients: Final results of the Pro-FINEST study, Proc. Intl. Soc. Mag. Reson. Med. 21 (2013)
[16] Broome D et al Gadodiamide-Associated Nephrogenic Systemic Fibrosis: Why Radiologists Should Be Concerned, AJR:188 Feb 2007.
[17]http://kidney.niddk.nih.gov/kudiseases/pubs/kustats/
[18] Lencioni R et al. Transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol. 2012 Oct;35(5):980-5
[19] Xinaida et al. Validation of a Screening Instrument for Nephrogenic Systemic Fibrosis. Arthritis Care and Research 2013;65 (4) 637-642.