Study Title: Imaging Cardiac Amyloid Burden: A pilot Study Using F-18 Florbetapir Positron Emission Tomography

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IMAGING CARDIAC AMYLOID BURDEN: A PILOT STUDY USING F-18 FLORBETAPIR POSITRON EMISSION TOMOGRAPHY

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Study Type: Single Center Pilot Study

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Study Enrollment Period: February 2013 to October 2018

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ABBREVIATIONS USED:

Myocardial Blood Flow: MBF

Positron Emission Tomography: PET

Computed Tomography: CT

Myocardial perfusion imaging: MPI

Amyloid light chain: AL

Transthyretin amyloid: TTR

Senile systemic amyloidosis: SSA

New York Heart Association: NYHA

Intravenous: IV

SYNOPSIS

Title of Study: Imaging Cardiac Amyloid Burden: A Pilot Study Using F-18 Florbetapir Positron Emission Tomography

Planned Study Period: From 2Q2013 - 2Q2017

Study Objective(s)

Specific Aim: The *primary aim* of this pilot study is to determine whether amyloid deposits in the heart can be measured non-invasively by F-18 florbetapir (Trade Name: Amyvid) positron emission tomography (PET) in 30 individuals with documented cardiac amyloidosis and in 15 volunteers without cardiac amyloidosis.

A secondary aim of this study is to determine reproducibility of F-18 florbetapir uptake in the myocardium.

Planned Total Number of Study Centers and Location

Single study center in the United States

Design and Methodology

This is a single-center pilot study in subjects with cardiac amyloidosis. All subjects will undergo evaluation of myocardial amyloid burden using F-18 labeled florbetapir PET/CT, blood tests, 6 Minute Walk Test, and 24 hour urine collection. No more than 45 subjects (15 cardiac light chain amyloid subjects and 15 cardiac senile/TTR amyloid subjects, 15 volunteers without amyloidosis including 10 elderly subjects with clinical heart failure with preserved ejection fraction (HFpEF) without amyloidosis) will be enrolled into the study. After successful screening, subjects will undergo PET/CT scanning following one intravenous injection of 10 mCi of F-18 florbetapir. One set of F18 florbetapir images will be acquired in a 3D list mode starting with the injection of F-18 florbetapir for 90 minutes. Images will be unlisted and quantitation of radiotracer uptake performed. Mean and maximum F-18 florbetapir uptake will be measured. Radiotracer biodistribution in the liver and subdiaphragmatic regions will be measured. A total of 10 AL and 10 ATTR amyloid patients will undergo a repeat F-18 florbetapir PET scan within a month of the initial study (next day to one month).

Number of Subjects Planned

No more than 45 subjects will be enrolled into the study.

Main Selection Criteria

Subjects will be eligible if they meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria for amyloid subjects:

- Age > 18 years
- Biopsy proven amyloidosis outside the heart with typical echocardiographic appearance of cardiac involvement, or a positive cardiac biopsy.
- Diagnosis of AL amyloidosis by standard criteria (evidence of plasma cell dyscrasia with appropriate tissue staining for AL) OR
- Diagnosis of TTR amyloidosis (no evidence of plasma call dyscrasia and positive TTR staining of amyloid in tissue biopsy)
- Able and willing to provide informed consent to participate in the study
- 10 subjects with HFpEF age >70 years will be included in the control group.

Exclusion criteria for both amyloid and volunteer subjects:

- Pregnancy
- In the 10 subjects with HFpEF age >70 years, prior coronary artery disease, coronary revascularization or severe valvular heart disease
- Serious non-cardiac medical illness (e.g., disseminated malignancy, severe neurological dysfunction at time of baseline PET study) which will preclude research study participation

Statistical Methods:

This is a pilot feasibility study using F-18 florbetapir to image myocardial amyloid deposits. Mean and maximal myocardial uptake of F-18 florbetapir will be estimated in the subjects with diagnosed cardiac amyloid. Mean liver to heart ratio will be estimated.

I. BACKGROUND AND SIGNIFICANCE:

a) Introduction

Cardiac involvement is a common manifestation of light-chain (AL) amyloidosis and is a ubiquitous and predominant finding in senile systemic amyloidosis (SSA).[1] In AL amyloidosis, it is a major determinant of treatment options and prognosis[2] and in SSA, it is almost invariably the cause of death.[3] In amyloidosis with cardiac involvement, the coronary microvasculature is subject both to extrinsic compression and to direct deposition of amyloid within the vessel wall. The resultant abnormalities in coronary microvascular perfusion (the small vessels of the heart) may be responsible for the high incidence of sudden death in AL amyloidosis[4] and the high treatment-related mortality in AL patients with cardiac involvement undergoing high-dose chemotherapy with autologous stem cell transplant.[5] Microvascular ischemia can be diagnosed noninvasively using standard rest and stress nuclear imaging techniques utilizing isotopes such as sestamibi or thallium, or N-13 ammonia or rubidium-82. However, these tests involve use of stress testing with vasodilator stress which is not well tolerated by patients with amyloidosis particularly those with neuropathy. At this time, although we can measure myocardial ischemia as an effect of myocardial amyloid deposition and/or toxicity, we do not have the capability to assess myocardial amyloid burden directly.

A newly developed radiotracer F-18 labeled florbetapir has been recently approved by the FDA for imaging beta amyloid in the brain of patients with Alzheimer's' disease.[6-10] If these F-18 labeled florbetapir binds to cardiac amyloid protein, then the potential to quantify myocardial amyloid burden is available. Assessment of myocardial amyloid burden holds the potential for better understanding the nature of cardiac dysfunction and can potentially help assess response of therapy specifically targeted against amyloid production. Data from this pilot study will aid the principal investigator in designing a more definitive larger prospective multicenter study of cardiac amyloidosis, a rare disease, using F-18 florbetapir to estimate myocardial amyloid burden and follow response to therapy with novel therapeutic agents.

b) Previous studies leading up to or supporting the proposed research

F-18 florbetapir has been studied in multiple clinical trials to image beta-amyloid deposition in the brain of subjects with Alzheimers' disease.[6-10] Florbetapir F-18 has been well tolerated in studies of more than 2000 human subjects.[9-10] Biodistribution studies in humans revealed predominantly hepatobiliary excretion. The tracer clears rapidly from the blood pool in about 20 minutes (6). This radiotracer has been recently approved for clinical imaging of brain amyloid in subjects with suspected Alzheimer's

disease. In this pilot study, F-18 florbetapir images will be acquired immediately after injection and at 90 minutes after injection to study radiotracer bio-distribution and understand the optimal time for imaging.

Preliminary studies using C-11 labeled PiB (another agent used to image beta-amyloid in the brain of patients with Alzheimer's disease)[11] show that this tracer can be taken up by cardiac amyloidosis (unpublished data in abstract form from Uppsala University, Sweden). However, this tracer is produced by a cyclotron and has a short half-life of 20 minutes; hence it can only be used in sites with a cyclotron on site, limiting its applicability for multicenter studies. We propose to test a longer half life tracer, F-18 florbetapir in a pilot study to evaluate their potential utility to image cardiac amyloidosis. If this agents works, that will enable us to plan a large multicenter study of this rare disorder allowing us the potential to detect preclinical disease as well as follow response to therapy.

Amyloid related heart disease is associated with LV wall thickening due to infiltration; however, this myocardial wall thickening is not definitively distinguishable from left ventricular myocyte hypertrophy from increased afterload to the heart from hypertension or aortic stenosis. Typically myocardial or other tissue biopsy with typical echo features of amyloidosis is required for confirmation of amyloidosis. This pilot study is designed to understand whether we can measure cardiac amyloid burden using a specific radiotracer targeted against amyloid protein (F-18 florbetapir). The longer half-life (120 minutes) of F-18 florbetapir, makes it a more attractive tracer for conducting a multicenter clinical study, since this radiotracer can be delivered to sites without an onsite cyclotron. At this point it is unknown if F-18 florbetapir will bind to either AL or TTR amyloid protein or to both of them or to neither of them. Hence, we would like to study 15patients with AL, 15 patients with TTR amyloidosis and 15 volunteer subjects without amyloidosis [including 10 elderly subjects with clinical heart failure with preserved ejection fraction (HFpEF)] to understand these differences if any. We also seek to understand if the signal to noise ratio of the circulating amyloid protein in the blood pool (AL amyloid disease) allows for good differentiation of myocardial amyloid uptake.

The purpose of the proposed research study is to examine in detail, using quantitative PET, myocardial F-18 florbetapir uptake in cardiac amyloidosis in order to better understand mechanisms of heart damage in this disease. The following specific aim is proposed:

II. SPECIFIC AIM:

The *primary aim* of this pilot study is to determine whether amyloid deposits in the heart can be measured non-invasively by F-18 florbetapir (Trade Name: Amyvid) positron emission tomography (PET) in 10 individuals with documented cardiac amyloidosis and in 5 individuals without cardiac amyloidosis.

A secondary aim of this study is to determine reproducibility of F-18 florbetapir uptake in the myocardium.

III. SUBJECT SELECTION

a) Inclusion and Exclusion Criteria:

The main goal of this pilot study is to prospectively study myocardial amyloid deposition using quantitative F-18 florbetapir PET/CT in 30 subjects with cardiac amyloidosis and 15 volunteers without cardiac amyloidosis including, 10 elderly subjects with clinical heart failure with preserved ejection fraction (HFpEF) over a period of 2 years. A total of 10 AL and 10 ATTR amyloid patients will undergo a repeat F-18 florbetapir PET scan within a month of the initial study (next day to one month). Subjects will be eligible if they meet all of the following inclusion criteria and none of the exclusion criteria:

Main Selection Criteria

Subjects will be eligible if they meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion criteria for amyloid subjects:

- Age > 18 years
- Biopsy proven amyloidosis outside the heart with typical echocardiographic appearance of cardiac involvement, or a positive cardiac biopsy.
- Diagnosis of AL amyloidosis by standard criteria (evidence of plasma cell dyscrasia with appropriate tissue staining for AL) OR
- Diagnosis of TTR amyloidosis (no evidence of plasma call dyscrasia and positive TTR staining of amyloid in tissue biopsy)
- Able and willing to provide informed consent to participate in the study procedures
- 10 subjects with HFpEF age >70 years will be included in the control group.

Exclusion criteria for both amyloid and volunteer subjects:

- Pregnancy
- In the 10 subjects with HFpEF age >70 years, prior coronary artery disease, coronary revascularization or severe valvular heart disease

b) **Source of subjects and recruitment methods**

Patients will be recruited from the advanced heart failure group at the _____ Hospital and from the cardiology practice of Dr. _____, an expert in cardiac amyloidosis. Among them, stable and eligible patients meeting all inclusion and exclusion criteria will be invited to participate in this study and those who provide informed consent will be enrolled. Majority of the subjects with be enrolled from the clinical practice of Dr. _____, an expert in Cardiac amyloidosis.

IV. SUBJECT ENROLLMENT

a) Methods of enrollment including procedures for patient registration and or randomization

The following recruitment methods will be used:

- This is a pilot study of subjects with a rare disease. Typically these subjects are well characterized clinically in terms of their evaluation. Majority of the subjects will be recruited from the clinical practice of Dr_____and we will enroll normal volunteers from internet advertising (for example RSVP for health, clinicaltrials.gov, Craigslist). Dr. _____ will introduce the study to the subjects and those subjects that are willing to consider the study will be given the written informed consent for the study for review. Subjects' questions will be answered by Dr_____ and/or by Dr. _____. There will be no time restriction to sign the consent form or participate in this study. Subjects that express an interest will be evaluated and provided they meet all the inclusion and exclusion criteria, they will be considered for this study.
- Special attention will be paid to enroll women and minorities in the study, although equitable patient selection may be challenging in this pilot study of a rare disease in 25 subjects.

b) Procedures for obtaining informed consent (including timing of the consent process)

For subjects interested in the speaking to a study staff, Dr._____ will go over the inclusion and exclusion criteria and will describe the study and procedures to the potential subject over the phone or in person. If the subject qualifies and is interested he/she is encouraged to discuss the study with

his/her primary care physician or family members. Upon arrival for the study, the subject will be given a copy of the consent form to read. After the subject has finished reading the consent form, Dr. _____ will describe the study in detail and answer any questions or concerns the subject might have. If the subject agrees to participate in the study they will be asked to provide his/her written informed consent. Subjects will be given a copy of the signed consent form for their records. The investigator will inform the subject that they have the alternative not to participate in the study and can withdraw their consent at any point during the study.

The subjects will be given as much time as needed to consider participation in the trial. Pregnant women and minors are excluded from this trial. Subjects that are determined by the physician to be unable to consent due to their physical or mental condition will not be enrolled in this trial.

V. STUDY PROCEDURES

a. Screening/Study visit 1

a. The subjects that are interested in the study will discuss in person or on phone with Dr. _____and or Dr. _____and go over the consent form and details of study participation.
b. This screening visit will take about 1 hour. The research study team will ask the subject questions about medical history to make sure that the subject qualifies for this study. Pregnancy is not allowed due to the unknown risks radioactivity may have on the mother or the unborn baby from the beginning of the study period through the end of the study.

b. Study visit 2

The screening and study visit 1 can be conducted on the same day. Study visit 1 is for the performance of the rest F-18 florbetapir imaging study, 6-minute walk test, and 24 hour urine collection as described below. This visit will take about 2 hours, preparation time of 30 minutes, scan time of one and a half hours, and 6 minutes of walking. A blood pregnancy test will be performed on the day of the PET scan in women with child bearing potential, using 5 cc / one teaspoonful of blood. The research procedures will include intravenous injection of 10 mCi a radiotracer agent (F-18 florbetapir) followed by a ninety minute image acquisition. Three teaspoonfuls of blood will be drawn for florbetapir metabolite analyses.

b. Study visit 3

The study visit 3 can be conducted on the next day or within the next 30 days. Study visit 3 is for the performance of the rest F-18 florbetapir imaging study as described below. This visit will take about 2 hours, preparation time of 30 minutes, and scan time of one and a half hours. A blood pregnancy test will be performed on the day of the PET scan in women with child bearing potential, using 5 cc / one teaspoonful of blood. The research procedures will include intravenous injection of 10 mCi a radiotracer agent (F-18 florbetapir) followed by a ninety minute image acquisition. Two teaspoonfuls of blood will be drawn for florbetapir metabolite analyses.

Detailed Description of F-18 florbetapir PET/CT Methods: The proposed research will utilize the resources of the Cardiovascular Imaging center at Brigham and Women's Hospital, Boston MA. Specifically, PET imaging will be performed on a state-of-the-art 64 slice cardiac PET/CT unit.

Before the test: All patients will receive written instructions to have a light breakfast such as toast or cereal with coffee, tea or juice prior to their scan and to bring all their medications (including prescription, over the counter, dietary supplements, herbal and vitamins) with them. Upon arrival for the test, all patients are given a written questionnaire about allergies and possibility of pregnancy. Women of child bearing age will undergo a blood pregnancy test prior to the injection of F-18 florbetapir, as per laboratory protocol. Written informed consent for the study is checked and IV line inserted and the patient brought into the PET/CT room for imaging.

F-18 florbetapir PET/CT image acquisition:

A typical image acquisition protocol will include a CT scout image (10 mA, AP scout) to localize the heart followed by a CT transmission image (10 mA, 120 KVp, non-gated, free tidal breathing) for correction of photon attenuation by soft tissues, followed by injection of 10 mCi of F-18 florbetapir. F-18 florbetapir images are acquired in a 3D list mode for 90 minutes. Rest emission images will be unlisted for analysis into a static file, a gated file and dynamic image frames. The same protocol will be used for study visit 3. 2.5 cc blood samples will be drawn for metabolite analyses at 6 time points for the first 60 minutes.

Interpretation and quantification of F-18 florbetapir images:

The myocardial F-18 florbetapir images will be processed and viewed in the standard cardiac imaging planes. Visual assessment of relative myocardial uptake of F-18 florbetapir will be performed and scored using a 0-3 scale (0=normal, 1= mild uptake, 2= moderate uptake, 3=significant uptake). Myocardial uptake of F-18 florbetapir will be quantified using software on the Hermes system (image viewing station). Also, specific uptake values of the radiotracer in the myocardium will be computed.

6-minute walk:
Subjects will be asked to walk back and forth along a flat corridor between two markers set a distance apart at their own pace. The test takes 6 minutes and the distance that is walked will be measured.

Total Amount of Blood Drawn:

During the course of this research study, we will draw a total of 35-40cc of blood. This includes 10 cc of blood for oxidative stress markers (if subject provides additional consent), 15 cc of blood for florbetapir metabolite analysis, 10 cc of blood for metabolomics and mito DNA measures (if subject provides additional consent), 5 cc for pregnancy test (in individuals who need them). Pregnant women and breastfeeding women cannot take part in this research study.

Serum F_2-isoprostane and Peroxynitrite— 10 cc of blood samples will be collected in EDTA tube before the PET/CT scan of Study Visit 2 to measure serum markers of oxidative stress. F_2-isoprostanes will be measured in Dr. Jane Leopold's laboratory using serum isolated from whole blood collected with EDTA and stored at -80°C using immunoassay (8-isoprostane EIA kit, Cayman Biochemical). If needed, findings can be confirmed using mass spectroscopy. Nitrotyrosine levels will be measured in serum that is stored at -80°C by immunoassay (Nitrotyrosine EIA kit, Oxis).

Serum metabolomic analysis—10 cc of blood samples will be collected in EDTA tubes before the PET/CT scan of Study Visit 2 for metabolomic and mitochondrial DNA analyses.

Urine Samples: 24 hour urine sample will be collected. The urine samples will be deindentified by a study subject code and used to extract light chains that will be infused into zebra fish with or without pretreatment with rapamycin to study cardiac function and survival.

VI. BIOSTATISTICAL ANALYSIS

This is a pilot feasibility study using F-18 florbetapir. Mean myocardial uptake will be estimated in the subjects. Mean liver to heart ratio will be estimated.

VII. RISKS AND DISCOMFORT

Time: Participation in this trial entails a rest F-18 florbetapir PET/CT scan. The total time spent for the study procedures is approximately 2 hours.

Intravenous line insertion: Possible side effects intravenous line insertion are pain, bruising, or infection where the needle entered the skin. Some people faint or get dizzy during insertion of the intravenous line.

Radioactive imaging agents may have the following side effects: The radiation exposure to the subjects from the use of F-18 florbetapir is calculated to be at 7.93 mSv that is equivalent to about ~~19~~ 31 months of background radiation in Boston. In the 20 subjects undergoing reproducibility evaluation, the scan will be repeated in another day, with additional radiation exposure from the use of F-18 florbetapir of 7.93 mSv for a total study related radiation dose of (15.86 mSv). Other side effects include: headache, musculoskeletal pain, nausea and fatigue. Radiation exposure associated imaging is within acceptable safety standards as set forth by the FDA. Radiation may cause physical or genetic damage to a fetus, so subjects that are pregnant or breast feeding will be excluded. A pregnancy test will be performed prior to enrolling patients with childbearing potential.

Risks from 6-minute walk test: The risks and discomforts associated with this procedure are very similar to those that subjects would incur with exercising on their own.

In addition to the risks or discomforts listed above, the study drug and procedures may have unknown side effects. There is always the possibility that subjects will have a reaction that is currently not known or not expected. All drugs can cause an allergic reaction that, if not treated promptly, could be life-threatening. Symptoms of such a reaction are: throat tightness, itching, hives, wheals, vomiting, difficulty breathing or turning blue.

VIII. POTENTIAL BENEFITS

No direct benefit is anticipated to individual subjects. The results of this study may benefit society through evaluation of the diagnostic utility of a novel radiotracer for directly imaging myocardial amyloid burden in subjects with cardiac amyloidosis.

IX. MONITORING AND QUALITY ASSURANCE

Subject safety will be ensured by strict adherence to inclusion and exclusion criteria and close monitoring. Subjects that experienced serious adverse events during the study will be removed from the study and followed up, but no other study procedures will be performed. This study does not involve treatment and hence a data safety monitoring board.

This is a pilot clinical study of about 45 subjects (15 light chain AL amyloid, 15 TTR or senile amyloid, 15 volunteers without cardiac amyloidosis, including 10 elderly volunteers with HFpEF). The study PI, Dr. _____ will be responsible for monitoring the study procedures after every subject is enrolled, including the accuracy and completeness of the case report form entries, source documents and informed consent after every enrollment. These documents will be appropriately maintained on submission.

Specification of Source Documents

The following information will be included in the source medical records:

- Demographic data (age, sex, and race)
- Inclusion and exclusion criteria details
- Participation in study and signed and dated informed consent forms
- Visit dates
- Adverse events and concomitant medication
- Results of relevant examinations
- Laboratory printouts
- Reason for premature discontinuation

Ethical Conduct of the Study

The investigator(s) and all parties involved in this study will conduct the study in adherence to GCP, ICH Guidelines and the applicable laws and regulations.

Subject Confidentiality

The principal investigator will be responsible for oversight on maintaining subject confidentiality. All study staff are trained in Partners HIPAA procedures as well as in ethical conduct of research. Documents relating to the study that contain personal data that may disclose the identity of the subject will remain with the investigator and kept confidential in a locked cabinet accessible only to study staff. Subject

confidentiality will be maintained by utilizing subject identification code numbers to correspond to treatment data in the study computer files. All study center personnel will comply with privacy rules of this institution, the ICH guideline for good clinical practice, HIPAA and applicable state law. Subject confidentiality will be maintained by limiting access to data collected to only co-investigators, study staff. Data and specimens will not be stored at Partners or non-Partners sites for future uses not described in the protocol.

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