Cleveland Clinic Foundation

Department of Cardiovascular Medicine

STUDY PROPOSAL

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Title: The role of F-18 florbetapir in the early detection of transthyretin cardiac amyloidosis

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Background: The gold standard to diagnose cardiac involvement in amyloidosis is endomyocardial biopsy. Non-invasive diagnostic modalities have become more commonplace in the recent past. Echocardiography with strain imaging, cardiac MRI and technetium-99m pyrophosphate (TcPYP) nuclear SPECT scintigraphy are often used. TcPYP is a bone radiotracer that binds to calcium in amyloid fibrils and demonstrates myocardial uptake in cases of TTR amyloidosis only. This tracer is FDA approved for imaging in cardiac amyloidosis, yet it is a non-specific tracer with unclear sensitivity and specificity in early disease. In addition, there is no current nuclear tracer that can be used for AL amyloidosis.

Florbetapir F-18 is a radiotracer approved by the FDA for the use in positron emission tomography (PET) imaging of cerebral amyloid deposits for Alzheimer diseases. With regard to cardiac disease, one small study has confirmed the uptake of Florbetapir in both ATTR and AL cardiac amyloidosis.[1] Similar to Alzheimer disease, we postulate that Florbetapir will show improved detection of cardiac amyloidosis over conventional non-invasive imaging techniques, particularly in early disease.

Our hypothesis is that F-18 florbetapir will detect amyloid deposition in myocardium prior to current non-invasive diagnostic measures, particularly echocardiography with strain and technetium pyrophosphate scintigraphy. We intend to use Florbetapir to assess the correlation between the standard TcPYP scintigraphy with this novel imaging modality. Additionally, we would like to examine the ability of florbetapir to detect early cardiac involvement by imaging patients with extra-cardiac biopsy proven TTR amyloidosis.

Study Aim

1) To assess the role of Florbetapir in the early detection of cardiac amyloidosis.
2) To assess the correlation between TcPYP scintigraphy and F-18 florbetapir

Significance of the Study

This tracer is currently used for the early detection of brain amyloid (Alzheimer's disease). Early detection of Alzheimer disease is paramount, as treatment options are most beneficial when diagnosed early. Several recent studies support early amyloid detection by brain PET imaging using Florbetapir. This concept parallels the significance of this tracer in cardiac amyloidosis. As novel therapies evolve for cardiac amyloidosis, early detection of end organ involvement is essential as treatment options are most beneficial when started early. In addition, a non-invasive sensitive tracer will allow for monitoring of disease progression with treatment and may be used as a surrogate endpoint in future studies.

This study will allow us to identify the sensitivity and specificity of this tracer and compare it to technetium pyrophosphate. In addition, we can subsequently follow patients who have uptake of florbetapir in the myocardium to see if they develop clinical events such as new heart failure or echocardiographic findings to suggest presence of cardiac disease.

Methods

This is a prospective, study that will recruit patients at Cleveland Clinic.

Inclusion Criteria:

1. Patients with extra-cardiac biopsy proven AL or ATTR amyloidosis
2. Patients with a ratio of affected to unaffected free light chains >5 or free light chain difference of >50

Exclusion Criteria:

1. Echocardiographic evidence of cardiac amyloidosis with septal and posterior wall thickness ≥ 13mm
2. Contraindication to florbetapir or its components
3. Refusal to participate in the study

Control group:

1. We will also include 10 “control” patients without amyloidosis who had a negative extra-cardiac biopsy for amyloidosis.

Patients will undergo PET/MRI imaging with florbetapir. The result will be available clinically and released to the provider. Patients will be followed as above.

Logistics:

- The amyloidosis clinical research fellow will screen patients and contact them, notifying them of the study
- HVI clinical research nurse will consent patient at the time of regularly scheduled outpatient visit or TcPYP scan
- Patient will be scheduled for F-18 florbetapir PET
- Patient will undergo F-18 florbetapir PET
    - Radiotracer will be supplied without cost from Avid pharmaceuticals
    - Siemens PETNET will process the tracer in the on-site cyclotron. This is already being done at Cleveland Clinic for brain imaging in Alzheimer’s disease
- The study PI and co-investigator will interpret images

Sample size: We aim to enroll 40 patients, as Avid pharmaceuticals have agreed to provide us with 40 doses of florbetapir.

Data Analysis: Images will be interpreted by two experienced readers blinded to clinical data and TcPYP scintigraphy results. Image will be read with both semi-quantitative measures (17 segment model with uptake graded 0-4) and quantitatively (with segmental uptake values).

Patient Risk: There is risk carried by the radiation for the scan. Each F-18 florbetapir scan is dosed at 10mCi and estimated to deliver an equivalent dose of radiation of 7 mSv based on dosing for a 70kg person. Based upon the BEIR VII preferred model, overall cancer incidence given this amount of radiation per nuclear

scan for a 60 year old was calculated to be 0.034% for males and 0.062% for females. This was calculated using Table 12D-1 from the BEIR VII report (see appendix) which reports the incidence of cancer cases based upon 100mSv equivalent doses per 100,000 persons exposed. The lifetime risk for cancer mortality is 0.022% for males and 0.029% for females per scan using Table 12D-2.

In addition, there is a risk of adverse reaction. In one trial, one patient with AL amyloidosis currently undergoing chemotherapy developed nausea during the scan. [1] There were no reported adverse events in the other study. [2] In the FDA approval of florbetapir, there were "no serious adverse reactions in the studies and the reported adverse reactions were predominantly mild to moderate in severity."

Variables:

- Clinical variables will be collected including age, sex, race, BMI, hypertension, diabetes, hyperlipidemia, coronary artery disease
- Echocardiographic variables including LA/LV/RA/RV volumes, LV mass, anterior and posterior wall thickness, LVIDD, LVISD, EF, E velocity, A velocity, deceleration time, septal and lateral e`, RVSP, valve lesion severity, RV s`, RV FAC, LV and RV longitudinal strain
- Laboratory variables including CBC, CMP, troponin T and NT-proBNP
- Florbetapir-PET variables including segmental semiquantitative scores and SUVs

References:

1. Dorbala, S., et al., *Imaging cardiac amyloidosis: a pilot study using (1)(8)F-florbetapir positron emission tomography.* Eur J Nucl Med Mol Imaging, 2014. **41**(9): p. 1652-62.
2. Osborne, D.R., et al., *A routine PET/CT protocol with simple calculations for assessing cardiac amyloid using 18F-Florbetapir.* Frontiers in Cardiovascular Medicine, 2015. **2**.