Comparison of Ejection Fraction in Patients with Wild-Type Transthyretin Cardiac Amyloidosis with Mutant V122I Transthyretin Cardiac Amyloidosis

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A. i) Study Purpose and Rationale

Transthyretin (ATTR) cardiac amyloidosis is an insidious disease caused by extracellular deposition of a misfolded plasma protein known as transthyretin resulting in an infiltrative cardiomyopathy.[1] ATTR can result from a mutated variant of transthyretin, one of which is substitution of isoleucine for valine at position 122 (V122I) occurring almost exclusively in African-Americans, or wild-type variant leading to senile systemic amyloidosis (SSA) occurring predominantly in elderly men.[2, 3] Although believed to be a rare disease, studies reveal that about 4% of African-Americans are heterozygous for the V122I mutation and that up to 25% of the elderly have SSA found in autopsy studies.[1, 4-6] Due to the infiltrative nature of the disease, there are significant abnormalities in passive diastolic function, with progressive inability of the ventricle to perform work and biventricular heart failure. There are currently few definitive treatment options available, the mainstay being liver transplant and rarely cardiac transplantation in younger patients.

The prognosis in ATTR cardiac amyloidosis depends upon the severity of cardiac involvement which is related to the duration of disease. However, because of the indolent course of ATTR and its association with other common cardiac conditions among older adults including heart failure with a preserved ejection fraction and atrial fibrillation, diagnosis is often delayed and it is often difficult to ascertain the precise onset of disease. In addition, it is not known whether there are differences in various clinical markers of disease severity in subjects with wild-type and those with hereditary mutations, such as V122I, leading to cardiac amyloidosis. A significant difference in ejection fraction between the two groups may indicate the need to initiate treatment earlier in those patients who have one particular variant as opposed to another variant. [7-9]

A small study was performed with twenty-nine subjects with ATTR cardiac amyloidosis that indicated a small but significant difference in ejection fraction. In this study, eighteen with SSA and eleven with V122I mutation were studied with respect to various variables, such as stroke volume, end-diastolic volume and pressure and ejection fraction. All of the subjects with the V122I mutation had significantly lower ejection fraction despite presenting with presumably similar duration of disease (unpublished data). The average EF±SD was 61±8% in the SSA group and 49±8% in the V122I group, with a p-value of 0.0005. However, all of the subjects with the V122I mutation were also African-American and all of the subjects with SSA were Caucasian, making it difficult to separate the effects of race from the effects of having a particular genotype to account for the difference in ejection fraction. Given the promising preliminary results, the next step was to evaluate for a significant difference in the ejection fraction in a larger population, but focusing on one specific race to remove race as a confounder. Currently, there is an international database being created of patients with ATTR cardiac amyloidosis with recruitment from various clinical settings (ie, hospitals and outpatient clinics)

and in multiple nations. The database will include EKG, echocardiogram, Holter and laboratory findings. This study will utilize the data on ejection fraction within the African-American population in those who have either the wild-type or V122I mutation.

ii) Hypothesis

African-Americans with the V122I mutation will have a significantly lower ejection fraction compared to the African-Americans with SSA cardiac amyloidosis.

B. Study Design and Statistical Analysis

The study design is a cross-sectional retrospective study exploring the difference in ejection fraction between the SSA and V122I cardiac amyloid subjects at one time point. As mentioned above, the study subjects are drawn from a database of subjects entered internationally after confirmed genetic diagnosis of ATTR cardiac amyloidosis. The subjects will be drawn from different clinical settings, including hospital and outpatient clinics. See Study Subjects for detailed inclusion and exclusion criteria. Information in the database include laboratory markers of myocardial impairment such as troponin and BNP, arrhythmias on EKG and Holter monitors, and structural changes on echocardiography, with the focus in this study being ejection fraction. Standard 2-dimensional transthoracic echocardiograms with full Doppler studies were performed on each subject during their baseline visit. Two-dimensional guided M-mode measurements of systolic and diastolic chamber dimensions and wall thickness were obtained according to recommendations of the American Society of Echocardiography. Left ventricular end-diastolic and end-systolic volumes and left ventricular ejection fraction were calculated with the Simpson biplane method, which is EF = 100 × (LV diastolic volume – LV systolic volume)/ LV diastolic volume. To reduce variability, all echocardiograms are read by one echocardiography specialist. The genetic testing was performed after the echocardiograms were performed and the echocardiogram specialist is blinded to the results of the genetic test.

Results for ejection fraction are expressed as continuous variables with mean ± standard deviation. The raw data was then analyzed using the unpaired Student's t-test since there are 2 groups with a continuous variable and the two groups are not paired. The T-test will be used with the assumption that the data follows a normal distribution, ie Bell Curve, if there is a large enough sample size. In addition, a two-sided p-value will be used to determine the difference in EF between the two groups since we could not be absolutely sure that the EF will be lower in the V122I patients in this larger sample. Assuming that two-tailed alpha is 0.05 and power is 0.80, an analysis was performed to determine the number of subjects needed in each group to ensure a sufficient sample size was used to detect a difference if there was indeed a difference. The standard deviation was set to 8% within each group based on pilot study and the effect size of the difference in EF between the two groups that will be considered clinically relevant was arbitrarily set to 12%. There is a risk of having overlap between the two groups, which is a limitation of choosing an effect size that is not much larger than the standard deviation, but if the null hypothesis is false, there should still be a significant difference in EF between the two groups. Using the unpaired t-test, the number of subjects needed in each group to have a power of 80% is 7.1 or roughly 8 subjects.

C. Study Procedure

Patients will undergo 2-D echocardiography and have genetic testing to determine their

transthyretin protein genotype.

D. Study Drugs
Not applicable.

E. Medical Device
Not applicable.

F. Study Subjects
Inclusion criteria: Age greater than or equal to18 yrs. Subjects with ATTR cardiac amyloidosis associated with a V122I mutation or wild type transthyretin (SSA). Subjects had either a cardiac biopsy with amyloid determined by the presence of Congo Red or Alcian blue staining, immunohistochemical staining or mass spectrometry to detect serum TTR protein variants or non-cardiac biopsy confirming the present of ATTR amyloid in the presence of an echocardiogram consistent with the diagnosis of cardiac amyloidosis.

Exclusion criteria: Subjects were excluded from enrollment if they had confirmed primary amyloidosis (AL) or secondary amyloidosis (AA), potential that left ventricular hypertrophy that was secondary to hypertension or valvular disease and not amyloid as evidenced by absence of amyloid deposition on endomyocardial biopsy, prior liver or heart transplantation, prior non-amyloid cardiac disease such as myocardial infarction due to obstructive coronary artery disease, active non-amyloid cardiomyopathy or active malignancy.

G. Recruitment of Study Subjects
Subjects will be recruited by physicians at each site from various clinical settings, such as hospitals and outpatient clinics.

H. Confidentiality of Study Data
To ensure confidentiality of participants, all data will be coded a unique code number. Data will be stored in a secure location, accessible only to the investigators.

I. Potential Conflict of Interest
There are no potential conflicts of interest for the study investigators.

J. Location of Study
The study will be carried out at multiple centers across the world, including New York-Presbyterian Hospital Columbia Campus in New York City, Massachusetts General Hospital in Boston and sites in Europe.

K. Potential Risks
There are no potential risks to study participants except for those related to phlebotomy to obtain the genetic test. The 2-D echocardiogram has minimal risk, the risk being potential allergy to the lubricant used for the echo probe. The biopsies were performed prior to entering the study.

L. Potential Benefits

There are no benefits to the study subjects.

M. Alternative Therapies
There are no alternative therapies.

N. Compensation to Subjects
Patients will not be compensated for participation.

O. Costs to the Subjects
There will be no cost to patients.

P. Minors as Research Subjects
All patients below the age of 18 will be excluded from this study.

Q. Radiation
Subjects will not be exposed to any radiation.

R. References

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