A novel quantitative method for assessing the therapeutic response to Tafamidis therapy in patients with cardiac TTR amyloidosis. A preliminary report

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Abstract

Objective: Cardiomyopathy is a common manifestation of transthyretin amyloidosis (ATTR), leading to heart failure, associated with high morbidity and mortality. The aim of this study was to investigate the effect of Tafamidis treatment by means of cardiac radiotracer uptake on myocardial scintigraphy. **Subjects and Methods:** Five male patients, mean age 76.2 years, with wild-type ATTR were included in the protocol. Total body scanning using technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) (in four patients) and technetium-99m-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) (in one) was performed pre- and one year post-Tafamidis therapy. A novel quantitation method for assessing radiotracer cardiac uptake was employed. The geometric mean was computed for both cardiac and thigh region of interest (ROI) and the heart-to-thigh (HtT) ratio was assessed by dividing the corresponding geometric mean counts. **Results:** Heart-to-thigh ratio was improved (decreased) in four of the patients receiving Tafamidis, in keeping with lower uptake to the cardiac region. These patients also demonstrated a relatively favorable clinical response to Tafamidis. The patient evaluated by ^{99m}Tc-HMDP exhibited minimal HtT ratio reduction and stable clinical and echocardiographic characteristics. **Conclusions:** Sequential HtT ratio measurements could potentially identify patients with a favorable response to Tafamidis treatment at earlier stages, compared to other imaging modalities or serological biomarkers.

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Introduction

Transthyretin amyloidosis (ATTR) is an under recognized systemic disease, caused by deposition of abnormal fibrils derived from transthyretin, a protein mainly produced by the liver [1, 2]. Cardiomyopathy is a common manifestation of ATTR, leading to heart failure, associated with high morbidity and mortality [2]. There are two types of ATTR; hereditary ATTR, caused by variable mutations of the TTR gene and wild type ATTR in which increasing age leads to transthyretin instability and amyloid fibril formation [3].

Myocardial scintigraphy with bone avid tracers; technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) and technetium-99m-hydroxymethylene diphosphonate (^{99m}Tc-HMDP), holds a pivotal role for early ATTR diagnosis, with high diagnostic accuracy [4, 5].

Until recently, available treatment for ATTR aimed only in symptomatic relief. Tafamidis, a transthyretin tetramer stabilizer, represented a breakthrough for the therapeutic management of ATTR, conferring significant prognostic benefit in this population [6, 7]. Nonetheless, high costs associated with this treatment as well as recognized time delay before prognostic benefits arise, have raised the need for careful patient selection, both with regards to treatment initiation and its continuation.

Several observational studies utilizing cardiac magnetic resonance T1 mapping and extracellular volume measurements to assess cardiac amyloid burden reported disease stability under Tafamidis therapy [8]. To date no study has been conducted, investigating the effect of Tafamidis treatment by means of cardiac radiotracer uptake on myocardial scintigraphy.

Subjects and Methods

Five male patients, mean age 76.2 years, with wild-type ATTR were included in the proto-

pcol. Total body scanning using ^{99m}Tc-DPD (in four patients) and ^{99m}Tc-HMDP (in one) was performed pre- and one year post-Tafamidis therapy. A novel quantitation method for assessing radiotracer cardiac uptake was employed. Clinical, echocardiographic and laboratory data were also examined. The study was performed according to the declaration of Helsinki and all patients provided written informed consent for their participation to the study.

Quantitation of bone avid radiotracer uptake

Sequential scans were obtained at baseline and after one year of Tafamidis therapy. Patients were imaged 2 hours post intravenous injection of 740-925MBq (20-25mCi) of either ^{99m}Tc-DPD or ^{99m}Tc-HMDP. No previous patient preparation was necessary. All images were acquired using a large field of view, dual-headsingle photon emission computed tomography (SPECT) gamma camera (Discovery NM630, General Electric Healthcare, Chicago, IL) equipped with a Low Energy High Resolution collimator. Planar Total Body (TB) anterior and posterior images were initially acquired (256x1024 pixels, zoom 1.0) using a patient table speed of 10cm/min, in order to obtain at least 3 million total counts per view. Static anterior, posterior, left lateral (LLAT) and 45° left anterior oblique (LAO 45) thoracic images were then obtained (256x256 pixels, zoom 0.92, 750Kcts per view). A cardiac tomographic acquisition (180° rotation, 60 projections, 15sec/projection, matrix size: 64×64 pixels, zoom 1.4, pixel size 6.3mm) was finally performed on all patients.

Images were processed at a Xeleris 3 processing & review workstation. For the quantitation, rectangular regions of interest (ROI) incorporating the entire heart area were placed on both anterior and posterior TB images by the same investigator. Identical ROI were placed at the left mid-thigh region. Care was taken not to include any vertebral activity at the posterior cardiac ROI. The geometric mean was computed for both cardiac and thigh ROI and the heart-to-thigh (HtT) ratio was assessed by dividing the corresponding geometric mean counts. Pre and post therapy ratios were then compared.

Results

All five patients were evaluated after a year on Tafamidis therapy. Three patients reported improved functional capacity, reflected by downscaling of New York Heart Association (NYHA) classification, whereas the other two remained stable. Two patients achieved longer distance on follow-up 6-minute walking test. With regards to cardiac biomarkers, two patients demonstrated a decrease of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and three of them a decrease in high sensitive Troponin T. The remaining patients had stable or mildly increased cardiac biomarkers.

Echocardiographically, most of the patients demonstrated a relative improvement in left ventricular diastolic function as reflected by a reduction in E/E' ratio and three of them a mild increase in global longitudinal strain absolute values.

Heart-to-thigh ratio was improved (decreased) in four of the patients receiving Tafamidis, in keeping with lower uptake to the cardiac region. The highest ratio reduction was observed in a patient who improved both his NYHA class and exercise capacity. In this patient, NT-proBNP remained relatively stable, however high sensitive Troponin T value was halved. Echocardiographically, both diastolic function and global longitudinal strain were mildly improved. On the other end, the patient evaluated by ^{99m}Tc-HMDP exhibited minimal HtT ratio reduction, demonstrating stable NYHA class and mild deterioration in 6-minute walking test. All clinical, echocardiographic and laboratory data are depicted in detail at the attached Table 1.

Discussion

This is an observational study utilizing a new quantitation method for assessing the cardiac uptake of bone-avid tracers in ATTR amyloidosis, pre- and at one year on Tafamidis therapy. A reduction in the ratio of the geometric mean of the heart and thigh counts (HtT) was observed in the patients who also demonstrated favorable clinical response. A possible pathophysiological explanation for this observation is degradation of amyloid deposits via fibroblast induced endocytosis (endogenous clearance mechanism) following successful stabilization of transthyretin tetramers by Tafamidis [9]. Similar findings were observed in patients with hereditary ATTR following liver transplantation [9]. The patient in whom the ratio remained almost unchanged was the patient evaluated using ^{99m}Tc-HMDP. At this point, it is not clear whether this finding is due to lesser response to Tafamidis therapy or related to inherent characteristics of the utilized radiotracer.

In conclusion, this is a preliminary study, introducing a novel semiquantitative scintigraphic method to assess cardiac amyloid burden. Sequential HtT ratio measurements could potentially identify patients with a favorable response to Tafamidis treatment at earlier stages, compared to other imaging modalities or serological biomarkers. Introducing this concept may trigger further research interest in the utility of the above-mentioned index in larger cohorts of Tafamidis treated cardiac ATTR patients.

Limitations

The low number of ATTR patients is a major limitation rendering this study as a preliminary observation only. Nonetheless, this observation may be hypothesis generating and stimulate further research in this area.

The authors declare that they have no conflicts of interest.

Table 1. *Clinical, echocardiographic and laboratory data of wild type ATTR patients before and 1 year after Tafamidis therapy.*

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
Age	**81**		**74**		**76**		**73**		**77**	
	Baseline	1st year	Baseline	1st year	Baseline	1st year	Baseline	1st year	Baseline	1st year
NYHA class	III	II	III	II	II-III	II	II	II	II	II
NT-proBNP (pg/ml)	4338	1116	1829	1599	320	547	509	740	800	873
High sensitive-Troponin T (ng/L)	116	58	17	22	45	22	31	16	30	33
6-minute walking test (m)	220	320	403	380	500	580	522	480	450	455
Left ventricular ejection fraction (%)	45	40	50	53	48	52	66	69	53	54
Maximal wall thickness (mm)	18	18	17	17	18	18	16	15	12	12
LA area (cm^2)	27	30	37	36	29	28	25	26	26	27
LA volume index (ml/m^2)	61	50	54	53	43	37	30	40	42	45
E/E' ratio	33	19	24	24	17	15	24	18	13	9
GLS (%)	-12	-8	-7.8	-10	-8	-10	-16	-14	-11	-14
Radiotracer used	DPD	DPD	DPD	DPD	DPD	DPD	HMDP	HMDP	DPD	DPD
HtT ratio	4.2	3.49	6.05	5.5	8.24	6.11	5.37	5.33	5.66	4.88

ATTR: transthyretin amyloidosis, DPD: 3,3-diphosphono-1,2-propanodicarboxylic acid, GLS: global longitudinal strain, HMDP: hydroxymethylene diphosphonate, HtT: heart to thigh, LA: left atrial, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, NYHA: New York Heart Association

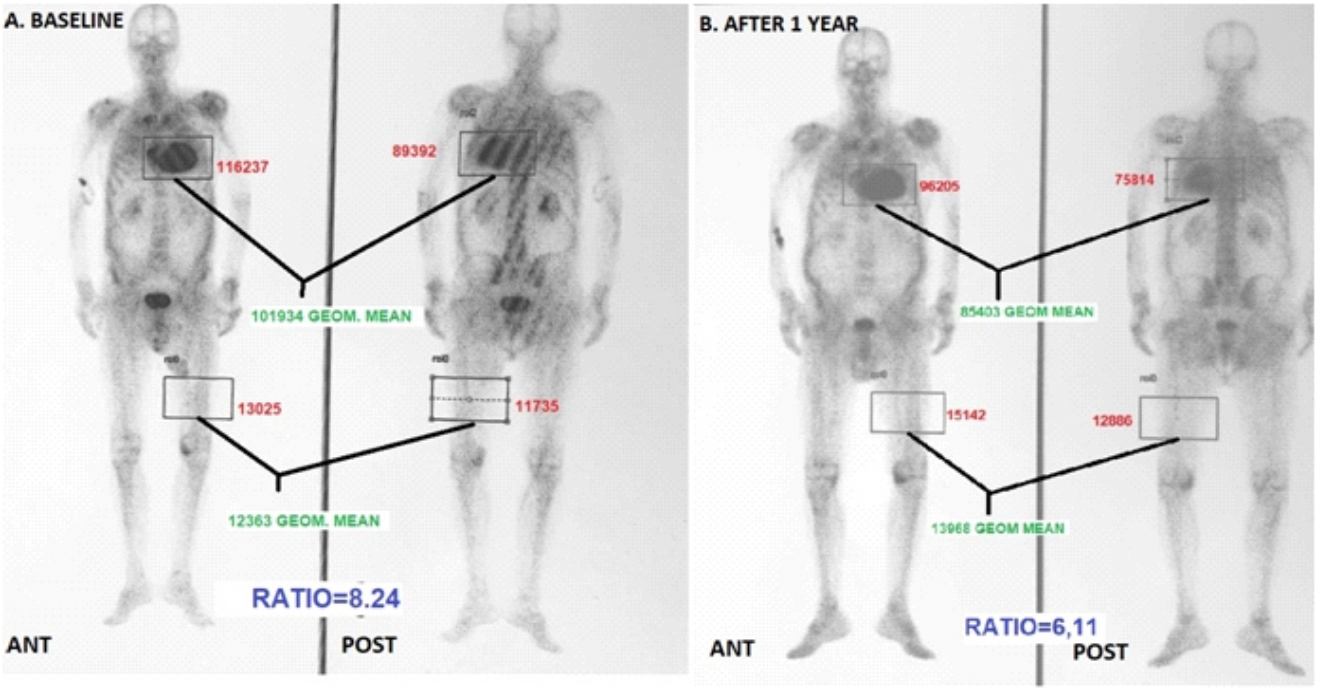

Figure 1. Myocardial scintigraphy with ^{99m}Tc-DPD in a patient with wild type transthyretin amyloidosis at baseline and after one year of Tafamidis therapy. The geometric mean was computed for both cardiac and thigh ROI and the HtT ratio was assessed by dividing the corresponding geometric mean counts.

Bibliography

1. Ruberg FL, Berk JL. Transthyretin (TTR) Cardiac Amyloidosis. *Circulation* 2012; 126:1286-300.
2. Ruberg FL, Grogan M, Hanna M et al. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019; 73: 2872-91.
3. Maurer MS, Bokhari S, Damy T et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. *Circ Heart Fail* 2019; 12: e006075.
4. Gertz M, Adams D, Ando Y et al. Avoiding misdiagnosis: expert consensus recommendations for the suspicion and diagnosis of transthyretin amyloidosis for the general practitioner. *BMC Fam Pract* 2020; 21:198.
5. Gillmore JD, Maurer MS, Falk RH et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation* 2016; 133: 2404-12.
6. Maurer MS, Schwartz JH, Gundapaneni B et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018; 379: 1007-16.
7. Zegkos T, Gossios T, Ntelios D et al. Wild type transthyretin amyloid cardiomyopathy. The Gordian-knot of novel therapeutic regimens. *Cardiol Rev* 10.1097/CRD.0000000000000427.
8. Shintani Y, Okada A, Morita Y et al. Monitoring treatment response to Tafamidis by serial native T1 and extracellular volume in transthyretin amyloid cardiomyopathy. *ESC Heart Fail* 2019; 6: 232-6.
9. Misumi Y, Ando Y, Gonçalves NP, Saraiva MJ. Fibroblasts endocytose and degrade transthyretin aggregates in transthyretin-related amyloidosis. *Lab Invest* 2013; 93: 911-20.