siRNA therapy improves multimodality imaging in hereditary transthyretin cardiac amyloidosis: a case report

Toru Awaya¹, Jin Endo ², Raisuke Iijima¹, Masayuki Shimoda ³, Masao Moroi¹

¹ Department of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan.
² Department of Cardiology, Keio University School of Medicine, Tokyo, Japan.
³ Department of Pathology, Keio University School of Medicine, Tokyo, Japan.

Corresponding author: Toru Awaya

Corresponding author at: Division of Cardiovascular Medicine, Toho University Ohashi Medical Center 2-22-36 Ohashi, Meguro-ku, Tokyo 153-8515, Japan

*Address correspondence to Dr T.Awaya, Division of Cardiovascular Medicine, Toho University Medical Center Ohashi Hospital, Tokyo, Japan.

E-mail: toru0228@gmail.com

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Learning points for clinicians

This case highlights small interfering RNA (siRNA) therapy in hereditary transthyretin amyloidosis and its post-treatment improvement through multimodality imaging, including $^{99m}\text{Tc}$-pyrophosphate (PYP) and $^{123}\text{I}$-metaiodobenzylguanidine (MIBG) scintigraphy. This is the first case report to recognize sympathetic reinnervation using $^{123}\text{I}$-MIBG scintigraphy. Scintigraphy may serve as a sensitive marker for siRNA treatment response.

Case presentations

A 78-year-old man was hospitalized for exacerbated heart failure. Electrocardiogram (ECG) revealed intraventricular conduction disturbances and low voltage in limb leads and the chest X-ray showed an enlargement. Transthoracic echocardiogram (TTE) revealed left ventricular hypertrophy and inferior region akinesis, with an ejection fraction (EF) of 30%. Blood tests showed elevated levels of high-sensitivity troponin T (hsTnT) at 0.042 ng/ml and N-terminal pro-brain natriuretic peptide (NT-proBNP) at 7041 pg/ml. Bone scintigraphy, $^{99m}\text{Tc}$-technetium-pyrophosphate ($^{99m}\text{Tc}$-PYP) (Symbia Intevo: Siemens Healthineers, Hoffman Estates, IL, USA), displayed diffuse uptake (Figure 1A). Coronary angiography (CAG) revealed proximal occlusion of the right coronary artery, necessitating a drug-eluting stent. Based on the ECG, TTE, and $^{99m}\text{Tc}$-PYP scintigraphy findings, cardiac amyloidosis was suspected, prompting a right ventricular endomyocardial biopsy. Pathological results confirmed the diagnosis of transthyretin (TTR) amyloidosis with Congo red-positive staining and immunohistochemical positivity for anti-TTR antibody (Figure 2). Genetic testing identified a Val30M mutation, confirming late-onset hereditary transthyretin amyloid cardiomyopathy (hATTR-CM). Treatment with small interfering RNA (siRNA) therapy (patisiran) was initiated. Eight months post-treatment, an implantable cardioverter-defibrillator (ICD) was implanted due to sick sinus syndrome, non-sustained ventricular tachycardia, and low EF (30%). One and a half years later, catheter ablation was performed for atrial fibrillation and flutter. Two years later, the siRNA therapy was switched from LNP-encapsulated siRNA (patisiran, first generation) to GalNAc-
conjugated siRNA (vutrisiran, second generation). No heart failure-related hospital admissions occurred post-siRNA therapy. Following treatment, $^{99m}$Tc-PYP scintigraphy, a tool for assessing amyloid deposition, showed decreased uptake (H/CL 1.98→1.83→1.72) (Figure 1A). Furthermore, cardiac sympathetic nerve damage, assessed by $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy, showed an improvement in the delayed H/M ratio (H/M 1.67→1.87→1.92) (Figure 1B). Cardiac MRI 1.5 T scanners (Ingenia, Philips Healthcare, Best, The Netherlands) indicated a decreasing trend in Native T1 values (Figure 1C). In contrast, NT-proBNP levels, hsTnT levels, or echocardiographic findings did not significantly change (Figure 1D).

**Discussion**

Hereditary transthyretin amyloidosis is a progressive and refractory disease caused by mutations in the TTR gene. Patisiran, an siRNA therapy, that inhibits the mRNA encoding the TTR gene and reduces amyloid deposition.$^1$ Patients receiving patisiran showed both less decline in their 6-minute walking distance and an improvement in their quality of life and overall health status, in contrast to the placebo group.$^2$

$^{123}$I-MIBG scintigraphy, previously indicative of sympathetic nervous system dysfunction in hATTR-CM, showed an improvement following patisiran treatment, a first in literature. H/M <1.6 is considered an adverse prognostic factor,$^3$ and in this case, it improved from 1.67 to 1.92 before and after patisiran treatment (Figure 1B). Moreover, a prediction model for 5-year cardiac mortality using $^{123}$I-MIBG imaging showed an improvement of 60% to 23%.$^4$

Recent reports have indicated that bone scintigraphy is a more sensitive marker for the response to patisiran treatment compared to conventional follow-up parameters. This study demonstrates reduced bone scintigraphy uptake in patients treated with patisiran, while NT-proBNP, hsTnT, and echocardiography parameters did not change.$^5$ Similar results were also observed in this case (Figures 1A and 1D).

Cardiac MRI showed valuable improvements in extracellular volume (ECV) after patisiran treatment.$^6$ In this case, ECV could not be measured due to chronic kidney
disease. Native T1, which does not require contrast agents, proves to be a highly valuable examination for patients like this case (Figure 1C).

In conclusion, NT-proBNP, hsTnT, and echocardiography parameters are valuable and less invasive tests. However, $^{123}$I-MIBG and $^{99m}$Tc-PYP scintigraphy may serve as more sensitive markers for evaluating the response to siRNA treatment. These methods are particularly effective in communicating the treatment efficacy to siRNA recipients.

Conflict of interest

None

Patient consent statement

Written informed consent was obtained from the patient for publication of the case and accompanying images.

A list of the definitions for any acronyms

small interfering RNA  siRNA

$^{99m}$Tc-pyrophosphate  $^{99m}$Tc-PYP

$^{123}$I-metaiodobenzylguanidine  $^{123}$I-MIBG

Electrocardiogram  ECG

Transthoracic echocardiogram  TTE

Ejection fraction  EF

high-sensitivity troponin T  hsTnT

N-terminal pro-brain natriuretic peptide  NT-proBNP
Transthyretin TTR
hereditary transthyretin amyloid cardiomyopathy hATTR-CM
Implantable cardioverter-defibrillator ICD
Extracellular volume ECV

References


Figure legends

Figure 1.

(A) $^{99m}$Tc-PYP scintigraphy, an assessment tool for amyloid deposition, revealed a decrease in uptake (H/CL $1.98 \rightarrow 1.83 \rightarrow 1.72$) (normal value $<1.3$ (3 hours later)) after siRNA therapy. (B) $^{123}$I-MIBG scintigraphy, an indicator of cardiac sympathetic nerve activity, showed an improvement in the delayed H/M ratio (using a standardized H/M) $(1.67 \rightarrow 1.87 \rightarrow 1.92)$ (normal range: 2.2–4.0) and washout rate (WR) $(50.5\% \rightarrow 46.4\% \rightarrow 41.7\%)$ (normal range: $< 34$). (C) Cardiac MRI exhibited a decreasing Native T1 trend after excluding artifacts caused by the ICD placement. (D) Trends in biomarker levels and transthoracic echocardiography before and after siRNA therapy.

siRNA, small interfering RNA; Tc-PYP, technetium-pyrophosphate; H/CL, heart-to-contralateral ratio; MIBG, metaiodobenzylguanidine; H/M, heart-to-mediastinum ratio; WR, washout rate; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; EF, ejection fraction; IVS, interventricular septal thickness; PWT, posterior wall thickness; LV, left ventricle; Dd, diastolic diameter; Ds, systolic diameter.

Figure 2.

Histological assessments were obtained from an endomyocardial biopsy specimen (original magnification $\times 20$). Hematoxylin and eosin staining (A) and Congo red staining (B) showed amyloid deposition in the myocardial interstitium. Under polarized light microscopy, the Congo red-stained amyloid was visualized as apple-green birefringence (C). Immunohistochemistry detected positive transthyretin staining (D), while neither kappa (E) nor lambda light chains (F) were detected.
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(A) 99mTc-PYP scintigraphy, an assessment tool for amyloid deposition, revealed a decrease in uptake (H/CL 1.98 → 1.83 → 1.72) (normal value <1.3 (3 hours later)) after siRNA therapy. (B) 123I-MIBG scintigraphy, an indicator of cardiac sympathetic nerve activity, showed an improvement in the delayed H/M ratio (using a standardized H/M) (1.67 → 1.87 → 1.92) (normal range: 2.2–4.0) and washout rate (WR) (50.5% → 46.4% → 41.7%) (normal range: < 34). (C) Cardiac MRI exhibited a decreasing Native T1 trend after excluding artifacts caused by the ICD placement. (D) Trends in biomarker levels and transthoracic echocardiography before and after siRNA therapy. siRNA, small interfering RNA; Tc-PYP, technetium-pyrophosphate; H/CL, heart-to-contralateral ratio; MIBG, metaiodobenzylguanidine; H/M, heart-to-mediastinum ratio; WR, washout rate; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; EF, ejection fraction; IVS, interventricular septal thickness; PWT, posterior wall thickness; LV, left ventricle; Dd, diastolic diameter; Ds, systolic diameter.
Histological assessments were obtained from an endomyocardial biopsy specimen (original magnification × 20). Hematoxylin and eosin staining (A) and Congo red staining (B) showed amyloid deposition in the myocardial interstitium. Under polarized light microscopy, the Congo red-stained amyloid was visualized as apple-green birefringence (C). Immunohistochemistry detected positive transthyretin staining (D), while neither kappa (E) nor lambda light chains (F) were detected.