CASE REPORT

Regression of left ventricular hypertrophy after tafamidis therapy in a patient with transthyretin amyloidosis variant

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Abstract : Transthyretin amyloidosis (ATTR) variant is a life-threatening hereditary disease predominantly affecting the peripheral nervous system and heart. Tafamidis, which prevents the deposition of amyloid by stabilizing transthyretin, is available for the treatment of neuropathy and cardiomyopathy of ATTR. However, whether tafamidis could eliminate established amyloid deposits and improve cardiac function remains unknown. We reported a case of regression of left ventricular hypertrophy after tafamidis therapy in a patient with an ATTR variant. J. Med. Invest. 69 : 320-322, August, 2022

Keywords **:** *cardiomyopathy, hereditary amyloidosis, hypertrophic hepertrophy*

INTRODUCTION

Hereditary transthyretin amyloidosis (ATTR), recently named ATTR variant (ATTRv), is a rare autosomal dominant, life-threatening disease predominantly affecting the peripheral nervous system and heart through the deposition of amyloid fibril derived from unstable transthyretin (TTR) produced by the liver. Physiological stable TTR plays a role in the transportation of retinol (vitamin A) and thyroxine (a thyroid hormone) ; however, unstable TTR due to gene mutation leads to the formation of amyloid fibril and its deposition. Tafamidis, which prevents the deposition of amyloid by stabilizing TTR, has been reportedly associated with not only delay in peripheral neurologic impairment but also a decreased incidence of cardiovascular events in patients with TTR cardiomyopathy (1, 2). Thus, tafamidis is available for patients with ATTRv to prevent neuropathy and/or cardiomyopathy, as well as the cardiomyopathy of wild-type ATTR in Japan (3). Tafamidis is a TTR stabilizer that selectively binds to TTR at the thyroxine binding sites and stabilizes the native tetramer of the TTR, thus slowing the dissociation of non-amyloidogenic tetramer into amyloidogenic monomers, leading to suppression of further deposition of amyloid. However, whether tafamidis could eliminate established amyloid deposits and improve cardiac function remains unknown. Here, we report a case of regression of left ventricular (LV) hypertrophy after tafamidis therapy in a patient with ATTRv.

CASE PRESENTATION

A 71-year-old man with no family history of heart disease complained of numbness in the extremities and walking difficulty due to peripheral polyneuropathy. The 12-lead electrocardiography showed low voltage and conduction abnormality with first-degree atrioventricular block. Echocardiography showed normal LV diameter with normal ejection fraction and severe anteroseptal hypertrophy. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement revealed positive area in the left ventricular epicardium (Figure A). Immunohistochemistry of the right ventricle revealed TTR deposition (Figure B). Genetic analysis revealed a mutation of Val30Met in the TTR gene, leading to a diagnosis of isolated ATTRv.

He was treated with 20 mg of tafamidis for polyneuropathy. Tafamidis treatment for nine months did not resolve his neuromuscular symptoms. However, echocardiography revealed regression of interventricular septal thickness compared to that before the therapy (22 : 18 mm) without changes in posterior LV wall thickness (10 mm) (Figure C, D), resulting in a reduction of LV mass index of 188 : 167 g/m^2, E/A ratio of 2.4 : 1.4 (Figure E), E/e' of 20 : 17, improvement of relative apical sparing of longitudinal strain (Figure F), and decrease in brain natriuretic peptide level of 648 : 527 pg/mL.

He was transferred to another hospital due to difficulty in hospital visit two years after tafamidis therapy and was hospitalized due to walking disturbance under tafamidis therapy.

DISCUSSION

It has been demonstrated that tafamidis treatment reduces all-cause death and the number of cardiovascular hospitalizations when compared with placebo in patients with ATTR cardiomyopathy (2). However, no significant regression of LV hypertrophy or increase of LV ejection fraction has been shown between the baseline and 30 months after tafamidis therapy evaluated by echocardiography. Tafamidis only reduces amyloid supply, which suppresses further deposition of amyloid. Thus, tafamidis theoretically is not able to eliminate established cardiac amyloid deposits. A regression of LV hypertrophy on imaging findings has been shown in the light-chain amyloid cardiomyopathy after stem cell transplantation (4). However, a small study showed that tafamidis decreased left ventricular mass index by ≧10% compared with that at baseline in six out of 15 hereditary

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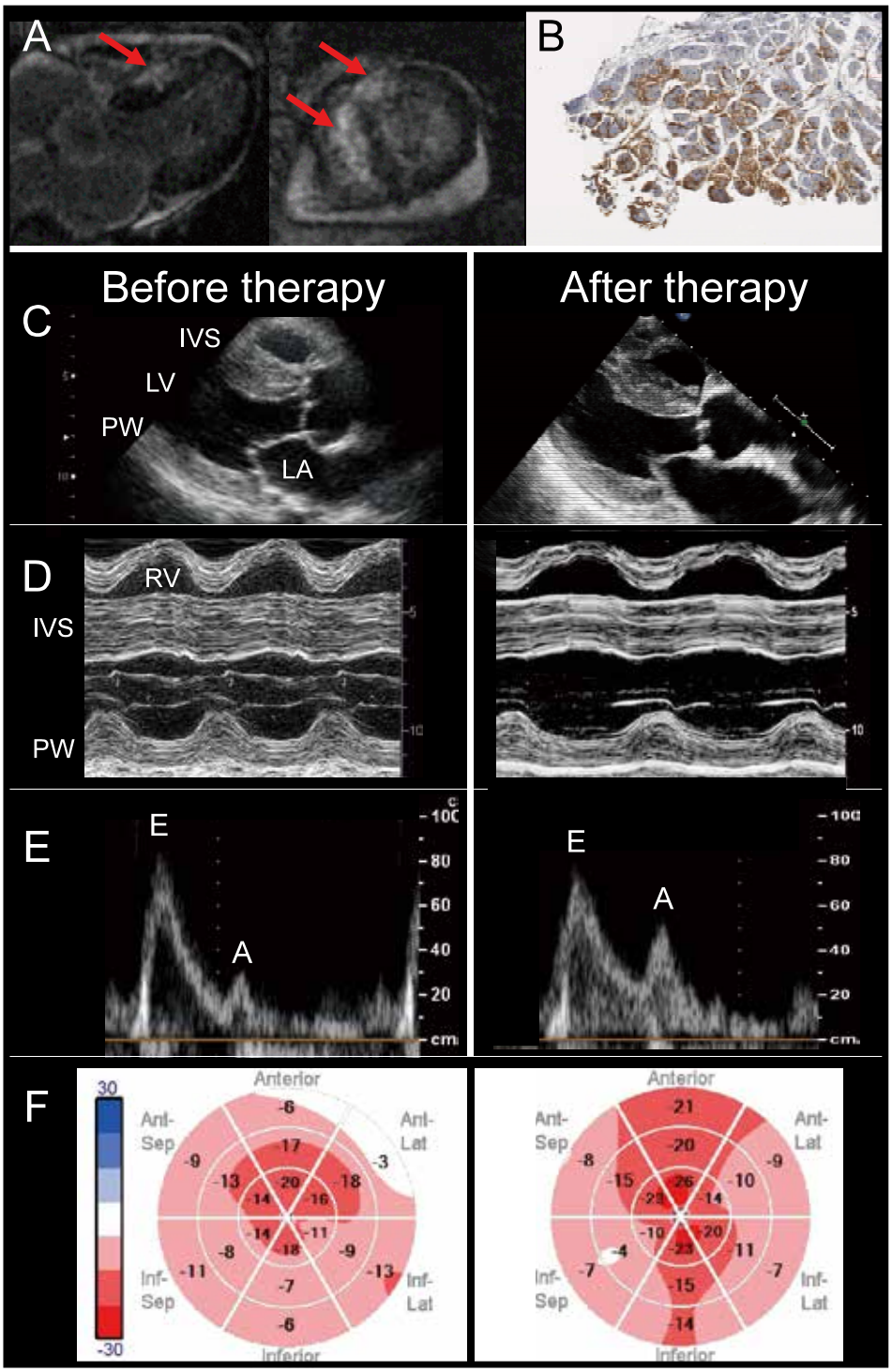

Figure.
A : Cardiac magnetic resonance imaging with late gadolinium enhancement indicating myocardial injury (red arrows indicate positive area in the left ventricular epicardium).
B : Immunohistochemistry with antibody for transthyretin of the right ventricle (brown area indicates the deposition of transthyretin).
C : B-mode images of echocardiography. LA, left atrium ; IVS, interventricular septum ; LV, left ventricle ; PW, posterior wall of the left ventricle.
D : M-mode images of echocardiography. RV, right ventricle ; IVS, interventricular septum ; PW, posterior wall of the left ventricle.
E : Doppler images of transmitral flow with echocardiography. E, E wave ; A, A wave.
F : Longitudinal strain images of echocardiography reflecting the deformation of the left ventricle in the longitudinal direction. Tafamidis treatment increased red area especially in LV anterior wall, indicating tafamidis treatment improved regional longitudinal LV systolic dysfunction.

ATTR patients evaluated by echocardiography (5). In addition, a case report showed a regression of LV wall from 15 to 14 mm and LV mass from 151 to 110 g evaluated by MRI after comprehensive therapy, including liver transplantation, inotensin (an antisense oligonucleotide inhibitor of the hepatic production of TTR), and tafamidis. These reports indicate that some cases are susceptible to tafamidis therapy regarding LV reverse remodeling. Tafamidis reportedly slows neurogenic disorder ; however, the neuromuscular symptoms were not improved by the therapy in this case. The susceptibility of tafamidis treatment may depend on the degree of organ damage. The mechanism of amyloid clearance has not been elucidated ; however, we speculated on the existence of some flux mechanism. A reversal in TTR flux (transfer/evacuation of unbound TTR from the myocardium to the intravasal volume) may occur due to tafamidis therapy (5). Tafamidis may induce an elimination of cardiac amyloid deposits, leading to regression of cardiac hypertrophy, which contributes to better outcomes in patients with ATTR. Cardiac MRI is a more accurate modality than echocardiography to evaluate cardiac hypertrophy, and troponin T/I are sensitive biomarkers for cardiac injury, which we could not follow-up. Further accumulation of cases of ATTRv treated by tafamidis is needed to evaluate the effect of tafamidis on regression of LV hypertrophy.

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