ABSTRACT

Transthyretin amyloid (ATTR) cardiomyopathy is a progressive disease caused by the infiltration of ATTR fibrils in the myocardium. Although it is a rare disease, ATTR cardiomyopathy is an important cause of heart failure with preserved ejection fraction, and its incidence is increasing due to improved diagnostic imaging tools. There has been a breakthrough in the field of transthyretin amyloidosis, which opens a new therapeutic door for the patients. In this review, an overview of tafamidis therapy in ATTR cardiomyopathy with recent results from clinical trials will be discussed.

Keywords: Amyloid; Cardiomyopathy; Restrictive; Tafamidis

INTRODUCTION

Transthyretin (TTR) amyloid (ATTR) cardiomyopathy is a progressive, fatal disease and is currently considered to be an underdiagnosed cause of heart failure (HF). The exact prevalence of ATTR cardiomyopathy is uncertain; however, its incidence is increasing due to improvements in the diagnostic imaging tools and therapeutic measures. ATTR cardiomyopathy is classified into 2 subtypes: hereditary and wild-type ATTR cardiomyopathy. The prevalence of hereditary ATTR, which occurs through autosomal dominant inheritance, varies according to the geographic regions. In endemic areas, some mutations are reported to range between 1 in 1,000,000 to 1 in 100,000. For wild-type ATTR, recent data suggest that in up to 10% of elderly patients with HF with preserved ejection fraction, the cause is wild-type ATTR cardiomyopathy. Tafamidis is a disease-modifying drug for the treatment of wild-type and hereditary ATTR cardiomyopathy, which terminates the amyloidogenesis of TTR protein by stabilizing TTR tetramers. This review will focus on the mechanisms of action and results of clinical trials with tafamidis.
DATA SELECTION

PubMed (1966 to December 2020) and ClinicalTrials.gov were searched using the following terms: tafamidis, Vyndaqel, and Vyndamax. Articles regarding tafamidis and ATTR cardiomyopathy were reviewed.

AMYLOIDOGENESIS OF TTR PROTEIN

TTR protein exists mainly as a tetramer, and each monomer is composed of 127 amino acids, forming extensive \( \beta \)-sheet structures. The TTR gene is located on chromosome 18, and the TTR protein is usually synthesized from the liver also produced by the choroid plexus and retinal pigmented epithelial cells. TTR proteins mainly transport the retinol-binding protein vitamin A complex and 15–20% of serum thyroxine. TTR protein is stable in its tetramer form, but when dissociated into unstable monomers, they undergo misfolding and aggregate into amyloid fibrils. Dissociation of tetramers into monomers is considered to be a rate-limiting process in TTR amyloidogenesis. A single mutation or aging process reduces the stability of TTR tetrameric forms and causes dissociations into the monomeric forms. Over 140 amyloidogenic mutations have been identified in hereditary ATTR, which are inherited as autosomal dominant traits with incomplete penetrance. In wild-type ATTR, the cause for dissociation of wild-type proteins into monomers and aggregation into amyloid fibril in the absence of mutations, is unknown; however, it is assumed to involve aging-associated oxidative stress. When TTR amyloid fibrils deposit into the organs, clinical manifestations are seen. In ATTR, the heart and nerves are mainly involved. In hereditary ATTR, the degrees of cardiac and nerve involvement vary according to the mutations. The common clinical presentation of ATTR cardiomyopathy is summarized in Table 1 and Figure 2.

CLINICAL PHARMACOLOGY

With the finding that TTR tetramers are kinetically stabilized by the binding of thyroxine or retinol-binding protein, attempts were made to develop small molecules that bind to TTR tetramers to prevent their dissociation into TTR monomers. These molecules are referred to as TTR stabilizers. Tafamidis is a TTR stabilizer that binds to the thyroxine-binding sites of TTR tetramers. Tafamidis is a member of the class of 1,3-benzoxazoles and

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**Figure 1.** Schematic diagram of TTR amyloidogenesis. Each monomer consists of 127 amino acids with 1 alpha helix and 8 beta strands. Tetrameric TTR protein has 2 binding sites in a central channel called the T4 pocket; however, the T4 hormone preferentially binds to only 1 of the 2 sites. Stability of TTR tetramers is reduced by mutation or aging processes. As a result, TTR tetramers dissociate into dimeric or monomeric forms. Unstabilized monomers undergo misfolding and aggregation, forming amyloid fibrils. ATTR = transthyretin amyloidosis; TTR = transthyretin.
Table 1. Clinical presentation of ATTR cardiomyopathy

| Clinical presentations                  | Echocardiography                                      | ECG                                      | Labs                                      | Cardiac presentation               | Extracardiac manifestation         |
|----------------------------------------|-------------------------------------------------------|------------------------------------------|-------------------------------------------|------------------------------------|------------------------------------|
| Unexplained increased in wall thickness (>12 mm) with non-dilated LV | Pseudo infarct-pattern or low voltage* | Mild increase in troponin levels on repeated occasions | Atrioventricular block in presence of increased LV wall thickness | Autonomic signs and symptoms (orthostatic hypotension, alternating constipation/diarrhea, sweating abnormalities) associated with peripheral neuropathy |
| Thickening of RV free walls, valves, or interatrial septum | | | Unexplained conduction block needing pacemaker | Musculoskeletal symptoms: carpal tunnel syndrome, particularly if bilateral, spinal stenosis |
| Small pericardial effusion             | | | Elderly HF with preserved ejection fraction refractory to conventional HF therapy | | |
| Reduced LV GLS with apical sparing pattern despite preserved ejection fraction | | | Intolerance to beta blocker, ACEi or ARB | | |
| ECG                                     | | | Self-improving hypertension              | | |
| Labs                                    | | | Low normal blood pressure with previous history of hypertension | | |
| Cardiac presentation                    | | | Restrictive hemodynamic profile          | | |
| Extracardiac manifestation             | | | *The 30% of ATTR cardiac amyloidosis meet low voltage ECG criteria of QRS amplitude less than 5 mm in limb leads or less than 10 mm in precordial leads. | | |

ACEi = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blockers; ATTR = transthyretin amyloidosis; ECG = electrocardiography; GLS = global longitudinal strain; HF = heart failure; LV = left ventricle; RV = right ventricle.

Figure 2. Clinical features of ATTR cardiomyopathy. A 47-year-old man visited the cardiology clinic complaining of dyspnea on exertion and bilateral pitting edema. The jugular vein was prominent. He had undergone surgery for bilateral carpal tunnel syndrome 3 years ago. He also complained of frequent episodes of diarrhea. The electrocardiography showed a pseudo-infarct pattern (A) and N-terminal prohormone brain natriuretic peptide was 3,600 pg/mL. Transthoracic echocardiography showed a thickened myocardium (15 mm at the septum), a relatively small left ventricle (end-diastolic dimension 45 mm), decreased e′ velocity (4.2 cm/s) with apical sparing of longitudinal strain (B-E). Cardiac magnetic resonance imaging revealed multifocal late gadolinium enhancement with subendocardial ring enhancement (F, G) Te-99m-3,3-diphosphono-1,2-propanodicarboxylic acid scan showed grade 3 cardiac uptake with increased radioactive uptake in the gastrointestinal tract as well (H). Gene analysis was performed, and Asp58Val mutation was discovered. He was diagnosed with ATTR with involvement of the heart, gastrointestinal tract, and peripheral nerves.

ATTR = transthyretin amyloidosis.
lacks non-steroidal anti-inflammatory (NSAID) activity. This is important because previous TTR stabilizers with NSAID activity, such as diflunisal, were associated with gastrointestinal, renal, and cardiac adverse effects. Therefore, they were not well-tolerated in HF patients with ATTR cardiomyopathy.\textsuperscript{15}\textsuperscript{16}

Tafamidis has a low toxicity profile and good oral bioavailability.\textsuperscript{15}

According to a healthy volunteer pharmacokinetic analysis, there is no metabolic induction or inhibition after the administration of tafamidis. The median time to reach the maximum concentration is 2 hours, and the mean half-life is 59 hours.\textsuperscript{13}\textsuperscript{16} Pharmacokinetics showed that similar renal excretion clearance between the groups with creatinine clearance <80 and >80 mL/min. In patients with moderate hepatic impairment, a 40% decrease in systemic exposure was observed, possibly due to the increased amount of unbound tafamidis.\textsuperscript{17}

Nevertheless, dosage adjustment is not necessary because TTR production from the liver is also decreased in patients with moderate hepatic dysfunction. Approximately 19% slower clearance was observed in subjects aged >65 years; however, dose adjustment is not required in elderly patients.\textsuperscript{15}

Tafamidis stabilizes both wild-type TTR protein and mutant TTR protein regardless of the mutant type. In wild-type TTR treated with tafamidis, a 73% decrease in the tetramer dissociation rate was observed, and the rate of dissociation showed a strong correlation with the concentration of tafamidis in plasma.\textsuperscript{13} A previous study with different mutation TTR protein variants showed that although TTR protein variants exhibited different thermodynamic and kinetic stabilities, tafamidis consistently stabilized TTR tetramers regardless of the mutation variability.\textsuperscript{13}

**CLINICAL OUTCOMES AND EFFICACY FROM PREVIOUS CLINICAL TRIALS**

The efficacy of tafamidis in ATTR cardiomyopathy was first described in 2019 as an open-label, single treatment arm study.\textsuperscript{10} In this phase 2 study, 35 patients with hereditary (n=4, Val122Ile mutations) and wild-type (n=31) ATTR cardiomyopathy patients were treated with 20 mg tafamidis for 12 months. TTR stabilization was the primary endpoint, and clinical outcomes, including mortality and hospitalization, were evaluated. After 6 weeks of tafamidis treatment, TTR was effectively stabilized in 30 of 31 patients. During the 12 months of the study, 22.6% of the patients were hospitalized due to cardiovascular events, and 2 patients died. N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels did not significantly increase during the study period. Troponin I and T were increased during the study period, and no clinically relevant echocardiographic changes were noted.\textsuperscript{19} Although
Tafamidis showed effective stabilization of TTR protein with generally good tolerability, the clinical benefits could not be adequately assessed due to the open-label design and short follow-up period.

In 2019, the results of the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial reported clinical benefits of tafamidis treatment in ATTR cardiomyopathy. A total of 441 patients with ATTR cardiomyopathy were randomly assigned in a 2:1:2 ratio to receive 80 mg of tafamidis meglumine, 20 mg of tafamidis meglumine, or placebo for 30 months. The primary endpoints of this multi-center, international, double-blind, placebo-controlled, phase 3 trial included hierarchial analysis of all-cause mortality and the frequency of cardiovascular-related hospitalizations according to the Finkelstein–Schoenfeld method. In this trial, patients with New York Heart Association (NYHA) class IV HF, estimated glomerular filtration rate less than 24 mL/min/1.73 m$^2$, liver enzymes exceeding twice the upper limit of the normal ranges, or patients with severe malnutrition (modified body mass index <600) were excluded. The median age of patients enrolled in the ATTR-ACT trial was 75 years, and the subjects were predominantly male (91% males in the tafamidis arm, 89% males in the placebo arm). Most patients had mild HF symptoms at baseline, with more than 50% of the enrolled patients classified as NYHA class II. Both arms included a higher proportion of wild-type ATTR cardiomyopathy than hereditary ATTR cardiomyopathy (76.1% and 75.7% in tafamidis and placebo groups, respectively). During the 30 months of follow-up, all-cause mortality was significantly lower in the tafamidis group than in the placebo group (Figure 4A) (29.5% vs. 42.9%; hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.51–0.96). Cardiovascular-related hospitalizations were lower (0.48 vs. 0.70 per year; 95% CI, 0.56–0.81) among patients treated with tafamidis. The number of patients required to be treated to prevent 1 event of all-cause death for 30 months of treatment was 8. Tafamidis also reduced the decline in the distance covered during the 6-minute test (mean±standard error [SE], 75.68±9.24) and a decline in the functional capacity, as measured by the Kansas City Cardiomyopathy Questionnaire–Overall Summary score (mean±SE, 13.65±2.13) (Figure 4B). The decrease in the distance covered during the 6-minute walk test and the reduced decline in functional capacity was seen as early as after 6 months of tafamidis treatment, while the reduction in all-cause mortality was observed after 18 months of treatment with tafamidis. In the subgroup analysis, the clinical benefit of tafamidis was consistent regardless of the TTR genotypes (hereditary vs. wild-type) or doses of tafamidis. Patients with baseline NYHA class III showed higher cardiovascular-related hospitalizations in the tafamidis group than in the placebo group. This finding is important. Since tafamidis is a kinetic stabilizer, it cannot reverse or reduce the already deposited TTR amyloid fibrils. Therefore, the clinical benefit of tafamidis is likely to be more profound in the earlier stages of ATTR cardiomyopathy. In this trial, the safety profiles of tafamidis meglumine 20 mg, 80 mg, and placebo were similar. Permanent discontinuation of tafamidis or placebo as a result of adverse events was more frequent in the placebo group. Previously reported adverse events in ATTR polyneuropathy patients taking tafamidis were diarrhea and urinary tract infection. In the ATTR-ACT trial, these adverse events were less common in the tafamidis group than in the placebo group. After 30 months of the study period, the ATTR-ACT trial was extended to investigate the optimal doses of tafamidis (80 mg vs. 20 mg). On completion of the 30-month double-blind study, patients were enrolled in a long-term extension (LTE) study and treated with tafamidis meglumine for an additional 60 months. Patients who had received placebo in the first phase of ATTR-ACT were re-randomized to receive either 80 or 20 mg tafamidis meglumine in the LTE (in a 2:1 ratio; stratified by TTR genotype [hereditary vs. wild-type ATTR]). All-cause mortality with tafamidis meglumine 80 mg compared with...
20 mg was assessed over a longer duration of treatment by combining data from the ATTR-ACT (median follow-up 30 months) with LTE (median follow-up, 51 months). Patients who were assigned to tafamidis meglumine 80 mg were significantly older, had more advanced NYHA class, higher NT-proBNP levels, and more functionally advanced HF than patients who were assigned to tafamidis 20 mg. All-cause mortality vs. placebo was reduced with tafamidis meglumine 80 mg (HR, 0.690; 95% CI, 0.487–0.979; p=0.038) and 20 mg (HR, 0.715; 95% CI, 0.545–1.04; p=0.156). There was a significantly greater survival benefit with tafamidis meglumine 80 mg than with tafamidis 20 mg (HR, 0.700; 95% CI, 0.501–0.979; p=0.0374). After adjustment for age, NT-proBNP, and 6-minute walk test, the survival benefit was greater in patients treated with tafamidis meglumine 80 mg (43% after adjustment of all covariates vs. 30% without adjustment).22 In the LTE study, tafamidis meglumine 80 mg and 20 mg were generally well tolerated and had a comparable safety profile. No patients required reduction in doses due to treatment-emergent adverse events.

Based on the ATTR-ACT and LTE studies, the recommended dosage for ATTR cardiomyopathy is tafamidis meglumine 80 mg (Vyndaque®, 4 tablets of 20 mg capsule) orally once daily or tafamidis 61 mg (Vyndamax®, one 61 mg capsule) orally once daily.23 Tafamidis
61 mg is a new, single capsule formulation bioequivalent to tafamidis meglumine 80 mg and was developed for patient convenience. In the LTE study, patients receiving tafamidis meglumine 80 mg were transitioned to tafamidis 61 mg after July 2018.

**SAFETY PROFILE**

Tafamidis is generally well-tolerated. There was a concern that tafamidis might decrease the serum concentration of total thyroxine; however, there has been no report of hypothyroidism in patients taking tafamidis.\(^5\) Most of the adverse events reported in the previous clinical trials in both ATTR cardiomyopathy and polyneuropathy are similar to the symptoms of the underlying disease. This is also reflected by the higher incidence of treatment-related adverse events in the placebo group in the ATTR-ACT trial.

**CONCLUSION**

Tafamidis is currently the only approved drug by the United States Food and Drug Administration to treat ATTR cardiomyopathy. Tafamidis is generally well tolerated, and the clinical benefits are more significant in patients with mild HF symptoms, which highlights the importance of early diagnosis and treatment. Although tafamidis 61 mg (Vyndamax\(^)\) is not yet available in Korea, patients with ATTR cardiomyopathy can finally be treated with evidence-based medication that can change the prognosis of the disease. In addition, there are other disease-modifying drugs that are likely to benefit patients with ATTR cardiomyopathy. The emerging drugs suppress TTR protein synthesis in the liver through small interfering RNA (Patisiran)\(^24\) or antisense oligonucleotide (irinotecan).\(^25\) These drugs are in the final phases of clinical trials. Along with tafamidis, the upcoming promising agents will offer more therapeutic options for patients with ATTR cardiomyopathy.

Since ATTR cardiomyopathy is a progressive disease, the current article explored the long-term cost-effectiveness of tafamidis for treatment.\(^26\) Based on prices in the United States, treating all eligible ATTR cardiomyopathy patients with tafamidis (estimated n=120,000) was estimated to increase the annual healthcare spending by $32.3 billion.\(^26\) On analyzing whether the efficacy of tafamidis could be limited by the high costs, it was concluded that a 92.6% price reduction would be necessary to make tafamidis cost-effective at $100,000/quality-adjusted life-year. Despite concerns, tafamidis is a breakthrough in treating patients with ATTR cardiomyopathy; it has good tolerability and proven clinical benefits.

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