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EDITORIAL



# Novel drug therapies for cardiac amyloidosis

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## 1. Introduction

Amyloidosis is a heterogeneous group of diseases characterized by extracellular deposition of misfolded proteins in the interstitium of tissues, especially that of the heart, kidney, liver, and nervous system. Monoclonal immunoglobin light chain (AL) and transthyretin (TTR) are the common amyloid proteins that have a predilection to affect the heart. Cardiac deposition of these amyloid proteins leads to restrictive cardiomyopathy, manifested initially as heart failure with preserved ejection fraction and at later stages with reduced ejection fraction. Cardiac amyloidosis can also manifest as arrhythmias and heart block when the conduction system is involved or as myocardial infarction when the microvasculature is involved [1]. Patients with amyloid cardiomyopathy have a poor prognosis with a median survival of about 11 months for AL amyloidosis and 2.5–3.6 years for TTR amyloidosis (ATTR), without specific treatment for these entities [2]. Non-invasive cardiac imaging techniques with high sensitivity and specificity like technetium pyrophosphate nuclear imaging for ATTR [3] and cardiac magnetic resonance imaging (MRI) for all forms of amyloidosis [4] have improved our ability to make an early diagnosis of cardiac amyloidosis. Familiarity with the current and emerging treatment options for cardiac amyloidosis is important to the clinician.

## 2. TTR amyloid cardiomyopathy

TTR amyloid protein is either a mutant type as seen in hereditary or mutation TTR (ATTRm) amyloidosis or non-mutant (wild type) as seen in senile cardiac amyloidosis (ATTRwt). Transthyretin, also known as pre-albumin is a transport protein that normally transports thyroxin and retinol in the body. TTR is mainly produced by the liver and in its normal form exists as homo-tetramers. The tetrameric protein is susceptible to dissociation to monomers, and they misfold to form the amyloid fibrils [5]. Liver transplantation is curative in selected patients with ATTRm. In patients not amenable for liver transplantation and ATTRwt, reducing the synthesis of TTR in the liver and preventing the disassociation of TTR tetramers are currently the targets of novel drug therapies.

### 2.1. Emerging drugs to treat TTR amyloid cardiomyopathy

#### 2.1.1. Tafamidis

Tafamidis is a small benzoxazole-derived molecule that selectively binds to the thyroxine binding site of TTR, stabilizes the tetramer and prevents its disassociation into amyloid forming monomers by acting as a chaperone. Tafamidis is administered as an oral medication and has been approved in Europe for delaying the progress of peripheral neuropathy in hereditary transthyretin amyloid neuropathy. In The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT), a multicenter, double-blind, placebo-controlled, randomized control trial, the efficacy and safety of tafamidis was studied in patients with hereditary and senile TTR amyloid cardiomyopathy [6]. Of the 441 patients enrolled, who had a median age of 75 years, 264 received tafamidis (80 mg or 20 mg) and 177 were given placebo, and they were followed up over 30 months. Patients on tafamidis started showing improvement in survival after 18 months and by about 30 months follow-up had a 30% reduction in all-cause mortality and also a reduction in cardiovascular-related hospitalizations compared to placebo group. There was also lower rate of decline in functional capacity and quality of life in tafamidis group. Subgroup analysis showed the efficacy of 20 mg and 80 mg dose of tafamidis to be similar. Tafamidis patients with New York Heart Association (NYHA) class III symptoms had a higher incidence of cardiovascular hospitalizations compared to placebo. This study also showed that tafamidis is safe with no increase in adverse effects compared to placebo. Tafamidis is not yet approved by the FDA for use in TTR amyloid cardiomyopathy.

#### 2.1.2. Diflunisal

The mechanism of action of diflunisal is similar to tafamidis. Diflunisal, usually given at a dose of 250 mg twice a day, is a non-steroidal orally active anti-inflammatory drug that binds to the thyroxine binding site of TTR and prevents the disassociation of TTR tetramer, thereby stabilizing it [7]. Despite diflunisal showing improvement in left ventricular apical rotation and torsion with preservation of longitudinal strain [8], reduction in left ventricular wall thickness, and increase in ejection fraction [9] in smaller studies, there are no published

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phase 3 trials on its efficacy and safety in TTR amyloid cardiomyopathy.

#### 2.1.3. Patisiran

Patisiran is a hepatically directed lipid nanoparticle containing double-stranded small interfering ribonucleic acid (RNA), which binds to the 3′-untranslated region of the transthyretin messenger RNA (mRNA) and leads to the cleavage of the mRNA. This results in a dose-dependent reduction in TTR levels with a median reduction of 81% in 18 months. Patisiran is administered at a dose of 0.3 mg per kg body weight, injected intravenously over 80 min, once in 3 weeks. In the Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis (APOLLO) trial, which is the largest phase 3 study of efficacy and safety of patisiran in treatment of ATTRm polyneuropathy, about 55% of patients had left ventricle thickness ≥13 mm at baseline in the absence of hypertension and aortic stenosis [10]. The patisiran group had a greater reduction in left ventricular wall thickness, left ventricular longitudinal strain, and N-terminal-pro beta – type natriuretic peptide levels compared to the placebo group. Cardiac adverse events and heart failure (HF) incidence were similar in both groups. Cardiac arrhythmias were less in the patisiran group compared to the placebo group (19% versus 29%). Although the all-cause mortality was 5% in the patisiran group and 8% in the placebo group, all the deaths in the patisiran group were from cardiac causes compared to none from cardiac causes in the placebo group. Patisiran has been approved for use in the European Union for treatment of ATTRm neuropathy, but the role of patisiran in treatment of TTR cardiomyopathy has not been studied in a randomized clinical trial yet.

#### 2.1.4. Inotersen

Inotersen is a 2′-O-methoxy ethyl antisense oligonucleotide that binds to the TTR mRNA in the liver and prevents its translation, thereby reducing the hepatic synthesis of transthyretin protein. Inotersen is administered subcutaneously as a weekly injection and has been shown to reduce the circulating TTR in a dose-dependent manner. At 13 weeks, the decrease in circulating TTR reaches a steady state with about 75% reduction from baseline levels with a 300 mg weekly dose of Inotersen. In the Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis (NEURO-TTR) randomized, double-blind placebo-controlled trial which studied the efficacy and safety of inotersen for treatment of peripheral neuropathy in hereditary TTR amyloidosis, about 60% of the 278 study patients had amyloid cardiomyopathy with either NYHA class I or II symptoms [11]. Over a 15 month follow-up period, the all-cause mortality in patients taking inotersen was 5% compared to none in the placebo group. Serious adverse drug effects of inotersen include severe thrombocytopenia and glomerulonephritis, each occurring in 3% of patients. Thrombocytopenia with platelet count less than 140,000 cells per $mm^3$ occurs in about half the patients taking inotersen. Nausea, pyrexia, chills, vomiting, and anemia are the other adverse events related to inotersen use. Although inotersen has been approved in Europe for use in patients with ATTRm neuropathy, it has not been studied in any phase 3 trials in ATTR cardiomyopathy.

## 3. Amyloid cardiomyopathy

Monoclonal immunoglobulin light chains are produced in excess in certain plasma cell dyscrasias such as multiple myeloma. The light chains deposit in tissues including the heart causing AL amyloid cardiomyopathy. The main treatment of AL cardiac amyloidosis is to treat the primary plasma cell dyscrasia. In selected patients, autologous stem cell therapy is the treatment of choice for AL amyloidosis. In patients who cannot undergo autologous stem cell therapy, various chemotherapeutic treatment regimens using medications such as cyclophosphamide, lenalidomide, thalidomide, melphalan, dexamethasone, and bortezomib [12].

## 4. Expert opinion

With newer medications showing promise for the treatment of ATTR cardiomyopathy, and with the increasing availability of technetium pyrophosphate nuclear scan as a highly sensitive and specific test for diagnosing ATTR amyloidosis, there should be an increased screening of appropriate patients with HF with preserved ejection fraction for the early diagnosis of TTR cardiac amyloidosis. With widespread use of technetium pyrophosphate nuclear scan, more patients with ATTR cardiomyopathy are likely to be identified. Use of cardiac MRI as a diagnostic modality for cardiac amyloidosis is also increasing, especially in the context of investigating left ventricular hypertrophy. Positron emission tomography (PET) imaging with 18F-Florbetapir and 18F-Florbetaben has also been studied for imaging cardiac amyloidosis in preliminary and small clinical studies [13,14]. These agents are primarily used for imaging amyloid deposits in brains of patients with Alzheimer's disease. Similar to MRI, these agents cannot differentiate between TTR and light chain amyloidosis in the heart. The utility of PET-MRI in the quantification of cardiac amyloid deposits still needs to be investigated.

At present, tafamidis is the only drug which has shown some benefit in the treatment of both hereditary and ATTRwt cardiomyopathy in a randomized control trial. Concerns regarding unfavorable outcomes in NYHA class III patients on tafamidis need to be addressed with further studies. Phase 3 randomized, placebo-controlled trials are yet to be conducted to study the efficacy of drugs such as diflunisal, inotersen, and patisiran in treating TTR amyloid cardiomyopathy. There are transgenic mouse model of mutant and wild type TTR which has been used for TTR polyneuropathy [15]. To the best of our knowledge, there are no animal studies that have been published which showed that these therapies can modulate cardiac TTR amyloid deposition. In the human trials with patisiran and inotersen used for neuropathy, there are secondary endpoints suggesting decreased ventricular hypertrophy and mass with the use of these agents versus placebo which would suggest that the decreased production of TTR results in a less cardiac deposition. These trials, however, were not powered to be conclusive in regards to cardiac disease. A single center, 24-month open-label study of the tolerability

and efficacy of inotersen in TTR amyloid cardiomyopathy patients has been designed and initiated in December 2018 by researchers at Brigham and Women's hospital, Boston, MA [16]. There is also an ongoing trial with an investigatory molecule AG10, for treatment of TTR cardiac amyloidosis [17]. All the current investigational drugs are aimed at reducing the production of amyloidogenic TTR, and none of these drugs are aimed at mechanisms for removal of the amyloid protein that has been already deposited in the tissues. Macrophages help in removal of the amyloid deposits from tissues, but it is a relatively slower process than the deposition of amyloid proteins in the tissues. Animal studies have shown the benefit of exploiting the tissue macrophage mechanisms for increasing the clearance of amyloid deposits in the brain [18]. Similar novel therapies directed at improving the rate of removal of amyloid deposits in the cardiac tissue in patients with amyloid cardiomyopathy need to be investigated.

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## Declaration of interest

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