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Transthyretin Cardiac Amyloidosis in Older Americans

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Abstract

Wild type transthyretin cardiac amyloidosis (ATTRwt), formerly called senile cardiac amyloidosis (SCA), is almost exclusively a disorder of older adults. As the population ages, the diagnosis of ATTRwt will increase making it the most common form of cardiac amyloidosis. An important precondition to reduce under-diagnosis and misdiagnosis is to maintain a high index of suspicion for cardiac amyloidosis. Several clues can be gleaned from the clinical history, physical exam, electrocardiogram and non-invasive imaging techniques. Nuclear scintigraphy agents using ^{99m}Tc-phosphate derivatives combined with assessment for monoclonal proteins are eliminating the need for tissue confirmation in ATTR cardiac amyloid. Morbidity and mortality from ATTRwt cardiac amyloid is high and the emergence of numerous therapies based on a biologic understanding of the pathophysiology of this condition including drugs to inhibit the synthesis of TTR, stabilize TTR, and degrade or extract amyloid provides new hope for those afflicted. This review will briefly cover the epidemiology, pathophysiology and clinical manifestations, as well as diagnostic strategies and treatment of older adults with ATTR cardiac amyloid.

Keywords

Transthyretin cardiac amyloidosis; geriatric heart failure; diagnostic strategies

INTRODUCTION

Amyloidosis is caused by unstable protein structures that misfold, aggregate and form amyloid fibrils leading to disruptions in organ function.[1] Two distinct types of transthyretin (TTR) amyloidosis that are known to have a predilection for the heart in patients of advanced age include wild type (ATTRwt), previously known as senile cardiac amyloidosis (SCA), [1, 2] and hereditary or mutant (ATTRm). Both cause restrictive cardiomyopathy, with thickened and stiffened ventricles that result in severe diastolic dysfunction.[1-5] ATTRwt cardiac amyloidosis is almost exclusively a disorder of adults

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over the age of 60 and represents a quintessential type of diastolic heart failure in the geriatric population.[6] This brief review focuses on increasing recognition of ATTRwt and ATTRm in older adults, including features that should elevate clinical suspicion for the condition, non-biopsy diagnosis and emerging treatment strategies.

EPIDEMIOLOGY

According to the US Census Bureau, the percentage of the population >65 years was ~12.4% in 2000 and is currently >26%. [7] Systemic light chain (AL) amyloidosis has been considered the most common form of systemic amyloidosis, but the diagnosis of ATTRwt and ATTRm cardiac amyloidosis are increasing because of the aging population and emergence of noninvasive diagnostic imaging technologies.[8] The most common mutation in the United States, the valine-to-isoleucine mutation at position 122 (Val122Ile), has a prevalence of ~4% in African Americans.[9] Cardiac involvement in ATTRwt was often a postmortem finding, considered to be a normal part of the aging process.[4] Using immunohistochemistry to identify the precursor protein, the prevalence of ATTRwt on autopsies in subjects 80 years old has been reported to be approximately 25%.[10] More recently, 32% of subjects with heart failure and preserved ejection fraction (HFpEF) 75 years old had TTR cardiac amyloid on autopsy, of which only 21% had a pre-morbid diagnosis of amyloid.[11] Multiple series of patients presenting to referral centers have found ATTRwt and ATTRm cardiac amyloidosis to be predominately disorders of older adult males.[6, 12, 13] However, using technetium scintigraphy to actively screen and identify subjects with TTR cardiac amyloidosis, 13% of subjects hospitalized with HFpEF and wall thicknesses 12 mm had ATTRwt cardiac amyloid, notably without gender differences, suggesting that both older adult men and women may be underdiagnosed.[14, 15]

The Transthyretin Amyloidosis Outcomes Survey (THAOS), the largest ongoing, global, multicenter, longitudinal, observational study has characterized differences in the disease course and outcomes in geographically dispersed patients with ATTR cardiac amyloidosis. In the United States, ATTRwt accounted for 48% of the ATTR cases, followed by the Val122Ile mutation which accounted for 23%. Of note, 85% of the Val122Ile patients in THAOS were from the United States. Outside of the United States, only 5% of patients had ATTRwt and 76% had ATTRm due to the Val30Met mutation.[16] Compared with ATTRm due to the Val122Ile mutation, subjects with ATTRwt were older (76 ± 7 vs. 69 ± 10 years) and almost exclusively male (97.4% vs. 75.8%). ATTRwt patients were mostly Caucasian (89.4%) while ATTRm Val122Ile patients were mostly of African descent (86.8%). These multicenter data confirm the marked racial differences that exist between those with ATTRwt cardiac amyloidosis and those with the Val122Ile mutation.[1, 11, 16]

PATHOPHYSIOLOGY

The TTR protein is a 127 amino acid structure rich in beta sheets and primarily synthesized in the liver.[17, 18] In its soluble state, TTR is a tetrameric complex made up of four single chain monomers of TTR. The primary function of the TTR tetramer is to carry thyroxine and retinol (vitamin A)-retinol binding protein complex. The prevailing theory for the

pathogenesis of TTR amyloidosis is that aging in ATTRwt or inherited mutations in ATTRm cause tetrameric TTR to dissociate into its monomeric subunits. These monomers misfold and aggregate into insoluble fibrillar structures that deposit in organs and tissues and eventually lead to organ failure. Distinct from AL amyloid where fibrils are toxic to myocardial cells, principally via the p38 MAPK signaling pathway[19], a toxicity of TTR has yet to be clearly elucidated.

Amyloid deposition in the myocardium resulting in heart failure is the leading cause of morbidity and mortality in patients with ATTR cardiac amyloidosis.[1, 8] Progressive left ventricular chamber dysfunction is mediated by physiologic derangements that include reduction in chamber capacitance, declines in chamber contractility and increases in arterial elastance, with resulting declines in the ventricle's ability to perform work.[20] ATTR cardiac amyloidosis has a similar echocardiographic appearance (Figure 1) as systemic light-chain cardiac amyloidosis (AL),[21] though wall thickness tends to be higher in ATTR than AL[22] despite a slower progression of disease in ATTR compared with AL. The worse survival in AL cardiac amyloid compared to ATTR cardiac amyloid has been attributed to the added toxicity of light chains to cardiomyocytes.[19, 23] Furthermore, ATTRwt cardiac amyloidosis appears to disproportionately afflict older adult men compared to women for reasons that have yet to be elucidated.

CLINICAL FEATURES AND PROGNOSIS

In the elderly patient with heart failure, several demographic, clinical, electrocardiographic (ECG), biomarker, and imaging characteristics should raise the suspicion for the diagnosis of cardiac amyloidosis, (Table 1), which has been underdiagnosed to date. First, demographically, ATTRwt cardiac amyloidosis predominately affects older men over 65 years of age.[6, 12, 13, 16, 21] While the vast majority of patients with ATTRwt and ATTRm Val122Ile had cardiac symptoms at presentation, those with ATTRwt had a higher incidence of rhythm disturbance (i.e. atrial fibrillation, sinoatrial block) than ATTRm due to the Val122Ile mutation (65.5% vs 32%). [16] ATTRwt is not typically associated with extra-cardiac organ involvement, although patients may present with a history of carpal tunnel syndrome or lumbar spinal stenosis that precedes a cardiac diagnosis by several years.[24, 25] Patients with ATTRm due to the Val122Ile mutation not only have a cardiac phenotype but may also have associated neuropathic and GI manifestations. In the Transthyretin Amyloid Outcomes Survey (THAOS), patients with ATTRm due to the Val122Ile mutation compared to ATTRwt had a higher incidence of gait instability (18.1% vs. 6.7%), gastrointestinal manifestations including diarrhea and/or constipation (18.9% vs 8.6%), neuropathic pain (33.8% vs. 12%), and urinary incontinence (4.1% vs. 0.6%), suggesting greater involvement of the peripheral and autonomic nervous system.[16] The third most common cause of ATTR cardiac amyloid in the United States reported in the THOAS registry is the Thr60Ala mutation (Appalachian mutation) which is associated with a greater degree of peripheral and autonomic involvement (Table 2)

Exercise intolerance is among the most common complaints expressed by patients with ATTR cardiac amyloidosis. Functional decline compounds risk associated with heart failure and results in diminished quality of life, increased frailty and higher mortality.

Cardiopulmonary exercise testing has shown that maximal oxygen consumption (VO_2max) was $13.5 \pm 4.9 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in ATTRwt, which is 54% of age predicted. The ventilatory equivalent ratio for carbon dioxide (Ve/VCO_2) slope, an index of ventilatory efficiency and predictor of mortality in heart failure, exceeded the upper limit of normal by $>35\%$. [6] The reduced VO_2max is mediated by severe diastolic dysfunction with an inability to augment stroke work with exercise as well as by significant chronotropic incompetence.

Progressive cardiac conduction system disease and cardiac autonomic dysfunction are common in ATTR cardiac amyloidosis. While low electrocardiographic voltage is widely considered a diagnostic marker of cardiac amyloidosis and has been linked with worse survival, its overall sensitivity is less than 30% and it cannot differentiate between amyloid subtypes. [26, 27] The absence of low voltage, therefore, should not preclude the diagnosis of ATTR cardiac amyloid. Instead, a low voltage-to-mass ratio, which can be expressed in a relatively complex way (voltage measured by Sokolow criteria and left ventricular mass defined as cross-sectional area [28]) or by a simpler ratio (total QRS voltage [sum of QRS voltages in all the ECG leads] divided by indexed LV mass (g/m^2)) [29] have demonstrated a higher sensitivity for identifying cardiac amyloidosis. [26, 29] A pseudo infarct pattern with pathologic Q-waves is also more sensitive than low voltage in identifying cardiac amyloidosis. [26] Relative to patients with AL cardiac amyloidosis, those with ATTRwt have a higher incidence of atrial fibrillation and atrial flutter as well as symptomatic bradyarrhythmias that may progress to heart block, which are rhythm disturbances most likely attributable to their older age. Subsequently, compared to patients with AL cardiac amyloidosis, those with ATTRwt cardiac amyloidosis have a higher incidence of permanent pacemaker placement, which is associated with worse survival compared to patients with ATTRwt without a pacemaker. [12]

Cardiac biomarkers (natriuretic peptides and troponin) are useful for both the identification of ATTRwt and ATTRm in the geriatric patient and for risk stratification. While elevated N-terminal pro-B-type natriuretic peptide (NT pro-BNP) and persistent low level troponin elevations due to myocardial apoptosis are features of all subtypes of cardiac amyloidosis, elderly patients with ATTRwt typically have lower NT pro-BNP compared with patients with AL cardiac amyloidosis. In one study, patients older than 70 years with an NT pro-BNP $<1420 \text{ pmol/L}$ were more likely to have ATTRwt relative to AL cardiac amyloidosis. [12] An elevated troponin in the absence of a clinical syndrome compatible with acute ischemia is often a clue to the presence of cardiac amyloidosis, as amyloid deposition in the myocardium causes apoptosis. In ATTRwt patients, using thresholds of troponin T (0.05 ng/ml) and NT-proBNP (3000 pg/ml), the respective 4-year overall survival estimates were 57%, 42%, and 18% for stage I (both values below cutoff), stage II (one above) and Stage III (both above), respectively. [30]

NON-BIOPSY DIAGNOSIS

Recently, single and multicenter studies of bone isotope imaging using the technetium ($^{99\text{m}}\text{Tc}$)-labeled bisphosphonates, pyrophosphate (PYP), 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), and hydroxymethylene diphosphonate (HMDP), have demonstrated excellent sensitivity and specificity for diagnosis of ATTR cardiac amyloidosis

and differentiation from AL cardiac amyloidosis (Figure 1).[31-36] Specifically, the diagnosis of ATTR cardiac amyloidosis is suggested by a score of 2 or 3 using the Perugini visual score of myocardial radiotracer enhancement (range 0-3: score 0, absent cardiac uptake and normal bone uptake; score 1, mild cardiac uptake, inferior to bone uptake; score 2, moderate cardiac uptake accompanied by attenuated bone uptake; score 3, strong cardiac uptake with mild/absent bone uptake). While endomyocardial biopsy and the use of mass spectrometry for tissue typing are considered the gold standard, in the context of advancements in diagnostic imaging, they may no longer be necessary.[35]

Using these imaging techniques, an algorithm for diagnosing elderly patients with ATTR cardiac amyloidosis has been proposed (Figure 2). An older adult with clinical, biomarker, ECG, echocardiographic, and/or cardiac magnetic resonance imaging suggestive of cardiac amyloidosis should first be offered patient-centered counseling about the risks and benefits of the diagnostic process that may lie ahead in order to advance their care. This may include counseling about further blood testing, nuclear imaging, genetic testing, and/or potential endomyocardial biopsy. Next, testing for AL cardiac amyloidosis with free light chain assay and serum/urine protein electrophoresis with immunofixation should be performed. Any patient with evidence of a monoclonal protein should proceed with tissue biopsy and typing, as AL amyloid can cause false positive myocardial uptake of technetium in some patients. A patient without evidence of a monoclonal protein may undergo bone isotope cardiac imaging, where diffuse myocardial enhancement and grade 2 or 3 uptake by Perugini score [31] is diagnostic of ATTR cardiac amyloidosis obviating the need for confirmatory tissue biopsy.[35] While the likelihood of hereditary ATTRm cardiac amyloidosis is low in an elderly white male, further genetic testing can differentiate ATTRm from ATTRwt cardiac amyloidosis, which has implications for genetic counseling of affected family members in patients screening positive for an inherited TTR mutation. Of note, there are a number of “non-pathologic” mutations, such as Gly6Ser, which are non-amyloidogenic. While bone isotope imaging can accurately differentiate ATTR from AL cardiac amyloidosis when there is no evidence of an abnormal monoclonal protein, it should be noted that up to 20% of patients with ATTRwt cardiac amyloidosis can also have a monoclonal protein, suggestive of an underlying plasma cell dyscrasia. In such patients, tissue biopsy with amyloid typing is required to definitively determine the type of cardiac amyloidosis (AL versus TTR).

MANAGEMENT

Heart failure in ATTR cardiac amyloid is managed with salt restriction and loop diuretics in combination with aldosterone antagonists. Often, loop diuretics with a higher potency or bioavailability (i.e. bumetanide or torsemide) are preferred, as many patients with ATTR cardiac amyloid have right sided heart failure which can result in gut edema and impair absorption of diuretics. For patients with advanced ATTRwt cardiac amyloidosis with hypotension and risk of syncope, midrodine may be employed. Angiotensin converting enzyme-inhibitors and angiotensin receptor blockers are often poorly tolerated due to concomitant autonomic dysfunction and risk of symptomatic hypotension.[3] High dose beta blockers are also poorly tolerated as the stroke volume in patients with cardiac amyloidosis is fixed and cardiac output is maintained by a physiologic increase in heart rate.[3] Non-dihydropyridine calcium channel blockers are contraindicated as they can bind avidly to

amyloid fibrils causing high-degree heart block and negative inotropic effects.[37, 38] Similar concerns have been raised about digoxin because it can cause cardiac rhythm disturbances and sudden death.[39, 40] Paradoxically, permanent pacemaker placement has been associated with an increased risk of long term adverse outcomes,[12] but this may be related more to the fact that conduction disease alone is a marker of advanced disease than the pacemaker. Prospective data are lacking regarding the use of implantable cardioverterdefibrillators (ICD) in ATTR cardiac amyloidosis, but in general, despite having significant burden of ventricular arrhythmias on routine monitoring, these patients do not usually die suddenly from ventricular arrhythmias. Therefore, concerns have been raised about the use of ICDs in this population. Placement of an ICD lead can also cause or worsen tricuspid regurgitation which could exacerbate an already difficult to manage restrictive cardiomyopathy.

Orthotopic heart transplantation (OHT) has been performed in selected patients with ATTRwt and ATTRm Val122Ile cardiac amyloidosis with improving outcomes in the modern era. [41, 42] However, OHT is rarely feasible as most patients are diagnosed at an advanced age and with comorbid conditions which are contraindications to cardiac transplantation. Cardiac amyloid is considered a contraindication to placement of a left ventricular assist device as the small ventricular chamber size and increased wall thickness makes such patients prone to suction events and amyloid deposition in the right ventricle predisposes to right ventricular failure. Limited data on left ventricular assist devices have shown higher rates of complications compared to those with a dilated cardiomyopathy [43] and increased mortality in subjects with ventricular chamber size less than 46 mm.[44]

There are emerging therapeutics that aim to inhibit synthesis of the TTR protein (silencers), stabilize serum TTR from breakdown into amyloidogenic monomers (stabilizers), or degrade and extract deposited amyloid fibrils (degraders and extractors). As outlined in Table 2, several compounds are in various phases of clinical development, but to date none of these agents are FDA approved for this condition. It is important to note that there has been a lack of animal models that recapitulate the human phenotype of TTR cardiac amyloid, which has placed more importance on non-invasive, repetitive imaging modality characterization of disease progression in a variety of clinical trials, as successful therapeutic application in a relevant animal model is limited.

TTR stabilizers have demonstrated efficacy in familial amyloid polyneuropathy (FAP)[45, 46], but their efficacy in ATTR cardiac amyloidosis is unknown. Diflunisal, FDA-approved as a non-steroidal anti-inflammatory drug, slowed neuropathy progression and improved quality of life in patients with FAP over 2 years but has risks of gastrointestinal bleeding, kidney injury, and heart failure exacerbation [47, 48] with conflicting studies regarding tolerance.[49, 50] Tafamidis is a TTR stabilizer that has no non-steroidal properties. In a phase 2 trial of subjects with senile cardiac amyloidosis, tafamidis effectively achieved and maintained TTR stabilization and was well tolerated. The absence of significant changes in most biochemical and echocardiographic parameters over a 12 month period was encouraging,[51, 52] and has led to a phase 3 trial that has completed enrollment with results anticipated in 2018.

Silencers consist of small ribonucleic acid (RNA) molecules that inhibit TTR protein synthesis.[53] Revusiran (ALN-TTRSc) is a specific small interfering RNA (siRNA) that is linked to the amino sugar galactose derivative, NAcetylgalactosamine (GalNAc) ligand. The GalNAc compound binds to the asialoglycoprotein receptor expressed on hepatocytes facilitating deliver of the siRNA to the liver which is the primary source of TTR production. Revusiran results in >80% knock down of circulating TTR.[54] Revusiran, delivered via subcutaneous injection, was being evaluated in patients with ATTRm but not ATTRwt cardiac amyloidosis in a phase III trial called ENDEAVOUR and in a phase II trial that included both ATTRm and ATTRwt subjects. The sponsor recently halted development of revusiran because of new onset or worsening peripheral neuropathy in the phase II trial and because of an imbalance in mortality between revusiran and placebo in the phase III trial, ENDEAVOUR. Notably, the drug, patisiran, a lipid nanoparticle formulation of an siRNA to silence TTR that is administered intravenously is being tested in a phase III clinical trial, APOLLO. Another silencer, IONIS-TTR-RX, is an antisense oligonucleotide, which is a synthetic peptide that binds directly to TTR messenger RNA and leads to its degradation by the endonuclease, ribonuclease H.[55] It is currently being tested in a phase II open label trial and a phase III investigation for neuropathy in patients with FAP, with potential for a future phase III trial in ATTRwt cardiac amyloid.

A third strategy under study is TTR degradation and extraction. Doxycycline disrupts fibril formation and when combined in an animal model with the bile salt, tauroursodeoxycholic acid (TUDCA), demonstrated a synergistic effect in removing tissue deposits of TTR.[56] A corresponding open label human clinical showed that historical controls had a greater percent decline in myocardial strain than subjects treated with doxycycline and TUDCA,[57] and while BNP increased after 12 months, those receiving treatment had no change in troponin I, interventricular septal thickness, ejection fraction or VO₂max.[58] Another strategy employs a proline-derived small molecule, R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC), that exploits the fact that all amyloid fibril deposits contain the non-fibrillar normal plasma protein, serum amyloid P component (SAP). CPHPC efficiently depletes SAP from the plasma but leaves some SAP in amyloid deposits, which can be removed when administering concomitant IgG anti-SAP antibodies, which incite an inflammatory multinucleated giant cell response. In a phase I trial, whole-body scans using iodinated SAP demonstrated depletion of hepatic amyloid in 50% of patients with liver involvement. Although patients with cardiac involvement were excluded from this trial, there were also reductions in the inflammatory markers, complement component 3 and C-reactive protein.[59]

Finally, 2 additional agents have demonstrated therapeutic potential. The molecule, AG10, was synthesized as a TTR stabilizer designed to bind the inner cavity and periphery of the thyroxine 4 binding site. It was shown to stabilize wild type TTR better than tafamidis and diflunisal in *in vitro* studies.[60] Tolcapone, an FDA-approved anti-Parkinsonian drug, was also recently studied for its ability to stabilize TTR. *In vitro*, tolcapone was also shown to bind TTR better than tafamidis, and *in vivo*, it had a stabilizing effect.[61]

SUMMARY

With the aging of the population, ATTRwt and ATTRm are likely to become the most common type of cardiac amyloidosis. ATTRwt and ATTRm cardiac amyloidosis can be diagnosed non-invasively (i.e. without histology) in patients with typical echocardiographic or cardiac MRI findings accompanied by grade 2 or 3 myocardial uptake on technetium pyrophosphate imaging and no evidence of a monoclonal protein. Morbidity and mortality from ATTRwt and ATTRm cardiac amyloidoses is high and the emergence of several therapies based on an understanding of the pathophysiology of this condition may provide alternate treatment strategies for those afflicted.

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Highlights

- TTR cardiac amyloidosis is the quintessential form of diastolic heart failure that almost exclusively affects older adults
- As the population ages, the diagnosis of ATTRwt will increase making it the most common form of cardiac amyloidosis.
- A high index of suspicion is critical for making the diagnosis of cardiac amyloidosis.
- Nuclear scintigraphy agents using ^{99m}Tc -phosphate derivatives combined with assessment for monoclonal proteins are eliminating the need for tissue confirmation in ATTR cardiac amyloid.

**Echo cannot
differentiate ATTR
from AL cardiac
amyloidosis**

**^{99m}Tc -PYP scan can
differentiate ATTR
from AL cardiac
amyloidosis**

Figure 1.
Imaging in ATTR and AL Cardiac Amyloidosis

Abbreviations: ATTR, transthyretin cardiac amyloidosis; ATTRm, mutant transthyretin cardiac amyloidosis; ATTRwt, wild type transthyretin cardiac amyloidosis; ECG, electrocardiogram; IFE, immunofixation; MRI, magnetic resonance imaging; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

Figure 2.
Proposed Diagnostic Algorithm for Older Patients with Suspected TTR Cardiac Amyloidosis

Table 1

Features that Should Elevate Suspicion for Cardiac Amyloidosis

Demographic	
✓	Age ≥ 60 years
✓	Male sex
Clinical history	
✓	HFpEF without hypertension
✓	Low flow aortic stenosis
✓	Carpal tunnel syndrome
✓	Lumbar spinal stenosis
✓	Intolerance to standard HF therapies (ACEi/ARB and Beta Blockers)
ECG	
✓	Low voltage or low voltage-to-mass ratio
✓	Pseudoinfarct pattern
✓	Heart block after the age of 55 years
Biomarker	
✓	Persistent low level troponin elevation without angina
✓	NT pro-BNP elevated out of proportion to HF syndrome
Imaging	
✓	Unexplained increased wall thickness
✓	Late gadolinium enhancement on cardiac MRI
✓	Apical sparing on echocardiography or MRI strain rate imaging

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; NT pro-BNP, amino-terminal pro-B-type natriuretic peptide; MRI, magnetic resonance imaging.

Table 2

Comparison of Most Common Type of ATTR Cardiac Amyloidosis in Americans

	ATTRwt	Val122Ile	Thr60Ala
Age			
Average	75	70	60
Age Range	65 and up	60 and up	45 and up
Gender	>90% Males reported to date	Male predominance	Equal
Ethnicity	Caucasian	Afro-Caribbean	Irish
Peripheral Neuropathy	+	++	+++
Autonomic Neuropathy	+	++	+++

TABLE 3

Ongoing trials

Drug	Trial Name	Mechanism of Action	Status	N	Primary Outcome	Anticipated Completion
Tafamidis	Open-label Safety And Efficacy Evaluation Of Fx-1006a In Patients With V122i Or Wild-type Transthyretin (TTR) Amyloid Cardiomyopathy (NCT00935012)	TTR Stabilizer	Enrollment completed	31	To obtain additional, long-term, open-label safety and efficacy data for tafamidis in patients with transthyretin amyloid cardiomyopathy	December 2021
Tafamidis	A Multicenter, International, Phase 3, Double-blind, Placebo-controlled, Randomized Study To Evaluate The Efficacy, Safety, And Tolerability Of Daily Oral Dosing Of Tafamidis Meglumine 20 Mg Or 80 Mg In Comparison To Placebo In Subjects Diagnosed With Transthyretin Cardiomyopathy (NCT01994889)	TTR Stabilizer	Enrollment completed	441	All-cause mortality and frequency of cardiovascular-related hospitalization	February 2018
Tafamidis	A Phase 3 Multicenter, Randomized, Double-blind, Extension Study To Evaluate The Safety Of Daily Oral Dosing Of Tafamidis Meglumine (Pf-06291826) 20 Mg Or 80 Mg In Subjects Diagnosed With Transthyretin Cardiomyopathy (NCT02791230)	TTR Stabilizer	Open only to those subjects who completed NCT01994889	330	All-cause mortality and incidence of treatment emergent adverse events	December 2021
Patisiran	APOLLO: The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the Treatment of Transthyretin (TTR)-Mediated Amyloidosis	TTR Silencer	Enrollment completed	225	Change from baseline of modified Neuropathy Impairment Score+7 (mNIS+7) after 18 months	July 2017
Revusiran	A Phase 2, Open-label Extension Study to Evaluate the Long-Term Safety, Clinical Activity, and Pharmacokinetics of ALN-TTRSC in Patients With Transthyretin (TTR) Cardiac Amyloidosis Who Have Previously Received ALN-TTRSC [NCT02292186]	TTR Silencer	Halted Development	25	Safety and tolerability of long-term dosing	Stop development
Revusiran	A Phase 3 Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ALN-TTRSC in Patients With Transthyretin (TTR) Mediated Familial Amyloidotic Cardiomyopathy (FAC) [NCT02319005]	TTR Silencer	Halted Development	206	6 Minute Walk Distance (6-MWD); Serum TTR levels	Stop development
IONIS TTR-Rx	Treatment of transthyretin cardiomyopathy with a TTR specific antisense oligonucleotide (IONIS-TTRx)	TTR Silencer	Recruitment complete	30	Safety and tolerability of the ASO compound.	2018
IONIS-TTR-RX	A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients With Familial Amyloid Polyneuropathy (NCT01737398)	TTR Silencer	Enrollment completed	172	Efficacy of IONIS-TTR Rx as measured by change from baseline in the modified Neuropathy Impairment Score +7 and the Norfolk Quality of Life Diabetic Neuropathy questionnaire	September 2017

Drug	Trial Name	Mechanism of Action	Status	N	Primary Outcome	Anticipated Completion
IONIS TTR-Rx	An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients With Familial Amyloid Polynuropathy (FAP) [NCT02175004]	TTR Silencer	Open only to those subjects who completed NCT01737398)	172	Types of adverse events that occur during treatment; change from baseline in blood pressure, heart rate, body weight, results of routine laboratory test panel, number of concomitant medications used, QTcF, visual acuity, and light detection ability	August 2020
IONIS TTR-Rx	An 18 Month Open Label Study Of The Tolerability And Efficacy Of An Antisense Oligonucleotide In Patients With Wild-Type Transthyretin Amyloid Cardiomyopathy (Semile Systemic Amyloidosis) (Phase 2) [NCT02627820]	TTR Silencer	On hold	50	Systolic strain imaging by echocardiographic speckle tracking	N/A