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Emerging Therapies for Transthyretin Cardiac Amyloidosis

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Abstract

Purpose of review Transthyretin cardiac amyloidosis is an underdiagnosed, undertreated disease which is associated with significant morbidity and mortality. This review will discuss the recent advancements in novel therapies for transthyretin amyloidosis.
Recent findings In recent phase 3 clinical trials, transthyretin stabilizers (tafamidis) and transthyretin silencers (patisiran and inotersen) have proven to be effective therapies for various forms of transthyretin amyloidosis.
Summary Understanding the recent and upcoming clinical trials for transthyretin amyloidosis will be important for improving the management of this challenging disease.

Introduction

Cardiac amyloidosis remains a deadly and often underdiagnosed disease [1]. Through a variety of mechanisms, precursor proteins can misfold and aggregate, leading to amyloid fibril formation and deposition in the myocardium. Gradual amyloid accumulation can cause restrictive cardiomyopathy, arrhythmias, and sudden death [2]. The two most common types of cardiac amyloidosis occur as a result of misfolded immunoglobulin light chain (AL) or transthyretin (ATTR). Over the past decade, significant advances have been made in treating AL amyloidosis. Plasma cell-directed therapies, such as proteasome inhibitors (e.g., bortezomib) and monoclonal antibodies (e.g., daratumumab), can often profoundly reduce the

deleterious plasma cell clone and thus the production of the amyloid-causing light chain [3–5]. These interventions can make a large difference in outcomes in patients at all stages of the disease, including those with significant cardiac involvement.

In contrast, until recently, there have been extremely limited therapies for ATTR amyloidosis. ATTR amyloidosis can arise from misfolding of wild type (wt) or mutant (m) transthyretin. ATTRwt cardiomyopathy is increasingly recognized as an important cause of heart failure with preserved ejection and is likely the most prevalent form of cardiac amyloidosis [6]. ATTRm amyloidosis typically occurs due to a single point mutation in transthyretin, has an autosomal dominant inheritance pattern, and can manifest with cardiac and/or neurologic involvement. ATTRm amyloidosis confers significant disease burden in specific subpopulations, such as African Americans, in whom 3–4% carry the V122I transthyretin mutation [7, 8].

The past few years has seen the rapid translation of extensive preclinical studies into effective treatments for ATTR cardiomyopathy and polyneuropathy as demonstrated by several recent positive phase 3 randomized controlled clinical trials. This review will explore these promising medications for ATTR amyloidosis and highlight additional therapies currently under development (Tables 1 and 2).

Transthyretin stabilizers

Transthyretin is a protein predominantly synthesized by the liver and functions as a transporter of thyroxine and retinol-binding protein. Its native structure consists of a homotetramer. Through incompletely described mechanisms, this structure can destabilize and dissociate into transthyretin monomers. These monomers are thermodynamically unstable and have an increased propensity to misfold, aggregate, and ultimately form amyloid fibrils. Consequently, tetramer dissociation represents the rate-limiting step in transthyretin amyloid formation. Comprehensive biochemical studies have identified several small molecules that are able to bind to the native transthyretin tetramer with high specificity and thus prevent tetramer dissociation and amyloid fibril formation (Fig. 1). The subsequent section will discuss the increasing clinical evidence that transthyretin stabilizers are effective in treating ATTR amyloidosis.

Table 1. Recent phase 3 ATTR clinical trials

Drug name (trial name)	Number of patients	Route	Primary outcome	FDA approval indication
Tafamidis (ATTR-ACT)	264 tafamidis (20 or 80 mg) 177 placebo	Oral	Lower rates of all-cause mortality and cardiovascular-related hospitalizations in the tafamidis group.	Wild-type and hereditary ATTR cardiomyopathy
Patisiran (APOLLO)	148 patisiran 77 placebo	Intravenous	Improvement in neurologic function in the patisiran group.	Hereditary ATTR polyneuropathy
Inotersen (NEURO-TTR)	112 inotersen 60 placebo	Subcutaneous	Less progression in neuropathy in the inotersen group.	Hereditary ATTR polyneuropathy

Table 2. Current and upcoming ATTR clinical trials

Drug name (trial name)	Drug class	Administration route	Trial type	Study population
AG10 (ATTRibute-CM)	Stabilizer	Oral	Phase 3	Wild-type and hereditary ATTR cardiomyopathy
Vutrisiran (HELIOS-A)	Small interfering RNA	Subcutaneous	Phase 3	Hereditary ATTR polyneuropathy
Vutrisiran (HELIOS-B)	Small interfering RNA	Subcutaneous	Phase 3	Wild-type and hereditary ATTR cardiomyopathy
AKCEA-TTR-L_{RX}	Antisense oligonucleotide	Subcutaneous	Phase 1/2	Hereditary ATTR polyneuropathy
PRX004	Monoclonal antibody against misfolded transthyretin	Intravenous	Phase 1	Hereditary ATTR cardiomyopathy and/or polyneuropathy

Tafamidis

Tafamidis is a small molecule stabilizer that was initially identified through a chemical library screen of benzoxazoles [9]. In vitro studies showed that tafamidis stabilizes the transthyretin tetramer under physiologic conditions and across a range of transthyretin mutations [10]. The first large clinical trial of tafamidis was a phase 2/3 study of patients with ATTR polyneuropathy. Patients ($n = 125$) were randomized to tafamidis 20 mg or placebo, and the

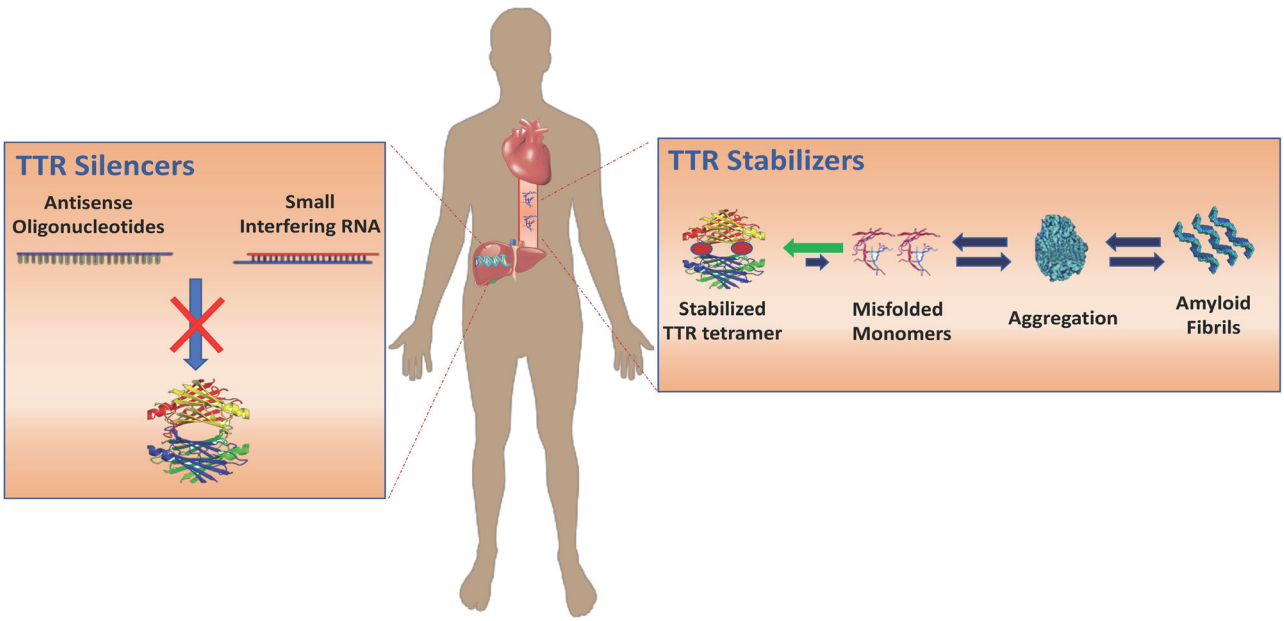

Fig. 1. Therapeutic targets for transthyretin amyloidosis.

primary endpoint was change in 2 polyneuropathy impairment clinical scores at 18 months. In the prespecified, intention-to-treat analysis, there was a statistically non-significant ($p = 0.068$) trend toward to more treatment responders in the tafamidis arm compared with placebo. Of note, a significant proportion of participants were on the liver transplant list at the time of study enrollment; 21% of patients underwent liver transplantation during the study and thus were counted as non-responders in the prespecified analysis. This high discontinuation rate significantly reduced the study's power to detect a statistical difference. Based on this trial, tafamidis was approved for treating ATTR polyneuropathy in Europe, Japan, and parts of Latin America, but not the USA [11].

Tafamidis was recently studied in ATTR cardiomyopathy patients in the Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) [12••]. ATTR-ACT was a relatively large ($n = 441$) phase 3 trial that randomized patients with ATTR cardiomyopathy to oral administration of placebo, 20 mg of tafamidis, or 80 mg of tafamidis in a 2:1:2 ratio. Of these study patients, 24% had ATTRm and 76% had ATTRwt. The primary endpoint was a composite of all-cause mortality and cardiovascular-related hospitalizations at 30 months. These endpoint components were assessed in a hierarchical manner using the Finkelstein-Schoenfeld method. Both all-cause mortality and cardiovascular-related hospitalizations were significantly lower in the tafamidis group compared with placebo (29.5% vs. 42.9%; 0.48 per year vs. 0.70 per year, respectively).

The reduction in mortality was observed as early as 18 months, and the number needed to treat to prevent death in 30 months was 7.5. In the subgroup analyses, both the 20 and 80 mg doses of tafamidis appeared effective. Tafamidis was well tolerated and had a similar incidence of adverse events compared with placebo. Less severe heart failure symptoms at baseline (i.e., New York Heart Association class 1 or 2) were associated with not only better outcomes but also a larger tafamidis treatment effect, compared with NYHA class 3 symptoms. This finding suggests that tafamidis may be more effective in patients in earlier stages of the disease. Based on these trial results, tafamidis has been approved for use in ATTR cardiomyopathy in Japan and in the USA.

AG10

AG10 is another transthyretin stabilizer currently being studied in ATTR cardiomyopathy patients. AG10 was first identified using a high-throughput chemical library screen of molecules that have high binding affinity and specificity for wild-type transthyretin [13]. Early studies showed that AG10 prevents cardiac cell toxicity induced by the V122I transthyretin. Subsequent in vitro experiments demonstrated that AG10 effectively stabilizes both wild-type and V122I transthyretin in patient serum [14].

A recent phase 2 trial randomized 49 patients with ATTR cardiomyopathy and NYHA class 2 or 3 heart failure to oral administration of placebo, 400 mg twice a day of AG10, or 800 mg twice a day of AG10 [15]. Most patients had ATTRwt (71.4%). Of the ATTRm patients, 78.6% had the V122I mutation. After 28 days of the administration, AG10 was well-tolerated and achieved a high degree of stability for both wild-type and mutant transthyretin. Previous data have suggested that serum transthyretin concentration may be a useful biomarker for ATTR cardiomyopathy. Lower levels are associated with a worse

prognosis, and transthyretin stabilizer therapy increases serum transthyretin concentration [16, 17]. In the AG10 trial, both doses of AG10 significantly increase serum transthyretin compared with placebo. Based on these safety and efficacy data, the phase 3, ATTRibute-CM trial was recently launched [18]. The trial aims to enroll 510 patients with ATTR cardiomyopathy who will be randomized to 800 mg twice a day or placebo. The primary endpoint is a change in 6-min walk test at 18 months and all-cause mortality and cardiovascular-related hospitalization at 30 months.

Diflunisal

Diflunisal is a non-steroidal anti-inflammatory drug that was discovered to have transthyretin-stabilizing properties [19, 20]. As a result, diflunisal was repurposed as a stabilizer therapy for ATTR amyloidosis. In a randomized trial of 130 patients with ATTR polyneuropathy, at 2 years, diflunisal was associated with significantly less neurological deterioration compared with placebo [21]. For ATTR cardiomyopathy, diflunisal has only been studied in small, single-center observational studies [22, 23]. Although diflunisal was well-tolerated overall in these small cohorts ($n = 13$ and $n = 23$), the risks of long-term non-steroidal anti-inflammatory drug use (e.g., cardiovascular events, kidney injury, and gastrointestinal), particularly for heart failure patients, remain a prominent concern. Given the emergence of tafamidis and AG10, which have benign safety profiles, diflunisal will likely be used less in the future for ATTR cardiomyopathy.

Transthyretin silencers

The liver is the main source of transthyretin synthesis (though small amounts are made by the retina and choroid plexus). In the case of ATTRm amyloidosis, eliminating the production of amyloidogenic mutant transthyretin has long been hypothesized as an effective treatment strategy. Indeed, liver transplantation has been used to replace the organ which produces mutant transthyretin with one that synthesizes wild-type transthyretin. This form of "gene therapy" can be effective in halting disease progression in ATTR polyneuropathy, but confers significant short- and long-term risks associated with solid-organ transplantation [24]. Recently, oligonucleotide drugs have emerged as a non-invasive form of gene therapy [25]. These drugs act by promoting the degradation of messenger RNA (mRNA), thereby reducing protein expression. Moreover, the liver appears to be a particularly accessible target for these therapies. For these reasons, oligonucleotide drugs may be well suited for treating diseases originating from the liver, such as ATTR amyloidosis [26] (Fig. 1).

Patisiran

Patisiran is a small interfering RNA (siRNA) that binds to the highly conserved 3′ untranslated region of both wild-type and mutant transthyretin mRNA to induce its degradation. This drug is carried in lipid nanoparticles to target drug delivery to hepatocytes [27]. Early clinical studies demonstrated that patisiran reduces serum transthyretin levels in a dose-dependent manner [28, 29]. These data led to the APOLLO study [30••]. This phase 3 trial randomized 225

patients with ATTRm polyneuropathy, in a 2:1 manner, to patisiran or placebo. Patisiran was administered intravenously (0.3 mg/kg) every 3 weeks and was associated with a median reduction in serum transthyretin of 81%. The primary endpoint assessed the change in neurological function using the modified Neuropathy Impairment Score+7 (mNIS+7). A higher mNIS+7 score reflects more severe neurologic impairment, with typical diabetic neuropathy progressing at approximately 3 points/year. Patisiran was associated with a significant improvement in the mNIS+7, and a dramatic difference in outcomes compared to placebo. The absolute difference of nearly 34 points on the mNIS+7 score is larger than with any other therapy to date and achieved a *P* value of 9.26×10^{-24} compared with placebo. Overall adverse events were similar between the treatment groups. The patisiran arm had a higher frequency of mild to moderate infusion-related reactions and peripheral edema. Based on this trial, patisiran was approved by the FDA for the treatment of patients with ATTRm polyneuropathy.

Patients with ATTRm polyneuropathy often have concomitant cardiomyopathy. In the APOLLO study, 56% of patients ($n = 126$) had evidence of cardiac involvement. In this prespecified cardiac subgroup, patisiran was associated with decreased left ventricular wall thickness, improved global and regional longitudinal strain, and reductions in NT-proBNP [31, 32]. Future studies will assess the safety and efficacy of RNA interference for ATTR cardiomyopathy populations. The APOLLO-B study will study patisiran in ATTRm and ATTRwt cardiomyopathy patients and will allow for the inclusion of patients receiving a transthyretin stabilizer as part of the standard of care. Vutrisiran is a next-generation transthyretin RNA interference therapy that, in contrast to patisiran, is administered subcutaneously and is administered every 3 months. The HELIOS-A trial, which is a phase 3 study, multicenter study, is currently randomizing ATTRm polyneuropathy patients to vutrisiran or patisiran [33]. The HELIOS-B trial has been announced and is planned to assess vutrisiran in patients with ATTRm or ATTRwt cardiomyopathy.

Inotersen

Inotersen is a 2′-O-methoxyethyl-modified antisense oligonucleotide that degrades transthyretin mRNA and decreases hepatic production of transthyretin protein. In animal studies and in healthy volunteers, inotersen was shown to significantly reduce serum transthyretin concentration in a dose-dependent manner [34]. The recent phase 3 NEURO-TTR trial evaluated the safety and efficacy of inotersen in patients with ATTRm polyneuropathy [35••]. In total, 172 patients were 2:1 randomized to receive weekly subcutaneous injections of 300 mg of inotersen or placebo. Inotersen led to median serum transthyretin reduction of 79%. The primary endpoint was a composite of the mNIS+7 and the Norfolk Quality of Life-Diabetic Neuropathy score. At 66 weeks, the inotersen group had significantly less worsening in both clinical scores compared with placebo, with a difference in mNIS+7 of 19.73 points ($P = 4 \times 10^{-8}$). Notable adverse events in the inotersen group were severe thrombocytopenia (3% of patients), including 1 death due to intracranial hemorrhage, and glomerulonephritis (3%). As a result, the study was modified to include weekly platelet monitoring. Regarding cardiovascular endpoints, in both the overall populations and the subgroups with evidence of concomitant amyloid

cardiomyopathy, there was no significant change in left ventricular wall thickness or global longitudinal strain. The NEURO-TTR trial led to FDA approval of inotersen for ATTRm polyneuropathy. A next-generation antisense oligonucleotide, AKCEA-TTR-L_{RX}, is currently being studied in a phase 1/2 trial in healthy volunteers and ATTR polyneuropathy patients [36].

Amyloid fibril antibodies

Both transthyretin stabilizers and silencers primarily aim to inhibit the formation of pre-amyloid species and subsequent amyloid fibril deposition. However, patients with ATTR cardiomyopathy often are diagnosed at a late disease stage when significant end-organ fibril deposition has already occurred. In this unfortunately common situation, therapies that prevent new fibril deposition may be ineffective at reversing the disease burden caused by the existing amyloid deposits. Indeed, in the ATTR-ACT trial, patients with more advanced heart failure (i.e., NYHA class 3) had an attenuated survival benefit from tafamidis compared with NYHA class 1 and 2 patients [12••]. Therefore, there is significant interest in identifying therapies that can disrupt and remove amyloid fibrils already deposited in tissues.

Miridesap/dezamizumab

Extensive preclinical and early clinical studies have examined targeting serum amyloid P component (SAP) as a mechanism of removing amyloid fibrils. SAP is a glycoprotein that is a key constituent of all amyloid fibrils, regardless of the precursor protein. Drugs have been developed to target clearance of circulating SAP as well as to bind SAP in tissue-deposited amyloid fibrils. Miridesap, formerly known as CPHPC, cross-links circulating SAP molecules, causing its clearance by the liver [37, 38]. Dezamizumab is a humanized anti-SAP antibody, which can bind to amyloid deposits in tissues and mediate fibril removal via complement factor fixation and macrophage clearance [39]. An open-label study of 15 patients with various types of amyloidosis showed that one-time administration of miridesap followed by dezamizumab reduced hepatic amyloid deposition as measured by ^{123}I SAP scintigraphy [40]. A subsequent study of 23 patients receiving repeated dosing of these therapies demonstrated amyloid clearance in the liver, kidneys, and spleen [41••]. Of note, only 6 patients in this study had cardiac amyloidosis. There is a theoretical concern that rapid, immune-mediated removal of large amounts of amyloid from the heart may acute exacerbate heart failure and arrhythmias. A recent study aimed to investigate the safety and efficacy of miridesap and dezamizumab combination therapy in patients with ATTR or AL cardiomyopathy [42]. This study was terminated in April 2019 with the investigators citing a "change in benefit/risk profile."

PRX004

PRX004 is a monoclonal antibody that selectively binds to misfolded conformations of transthyretin via a cryptic epitope [43]. PRX004 is currently being

assessed in a phase 1, open-label, dose-escalation study of patients with ATTRm cardiomyopathy and/or neuropathy [44].

Conclusion

Recent breakthroughs have drastically changed the management of ATTR amyloidosis. There have recently been multiple strongly positive phase 3 clinical trials with subsequent FDA approval for tafamidis (ATTR cardiomyopathy) and patisiran and inotersen (ATTRm polyneuropathy). Moreover, additional transthyretin stabilizers and silencers are being studied. The arrival of the first disease-specific therapies for ATTR amyloidosis raises many new clinical management questions. Considerations include developing diagnostic protocols to promote early disease diagnosis, determining the role of combination therapy (e.g., concomitant use of a transthyretin stabilizer and silencer), and identifying biomarkers of treatment response. The field of ATTR amyloidosis will likely continue to evolve rapidly over the next several years.

Compliance with Ethical Standards

Conflict of Interest

Kevin M. Alexander has received an investigator-initiated research grant from Pfizer.
Alessandro Evangelisti declares no potential conflicts of interest.
Ronald M. Witteles has received consulting fees (modest) from Pfizer and Alnylam, and has received clinical trial support from Pfizer, Alnylam, and Eidos.

Human and Animal Rights and Informed Consent

The article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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