Transthyretin Amyloidosis
A “Zebra” of Many Stripes*

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Amyloidosis is a systemic disease characterized by the deposition of misfolded protein fibrils into the extracellular matrix of organs, disrupting their function. Transthyretin (TTR), previously known as prealbumin, is a circulating homotramer carrier protein that binds either thyroid hormone or retinoic acid. It is in equilibrium with its composite monomers, which can unfold and aggregate into fibrils that deposit in the heart, peripheral nervous system, skin, and elsewhere, causing organ dysfunction. The presence of mutations leading to amino acid substitutions in TTR destabilizes the tetramer, promoting amyloid fibril formation. Varying TTR mutations (mt-ATTR) have different predilections for the heart or nervous system, leading to either familial amyloid polyneuropathy (FAP) or familial amyloid cardiomyopathy (Figure 1). Wild-type TTR (wt-ATTR) deposition can also lead to heart failure (HF) and has been associated with HF with preserved ejection fraction in one-third of the elderly population (1).

The past decade has seen development of therapies targeting hepatic TTR production, stabilization of the tetramer, and tissue deposition. Both antisense oligonucleotides (2) and small interfering ribonucleic acid (siRNA) (3) delivered via lipid nanoparticles to the hepatocyte have been shown to suppress translation of TTR messenger ribonucleic acid. Trials of both antisense oligonucleotides and siRNA to determine clinical efficacy in FAP are underway, as are studies of siRNA in familial amyloid cardiomyopathy. The nonsteroidal anti-inflammatory drug diflunisal stabilizes the TTR tetramer (4) and has shown clinical efficacy in a pilot study of patients with FAP (5). The utility of this nonsteroidal anti-inflammatory drug in TTR cardiac amyloidosis may be limited by its potential to promote sodium retention and renal dysfunction. Tafamidis binds to TTR’s thyroxine-binding site, stabilizing the tetramer. In a blinded, placebo-controlled trial (6), it slowed disease progression in patients with FAP with the Val30Met mutation and is approved in the European Union for this indication. In patients with wt-ATTR and mt-ATTR cardiomyopathy, tafamidis treatment in an open-label trial stabilized ex vivo urea-mediated TTR tetramer dissociation and echocardiographic indexes of left ventricular filling and systolic function (7). In an approach targeting fibril removal from tissue, the combination of doxycycline and the bile acid derivative taurolursodeoxycholic acid was effective in a murine model of FAP (8), and it stabilized N-terminal pro-B-type natriuretic peptide and echocardiographic parameters in an open-label pilot study of patients with wt-ATTR and mt-ATTR (9).

As a part of the tafamidis clinical development program, the THAOS (Transthyretin Amyloidosis Outcomes Survey) patient registry was established to characterize the clinical expression of TTR genotypes, including wild-type. The registry comprises demographic, genotype, symptom, quality-of-life, clinical outcome, and laboratory data, including biomarker, electrocardiographic, and echocardiographic measures. In this issue of the Journal, Maurer et al. (10) present an analysis of >2,500 patients in the registry, focusing on comparing patients in the United States with those from other regions of the world (ROW), as well as comparing U.S. patients with the Val122Ile mutation versus those with wt-ATTR.

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The major findings in the comparison of the registry's U.S. patients versus ROW patients were that U.S. patients were older and more likely to be male, of African descent, and have cardiac amyloidosis (10). Of the ROW patients, 95% were mt-ATTR, which was true of only 52% of U.S. patients. The greater prevalence of cardiac symptoms in the U.S. patients is explained by the finding that most common mt-ATTR patients enrolled in the United States (Val122Ile and Thr60Ala) are most likely to have a cardiomyopathy phenotype (Figure 1) and that wt-ATTR patients (twice as prevalent in the United States than in the ROW) almost universally have an isolated cardiomyopathy phenotype. This geographic distribution of mutations explains the greater frequency of cardiac amyloidosis in U.S. registry patients.

These findings (10) should be interpreted cautiously, as more than one-half of the ROW patients were enrolled in Portugal, where the Val30Met TTR mutation is common. The age of onset of neurological symptoms in Val30Met patients occurs during their 30s (9), which may account for the ROW patients' younger age at registry entry. In addition, 28% of the ROW patients were asymptomatic carriers of a TTR mutation. The presentation of Val122Ile and wt-ATTR amyloidosis with cardiac symptoms, compared with the presentation of Val30Met with neuropathy, likely accounted for the difference in utilization of cardiac biopsy for diagnosis between the United States (64% of biopsies) and ROW (12% of biopsies). The Val122Ile mutation was, by far, the most common mt-ATTR present in the United States, whereas the Val30Met mutation was most common in the ROW, regardless of whether the ROW site had a cardiology principal investigator or a neurology principal investigator.

Of interest is the comparison between wt-ATTR and Val122Ile amyloid patients in the United States (10). The large majority of Val122Ile patients were of African descent versus 4.2% of wt-ATTR, unsurprising given that the founder population of Val122Ile is likely West African (11). Val122Ile patients were younger and had more severe HF than the wt-ATTR patients based on their symptoms (56% vs. 35% New York Heart Association functional classes III and IV) and B-type natriuretic peptide levels (but surprisingly not N-terminal pro-B-type natriuretic peptide). The similarity in survival of the Val122Ile and wt-ATTR patients, despite apparently greater HF severity in the former, was explained by the results of the multivariate analysis, in which increasing age had a strong negative effect on survival. The difference in survival free from transplantation between the 2 groups of U.S. patients was likely due to greater availability of organ transplantation in younger patients.

It is interesting to compare survival in the Val122Ile population in the ARIC (Atherosclerosis Risk in Communities) study (12) versus that of patients in the THAOS registry (10). With an overall 1-year survival >95%, the ARIC population was an average of 13 years younger than the THAOS group and 8% had HF compared with 90% of the THAOS Val122Ile population who had HF and a 1-year survival of 75%. This finding suggests that asymptomatic Val122Ile patients be monitored in their sixth and seventh decades for onset of cardiac dysfunction to ensure early initiation of appropriate therapies, whether they are standard HF treatments or novel approaches currently under development. For example, the Phase III, blinded, placebo-controlled trial ATTR-ACT (Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy; NCT01994889) is evaluating the effect of tafamidis on mortality and cardiovascular hospitalization in patients with HF who have either wt-ATTR or mt-ATTR cardiomyopathy. It has completed enrollment and, hopefully, will soon be reporting results. Indeed, 1 lesson from the THAOS registry is that as new approaches to TTR amyloidosis evolve, U.S. clinicians may need to act similarly to those in the ROW, where more than one-quarter of the patients followed up by the clinicians were asymptomatic mutation carriers, identified solely by genotyping.

The THAOS registry identified the duration between onset of symptoms and registration to be >4 years (10), meaning diagnosis of amyloidosis remains woefully delayed. Our knowledge of the
epidemiology and pathophysiology of amyloidosis is evolving rapidly, driven by advances in molecular genetics, protein chemistry, and diagnostic imaging. In the next several years, we will see increasing awareness of the spectrum of pathogenic mutations in TTR and their clinical presentations, the role of wt-ATTR in HF with preserved ejection fraction (1), and development of novel therapies targeting TTR synthesis and tissue deposition. During this period, knowledge gained from registries such as THAOS will help drive development of algorithms to more easily and rapidly diagnose amyloidosis as well as clinical effectiveness studies targeting appropriate populations and, therefore, best able to succeed in identifying appropriate therapeutic interventions.

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