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GUEST EDITOR'S PAGE

Disease-Modifying Therapy for Transthyretin Amyloidosis

Where to Start? Where to Stop?

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Tremendous recent advances have been made in the field of cardiac amyloidosis. Although this is true for light-chain (AL) amyloidosis, a hematologic malignancy caused by clonal plasma cell proliferation resulting in extracellular deposition of misfolded immunoglobulin light-chains, it is perhaps most significant for transthyretin amyloidosis (ATTR) caused by misfolding of the hepatically derived transport protein transthyretin (TTR), resulting from either a mutation in the *TTR* gene (hereditary or variant ATTR [ATTRv]) or an age-related disorder occurring in the absence of a gene mutation (ATTR wild-type [ATTRwt]) (1,2). Important developments for ATTR cardiomyopathy (ATTR-CM) include recognition that both of these subtypes are underrecognized causes of heart failure in the community and improved imaging techniques that allow for noninvasive diagnostic confirmation and, perhaps most significantly, approval and ongoing development of novel ATTR disease-modifying therapies (2,3). As a result of these advances, interest in and awareness have improved substantially for a disease that was previously regarded as both rare and fatal.

Presently, only the TTR-stabilizer tafamidis is approved for the treatment of ATTR-CM. Tafamidis binds to the TTR tetramer and prevents its dissociation into monomers, which is the rate-limiting step of the ATTR pathophysiologic pathway. The ATTR-ACT (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) demonstrated improved survival and reduced cardiovascular hospitalizations for patients who received tafamidis compared with those who received placebo (4). On the strength of these results, tafamidis received expedited approval in the United States by the Food and Drug Administration in May 2019 and has also been approved in other countries for this indication. Of note, 2 other agents have been approved for the treatment of ATTRv-polyneuropathy (ATTR-PN) following publication of clinical trial evidence demonstrating attenuation of disease progression with these therapies (5,6). Both agents are *TTR* gene silencers that reduce hepatic production of the TTR protein; inotersen, an antisense oligonucleotide, and patisiran, a micro-RNA inhibitor. Agents in this therapeutic class may also hold promise for the treatment of ATTR-CM. In a subgroup analysis of the APOLLO (Study of an Investigational Drug, Patisiran [ALN-TTR02] for the Treatment of Transthyretin-Mediated Amyloidosis) trial, a trend toward reduced mortality and cardiovascular hospitalizations was demonstrated for ATTR-PN patients with suspected cardiac involvement (based on echocardiography findings) who received patisiran compared with placebo (7). Patisiran is presently being evaluated in a clinical trial for the treatment of ATTR-CM (APOLLO-B [A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy]; NCT03997383). There are also a number of other agents in different stages of development and clinical trial investigation for the treatment of ATTR-CM, including a next generation micro-RNA inhibitor, vutrisiran (HELIOS-B [A Study to Evaluate Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy]; NCT04153149), a next-generation antisense oligonucleotide (CARDIO-TTRansform [A Study to Evaluate the Efficacy and Safety of AKCEA-TTR-LRx in Participants With Transthyretin-Mediated Amyloid Cardiomyopathy]; NCT04136171) and another oral TTR-stabilizer, AG10 (ATTRIBUTE-CM [Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy]; NCT03860935).

Although the development and approval of disease-modifying therapies for ATTR has generated

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tremendous excitement and new hope for patients whose treatment was previously focused only on symptom control, it has also raised a number of questions and considerations regarding how best to use these therapies. Perhaps principal among these is the high cost of these medications. The list price for tafamidis in the United States is $225,000/year, making it the most expensive cardiovascular drug ever introduced there. The United States list prices for inotersen and patisiran are $450,000/year, and it is anticipated that newer therapies in development may also be launched at similarly high list prices, raising concerns about access, affordability, and cost-effectiveness of ATTR therapies. A recently published study examined the cost effectiveness of tafamidis in terms of quality-adjusted life years (QALY) gained using a simulation model calibrated to the results of the ATTR-ACT trial (8). The study reported an incremental cost-effectiveness ratio of $880,000/QALY gained with tafamidis treatment, well above the $100,000/QALY gained ratio generally recognized as an acceptable threshold for new therapies (8,9). The study estimated that treating all eligible ATTR-CM patients in the United States with tafamidis would increase annual health care costs by $32.3 billion (8). The high cost of tafamidis may necessitate payers in some regions to examine indications for starting therapy. The ATTR-ACT trial excluded patients with advanced disease characterized by New York Heart Association functional class IV symptoms or 6-min walk distance <100 m or other advanced end-organ dysfunction such as renal insufficiency or severe malnutrition (4). It was also demonstrated through subgroup analysis that the patients most likely to benefit were those with earlier stage disease (4), a characteristic common to many infiltrative disorders managed by disease-modifying therapy. Most ATTR-CM patients are older at the time of diagnosis (especially ATTRwt) and may have a significant burden of comorbidities that limits their prognosis, despite receiving ATTR treatment. It may be valuable to develop additional markers of disease stage along with predictive models for response to therapy to help improve patient selection for these high-cost therapies.

Approval of tafamidis and the ongoing development of other ATTR-CM disease-modifying therapies raises other questions regarding the timing of initiating therapy. This is especially true for patients with early stage disease, particularly patients whose ATTRv may be diagnosed through screening of family members prior to the onset of symptoms. The refurbishment of nuclear scintigraphy with a bone-seeking radiotracer to noninvasively detect ATTR-CM has facilitated earlier diagnosis in many patients (10,11). The optimal timing of initiation of therapy for asymptomatic ATTR-CM patients remains unclear, as does the optimal monitoring approach and frequency. This is also true for asymptomatic carriers of a *TTR* gene mutation who show no evidence of cardiac infiltration but who are at risk of developing ATTR-CM in the future. The consensus approach is to begin screening assessments of asymptomatic carriers at an age that is 10 years prior to the affected proband's age of disease onset, given that disease penetrance is age-dependent; however, this approach has not been validated, and both the penetrance and the natural history of ATTR may be highly variable (2,12).

Other important considerations include the lack of consensus criteria to define disease progression and treatment failure. Various measurements have been proposed, including functional, laboratory, and imaging markers; however, none has been rigorously tested, and the optimal surveillance approach for all patients, including those not on disease-modifying therapy, is also not well defined. An emerging potential measurement of response to therapy is the serum TTR level (also known as pre-albumin); however, its role in the routine follow-up of patients receiving disease-modifying therapy requires further investigation (13). Furthermore, as more therapies become available, considerations with respect to which agent to initiate first and which to switch to and when in the setting of ongoing disease progression will need to be addressed. Many patients with the ATTRv disease have a mixed cardiomyopathy and the polyneuropathy phenotype and, therefore, are eligible for treatment with either tafamidis or gene-silencer therapy (inotersen or patisiran). Currently the recommended approach in this setting is to base therapy selection on the predominant ATTR disease phenotype (cardiac vs. neurologic) that a patient is manifesting (1); however, again, evidence to support this approach is lacking. As more disease-modifying agents become available, this decision will become more challenging in the absence of evidence directly comparing different therapies. This also raises the question of potential combination therapy with multiple disease-modifying agent classes. At present the high cost of these therapies makes this approach unrealistic for most ATTR patients; however, over time as more therapies become available and the cost hopefully improves, this approach may warrant further research and consideration, particularly for patients with a more rapidly progressive disease course.

The extraordinary advances in the diagnosis and management of ATTR amyloidosis have resulted in a landscape that is rapidly changing for both health care providers and patients. The development of multiple new therapies over a relatively short period of time for this infiltrative disorder has created an exciting environment with few if any comparable precedents in the modern era. Such a swift evolution has given rise to many questions regarding the optimal approach to treatment and surveillance, and many areas of uncertainty remain. What is certain is that more research is needed to best address these knowledge gaps. In the immediate future, the high cost of these therapies represents a significant barrier for some patients, and improving access and affordability is an important objective towards achieving optimal care for all ATTR-CM patients.

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