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HEART FAILURE AND CARDIOMYOPATHIES

VIEWPOINT: VOICES IN CARDIOLOGY

Drug Development for Transthyretin Amyloidosis

Time to Fix the System?

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PATIENT 1

In Canada, an active 66-year-old man with no signs or symptoms of heart failure is diagnosed with atrial fibrillation after experiencing several weeks of intermittent palpitations. He is referred for an echocardiogram, which demonstrates severely increased concentric left ventricular wall thickness with preserved ejection fraction, suspicious for cardiac amyloidosis. Further evaluation with laboratory testing and technetium-99m-pyrophosphate scintigraphy confirms a diagnosis of wild-type transthyretin amyloid cardiomyopathy (ATTR-CM). His cardiologist explains to him that although there is an approved therapy for attenuating disease progression named tafamidis, public reimbursement is only available to patients with a history of heart failure in compliance with provincial eligibility criteria based on recommendations from the Canada Drug Agency; in the absence of private health insurance that would cover the cost, his only other option is to pay out of pocket in order to get treatment. Without private insurance or the means to pay for the medication himself, he is told that he will have to wait until he develops symptoms of heart failure before he can access treatment.

PATIENT 2

In the United States, a 68-year-old man has NYHA functional class 2 heart failure, 3 years after being diagnosed with ATTR-CM. Despite being treated with tafamidis from the time of diagnosis, his disease has inexorably progressed. He is excited to participate in a phase 3 clinical trial of a new therapy, mechanistically distinct from the only currently approved therapy, and already approved for an indication in what is essentially the same disease, just manifesting in another organ system. The makers of the therapy cleared all the hurdles to bring it to a phase 3 clinical trial, and aligned with the Food and Drug Administration (FDA) on the primary endpoint before the trial began. The trial is a clear success: the primary endpoint and multiple prespecified secondary endpoints are achieved.[1] Though the trial was not powered for mortality or hospitalizations, the trends there also point in the right direction. There are no safety issues. With this clean result, FDA approval seems a formality. However, the FDA surprisingly takes the unusual step of convening a formal advisory committee to provide a recommendation. The advisory committee votes 9 to 3 in favor, which by precedent nearly always leads to formal approval.[2] The patient is therefore dismayed when the FDA overrules the advisory committee, cutting off access for a new therapy to him and thousands of other patients diagnosed with the disease.

How did we get here? Does any of this make sense? We believe it is time for a reassessment to aid patients with this devastating disease.

DISCUSSION

Over a relatively short period of time, there have been tremendous advancements in the care of ATTR amyloidosis, an infiltrative disease caused by misfolding of the hepatically-derived transport protein transthyretin. Although considered a rare disease, ATTR amyloidosis diagnosis rates are increasing due

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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to improved diagnostic approaches, increased patient and physician awareness, and available treatment options. ATTR amyloidosis is caused by either a mutation in the transthyretin protein, known as hereditary/variant ATTR (ATTR-v), or an age-related disorder occurring in the absence of a gene mutation, known as wild-type ATTR (ATTR-wt). Phenotypically, ATTR amyloidosis can present with a cardiomyopathy-dominant phenotype (ATTR-CM) or a polyneuropathy-dominant phenotype (ATTR-PN), in addition to other organ system manifestations (eg, dysautonomia, orthopedic manifestations, ocular manifestations). This multisystem involvement can make ATTR amyloidosis a particularly challenging disease to manage.

There are currently 2 classes of approved ATTR amyloidosis disease-modifying therapies: stabilizers (eg, tafamidis), which prevent dissociation of the transthyretin protein into subunits which are the substrate for formation of amyloid fibrils, and silencers (eg, inotersen, eplontersen, patisiran, vutrisiran), which reduce hepatic transthyretin production. These agents—when available to patients—have significantly improved outcomes for patients with ATTR amyloidosis. In addition, new therapeutic classes are currently undergoing clinical trials, including depleters (which aim to reduce amyloid tissue deposits), and a clustered regularly interspaced short palindromic repeat (CRISPR-Cas9) therapy designed to edit the transthyretin gene and reduce hepatic production. As is common for rare disease therapies, the annual cost for currently approved medications is extremely high. For example, tafamidis was introduced in the United States at $225,000/year and is the most expensive cardiovascular medication ever approved,[3] whereas other approved ATTR agents are even more expensive. The high cost of therapy has already created significant global disparities in access to treatment because most patients cannot afford to pay for therapy and rely on public reimbursement programs for access.[4]

Current indications for approved medical therapies are based on both subtype and phenotype, a consequence of the inclusion criteria of the clinical trials their approval is based upon. For example, tafamidis is only approved in the United States and many other countries for the treatment of ATTR-CM based upon the inclusion criteria of the ATTR-ACT (Tafamidis Treatment of Patients with Transthyretin Amyloidosis Cardiomyopathy) trial,[5] whereas silencer medications are only approved for ATTR-PN based upon their respective clinical trial designs. These clinical trial designs were heavily influenced by the 2 largest medication regulatory agencies, the FDA in the United States and the European Medicines Agency (EMA) in Europe. The result of this is a unique ATTR medication approval paradigm, whereby 1 systemic disease is effectively subdivided into 2 or more. However, it is now recognized that many patients, particularly those with ATTR-v, can have a mixed phenotype of both cardiomyopathy and polyneuropathy. The regulatory paradigm has therefore created a limited and artificial approach to treatment decisions (ATTR-CM patients cannot currently be treated with silencers, whereas ATTR-PN patients cannot be treated with stabilizers). Combination therapy may seem like an attractive option but is not realistic in most regions where patients rely on public reimbursement for access. Furthermore, this paradigm has direct consequences on both cost and availability of newer ATTR medications. For example, in order to receive approval to treat all ATTR patients, both eplontersen and vutrisiran were required to conduct separate cardiomyopathy and polyneuropathy clinical trials, a process that will undoubtedly drive up the cost of both agents, and also delay access to these treatments for some patients while the research and approval processes run their course.

The need to conduct 2 large clinical trials for the treatment of 1 disease is unusual in the context of a multisystem disorder, especially for a rare disease. Multiple examples exist where such an approach is not necessary. Perhaps the best-known example is diabetes mellitus, which can have multisystem manifestations including cardiovascular, neurologic, renal, and many others. New diabetes therapies are not approved on an end-organ system-specific response basis as we currently do for ATTR amyloidosis; they are approved for treatment of the systemic disease. Another comparison is Fabry disease, another rare infiltrative disorder with multisystem involvement, including cardiomyopathy and polyneuropathy. There are multiple expensive approved disease-modifying therapies for Fabry disease, with new classes of agents currently in development. Just as is the case with diabetes mellitus, these medications are approved for the systemic disease, rather than for end-organ system-specific indications.

Another important aspect of the development and approval paradigm for ATTR amyloidosis therapies is the selection of primary endpoints for clinical trials, which are heavily influenced by the FDA and EMA. ATTR-PN trials have frequently used a polyneuropathy severity scale as the primary endpoint, whereas ATTR-CM trials have used mortality or a composite of mortality and cardiovascular hospital

admissions. Although such cardiovascular endpoints are common for clinical trials involving patients with heart failure, their necessity for a rare disease with multisystem manifestations like ATTR amyloidosis can again create challenges with access and can lead to confusing clinical scenarios for both patients and clinicians. For example, although a mixed phenotype ATTR-v patient may have the option of being treated with a stabilizer (approved for their cardiomyopathy) or a silencer (approved for their polyneuropathy), this choice may be framed as choosing between one medication that will stabilize their polyneuropathy or another that will prolong their life, a distinction that is both artificial and lacks biological plausibility. It is also uncommon for a rare disease to require such hard endpoints to receive approval, given the limited patient population to recruit from.

For ATTR amyloidosis, the combination of splitting a single systemic disease into organ-system-specific regulatory approvals and insisting on the hardest of endpoints for drug approval in a rare disease has greatly raised the expense of drug development and delayed access to life-improving and lifesaving therapies. The FDA's decision to not approve patisiran for ATTR-CM (the trial for patient 2 above) was particularly baffling, was inconsistent with the agency's guidance at the time of trial design, and was most of all unfair to patients with this devastating disease. For patient 1, public reimbursement eligibility in Canada (and other countries) often strictly adheres to clinical trial inclusion criteria. Patients like this one with early-stage disease are often excluded from ATTR amyloidosis clinical trials to ensure they are adequately powered to reach a "hard" primary endpoint such as mortality, even though they may arguably benefit the most from disease-attenuating therapies.

With multiple exciting new therapies currently in development, the time is now to reconsider our approach to drug approval and drug coverage for ATTR amyloidosis. These decisions directly impact not only the 2 patients whose stories are told here, but the tens of thousands of patients affected by this disease. Let us rethink and learn history—and commit to bringing what are clearly safe and effective therapies to patients in desperate need of options.

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