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EDITOR'S PAGE

The Tafamidis Drug Development Program

A Translational Triumph

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The announcement at the 2018 European Society of Cardiology meeting regarding the results of the phase III ATTR-ACT (Safety and Efficacy of Tafamidis in Patients with Transthyretin Cardiomyopathy, NCT01994889) clinical trial (1), which showed that treatment with tafamidis was associated with a reduction in all-cause mortality and cardiovascular (CV) hospitalizations in patients with transthyretin (TTR) amyloid cardiomyopathy, engendered a great deal of excitement within the CV community. As is discussed in this Editor's Page, the ATTR-ACT clinical trial represents an example of how investigators successfully learned to cross the translational "valley of death" by linking basic research observations with innovative clinical trial design. The successful pathway for the tafamidis development program emphasizes the value of learning from mistakes, and illustrates why Robert Sutton's bon mot (2), "failure sucks, but instructs," should become the quintessential credo for investigators interested in translational science. Here, we review several unique aspects of the tafamidis development program, with a focus on some of the strategies that resulted in a successful phase III clinical trial and a Breakthrough Therapy designation from the Food and Drug Administration in May 2018.

TTR amyloid cardiomyopathy is a life-threatening systemic disease that is characterized by the accumulation of misfolded TTR proteins, termed amyloid fibrils, in the heart. The condition can be acquired by the deposition of wild-type TTR protein (ATTRwt [previously termed senile cardiac amyloidosis]), or inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin *TTR* gene (ATTRm). The elucidation of the biological mechanisms underlying the development of TTR amyloidosis was critically important to the successful development of tafamidis as a treatment for TTR cardiomyopathy. In seminal studies, evaluating what has been described as a "gift from mother nature," Jeffrey Kelly and colleagues discovered that dissociation of the native TTR tetramer was the rate-limiting step for the deposition of amyloid proteins. Previous observations had shown that compound heterozygotes who carried both the disease-causing Val30Met mutation and a Thr199Met TTR mutation were protected against familial TTR amyloid polyneuropathy. Moreover, these patients had dramatically slower dissociation rates of TTR tetramers (3). Kelly and colleagues subsequently found numerous, structurally distinct, small molecules that kinetically stabilized the quaternary structure of the TTR tetramer, thereby inhibiting the formation of amyloid fibrils. These TTR kinetic stabilizers included certain nonsteroidal anti-inflammatory drugs (NSAIDs), such as diflunisal. However, because NSAIDs were associated with gastrointestinal, renal, and CV side effects, Kelly focused on benzoxazole carboxylic acids, which lacked nonsteroidal activity. Using a rational drug design approach, tafamidis (2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid) was the compound chosen for clinical development because it lacked NSAID activity, had good oral bioavailability, and had a low toxicity profile. Tafamidis selectively binds to TTR with negative cooperativity and kinetically stabilizes both wild-type native TTR and mutant TTR. Tafamidis was evaluated in subjects with familial amyloid polyneuropathy secondary to a Val30Met mutation in the phase II/III FX-05 clinical trial (4).

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Unfortunately, the results of this study did not lead to regulatory approval by the Food and Drug Administration because the coprimary endpoints of the trial did not meet statistical significance ($p = 0.068$) when compared with placebo, although the overall results demonstrated the potential of tafamidis to slow neurological deterioration and maintain nutritional status.

The ATTR-ACT trial (1) was a randomized, double-blind, placebo-controlled, international, multicenter study that evaluated whether tafamidis was safe and effective for patients with ATTRwt and ATTRm. The trial enrolled 441 subjects with amyloid deposits in biopsy tissue (cardiac and noncardiac) secondary to TTR precursor protein, as determined by mass spectrometry, immunohistochemistry, or scintigraphy. Subjects had evidence of cardiac involvement by echocardiography and a medical history of heart failure with at least 1 prior hospitalization for heart failure requiring a diuretic for improvement or an N-terminal pro-B-type natriuretic peptide concentration ≥600 pg/ml. Subjects with class IV heart failure, a 6-min hall walk test distance ≤100 m, severely reduced estimated glomerular filtration rate <25 ml/min/1.73 m^2, concomitant treatment with certain NSAIDs that can stabilize TTR, or severe malnutrition as evidenced by a modified body mass index <600 kg/m^2 · grams per liter were excluded. Randomization was performed in a 2:1:2 fashion: patients received tafamidis at a dose of 80 mg or 20 mg, or placebo for a fixed duration of 30 months. Subjects who completed the trial were offered to receive tafamidis in an open-label extension study. The primary efficacy analysis was a hierarchical combination of all-cause mortality and frequency of CV-related hospitalizations comparing the pooled tafamidis data (both 20- and 80-mg doses) with placebo, using the Finkelstein-Schoenfeld method (5). The ATTR-ACT trial demonstrated a robust effect of tafamidis on the primary endpoint ($p = 0.0006$), with a win ratio (number of pairs of tafamidis-treated patient wins divided by number of pairs of placebo patient wins) of 1.695 (95% confidence interval: 1.255 to 2.289). Additionally, tafamidis reduced the decline in 6-min walk test distance by 75.68 m at 30 months and also reduced the decline in quality of life at month 30 by 13.65 points, as assessed by the Kansas City Cardiomyopathy Questionnaire-Overall Summary; moreover, significant differences in these prespecified key secondary endpoints were also observed after month 6. The overall relative risk of mortality was reduced by 33%, and there was a 13% decrease in absolute risk reduction with a number needed to treat of 7.5 to prevent 1 death over the 2.5-year study period. The reduction in CV hospitalizations was similarly robust with a 32% relative risk reduction in the rate of CV hospitalizations with tafamidis, and a number needed to treat of 4 to prevent 1 hospitalization per year. The primary endpoint was also met when all-cause hospitalizations, not CV hospitalizations, were used ($p = 0.0088$). The consistent benefit of tafamidis was uniform across multiple endpoints and 11 pre-defined subgroups except for New York Hospital Association functional class III patients, in whom the rate of CV hospitalizations was higher with tafamidis than placebo, which may be attributable to longer survival with tafamidis treatment during a more severe period of the disease.

WHAT ASPECTS OF THE TAFAMIDIS DEVELOPMENT PROGRAM CONTRIBUTED TO THESE REMARKABLE RESULTS?

First, the tafamidis development program benefitted greatly from the use of reverse genetics (i.e., gene to phenotype), wherein genetic observations arising in patients with amyloidosis were combined with a rational drug design approach that directly targeted the purported mechanism of action of the disease identified through genetic analysis. Second, there were several aspects of the ATTR-ACT trial that were critical to the success of the trial, including the choice of trial duration, randomization approach, use of the Finkelstein-Schoenfeld method to analyze the endpoint, as well as the ascertainment of endpoints at the end of the trial. Given that the mechanism of action of tafamidis was mediated through TTR stabilization, rather than an early pharmacological effect of the drug, the trial duration of 30 months enabled the investigators to demonstrate divergence in survival curves using traditional Kaplan-Meier analyses ($p = 0.0259$). The Finkelstein-Schoenfeld method of analyzing endpoints increases the sensitivity and power of the data analysis, which is particularly important in small trials, because it still allows for prioritization of all-cause mortality in the primary endpoint analysis (5). This statistical test is based on the principle that each patient in the trial is compared with every other patient within each stratum (all-cause mortality is compared first, and if both subjects survive till the end of the trial or do not differ in the length of survival, then the subjects are compared on the number of CV hospitalizations) in a pairwise manner. The Finkelstein-Schoenfeld method facilitated rigorous testing of the efficacy of tafamidis compared with placebo on clinically meaningful endpoints using a relatively modest number of

patients compared with other CV trials. Additionally, the hierarchical combination of endpoints better delineates the efficacy of tafamidis on the total burden of disease, rather than on survival alone, analogous to the concept of days alive out of hospital. Finally, the recommendation by regulators that ascertainment of survival status in all randomized subjects should be obtained at 30 months reduced the impact of dropouts on the primary endpoint. Allocation of 60% of subjects to therapy with tafamidis, the use of a fixed duration rather than an event-driven design, coupled with the opportunity to enroll in an open-label extension after the 30-month trial, all contributed to enrollment and engagement of a cohort of representative patients with the disease, and capitalized on the most common motivation to participate in clinical trials—namely, access to a novel therapy that can prolong life.

CONCLUSIONS

Translational research for patients with TTR cardiac amyloidosis has, in the words of Winston Churchill, arrived at the "end of the beginning" (6). Indeed, a brief review of the number of clinical trials focused in TTR amyloidosis on the ClinicalTrials.gov website revealed that there were more than 50 clinical trials in this therapeutic space. Leveraging an approach to diagnosis of TTR amyloidosis without biopsy, in which technetium-labeled bone scintigraphy tracing is used instead, has the potential to detect amyloid deposits before an increase in left ventricular wall thickness or the clinical syndrome of heart failure and a rise in cardiac biomarkers has occurred (7). This diagnostic advance, when coupled with more widespread use of genetic testing, will facilitate early identification and treatment of TTR amyloidosis, at a time when tafamidis has the greatest benefit. Finally, the focus on diagnosing affected individuals with early disease will ensure the greatest benefit to patients with TTR cardiac amyloidosis from tafamidis. As always, we welcome comments and suggestions from investigators in academia and industry, patients, societies, and all of the governmental regulatory agencies about your thoughts about how to cross the translation valley of death, either through social media (*#JACC:BTS*) or by e-mail (JACC@acc.org).

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