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ORIGINAL RESEARCH ARTICLE

Annual Cardiovascular-Related Hospitalization Days Avoided with Tafamidis in Patients with Transthyretin Amyloid Cardiomyopathy

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Abstract

Background Patients with transthyretin amyloid cardiomyopathy (ATTR-CM) experience infiltrative cardiomyopathy and heart failure symptoms requiring costly hospitalizations. The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) demonstrated the efficacy of tafamidis on the frequency of cardiovascular (CV)-related hospitalizations in patients with ATTR-CM.

Purpose As length of stay can affect the total hospitalization burden, our study aimed to better understand the impact of tafamidis on the number of CV-related hospital days avoided in the management of ATTR-CM patients.

Methods Data from ATTR-ACT were used to calculate the total burden of CV-related hospitalization (days) by treatment arm in this post hoc analysis.

Results In the total trial population, patients receiving tafamidis had significantly fewer CV-related hospitalizations per year (relative risk reduction [RRR] 0.68; 0.4750 vs. 0.7025, $p < 0.0001$) and a shorter mean length of stay per CV-related hospitalization event (8.6250 vs. 9.5625 days) than patients receiving placebo. Taken together, tafamidis prevented 2.62 CV-related hospitalization days per patient per year. A subgroup analysis showed that with earlier treatment initiation of tafamidis, the annual number of CV-related hospitalizations was significantly lowered by 52% compared with placebo (RRR 0.48; 0.3378 vs. 0.7091, $p < 0.0001$). With 1.14 fewer days per hospitalization, tafamidis reduced the annual number of CV-related hospitalization days by 3.96 days per New York Heart Association class I/II patient.

Conclusions In patients with ATTR-CM, tafamidis was associated with a lower rate of CV-related hospitalizations and shorter length of hospital stay. Timely diagnosis and treatment with tafamidis could further decrease the total number of CV-related hospitalization days per year.

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Key Points

Analyses informed by data from the pivotal Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) illustrate the beneficial effect of tafamidis treatment, especially if initiated early in the disease course, on reducing cardiovascular (CV)-related hospitalization frequencies and length of stay.

Translating our findings to the real-world and assuming that current patients followed the trend of trial participants, tafamidis could prevent over 27,500 CV-related hospitalization days per year in the USA. Treating more patients with tafamidis can lead to a greater number of avoidable CV-related hospitalization days in the real world.

1 Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is an under-recognized disease characterized by abnormally folded transthyretin amyloid fibrils that deposit in various tissues, leading to end-organ dysfunction [1]. There are two main subtypes of the disease; ATTR-CM can be either hereditary/variant, resulting from mutations in the *TTR* gene, or wild-type, resulting from misfolded native or nonmutant *TTR* and associated with aging. Median survival ranges from 2.1 to 3.7 years in variant ATTR-CM and from 3.1 to 3.6 years in wild-type ATTR-CM, with both subtypes of ATTR-CM being ultimately fatal within 10 years from diagnosis without intervention [2–5].

Amyloidosis is a systemic and multiorgan disease, and symptoms will depend on the type and extent of organs or tissues involved [6]. When it affects the heart (accumulation in the myocardium), patients with ATTR-CM predominantly experience infiltrative cardiomyopathy and progressive heart failure (HF) symptoms that can require costly hospitalizations [1, 7, 8]. The burden of cardiovascular (CV) symptoms and associated healthcare resource use are considerably high in ATTR-CM, and HF-related hospitalizations can account for the majority of costs [7–10].

While the frequency of hospitalizations is a significant contributor to overall healthcare expenditures and patient morbidity, the duration of hospital stay is another important factor that can negatively affect the total hospitalization burden. Reducing hospitalization burden is of particular relevance to several stakeholders, including the clinicians who are managing ATTR-CM patients, the patients and their caregivers, the hospitals, and insurers/payors.

The Transthyretin Amyloidosis Cardiomyopathy Clinical Trial (ATTR-ACT) was a multicenter, international, phase III, randomized clinical trial that evaluated the efficacy and safety of tafamidis (pooled doses of 80 or 20 mg) compared with placebo in patients with hereditary and wild-type ATTR-CM (ClinicalTrials.gov number, NCT01994889) [11]. All patients who were eligible to participate in ATTR-ACT had a confirmed diagnosis of ATTR-CM and evidence of cardiac involvement, but patients were excluded if they were in New York Heart Association (NYHA) class IV at baseline. The frequency of adjudicated CV-related hospitalizations over the 30-month duration of the trial was shown to be significantly lower in tafamidis-treated patients with ATTR-CM [11]. The reduction in the number of CV-related hospitalization days by treatment arm, however, has not yet been reported from the trial. Therefore, we sought to understand the treatment benefit of tafamidis on the total number of CV-related hospital days avoided as a measure of the cumulative burden of ATTR-CM.

2 Methods

Two outcomes of interest were derived from ATTR-ACT data: (1) the mean annual frequency of CV-related hospitalizations by treatment arm and (2) the mean length of stay per hospitalization event by treatment arm.

In the ATTR-ACT trial, CV-related hospitalization is any non-elective admission to an acute care setting for medical therapy that resulted in at least a 24-h stay (or a date change if the time of admission/discharge was not available) with a discharge diagnosis that included a CV reason for hospitalization including HF, arrhythmia, myocardial infarction, transient ischemic attack or stroke, and other CV causes. The frequency of CV-related hospitalizations by treatment arm (defined as the number of times a patient was admitted to hospital for CV-related morbidity over the duration of the trial) was a component of the primary analysis and was captured as a secondary efficacy endpoint in the pivotal trial. Annualized frequencies were derived through a Poisson regression analysis with treatment, *TTR* status (variant and wild-type), NYHA baseline classification (NYHA classes I/II vs. III), treatment-by-*TTR* status interaction, and treatment-by-NYHA baseline classification interaction terms as factors adjusted for treatment duration.

With the mean number of CV-related hospitalization events per year determined for each treated patient, the next step was to calculate the total number of CV-related days hospitalized per year. This required the mean length of stay per hospitalization event, which was not available as a prespecified endpoint in the trial. Therefore, the mean ‘number

of days hospitalized per CV-related hospitalization' was derived from a post hoc analysis of all CV-related hospitalizations that occurred during the 30-month trial; any hospitalizations prior to the randomization date were not included.

Both of these outcomes were used in this current post hoc analysis to calculate and compare the total burden (in days) of CV-related hospitalization for pooled tafamidis and placebo and, accordingly, the number of hospitalization days that can be avoided with tafamidis in a hypothetical patient within the total intent-to-treat population of ATTR-ACT.

We also applied the predicted number of hospitalization days avoided in the total population to actual estimated patient numbers to provide a real-world context. Real-world patient numbers were estimated using the number of dispensed tafamidis units from specialty pharmacies, integrated delivery networks, and Pfizer's Patient Assistance Program. Based on these data, it was estimated that treatment with tafamidis has been initiated in 10,500 patients in the US as of May 2020.

An important takeaway from the ATTR-ACT study was that the CV-related hospitalization outcomes were markedly lower in tafamidis-treated patients who were NYHA class I or II at baseline, according to subgroup results of ATTR-ACT [11]. A subgroup analysis was, therefore, conducted for the baseline NYHA class I/II only patients to explore the impact of earlier treatment on the number of CV-related hospitalization days.

3 Results

Table 1 summarizes the CV-related hospitalization outcomes for tafamidis and placebo from the ATTR-ACT post hoc analyses. Tafamidis significantly reduced the rate of CV-related hospitalizations per year by 32.4% compared with placebo in the total intent-to-treat population of ATTR-ACT (relative risk reduction 0.68; 0.4750 vs. 0.7025, $p < 0.0001$). Additionally, in the total population, patients receiving tafamidis had a shorter mean length of stay at 8.63 days compared with placebo at 9.56 days per CV-related hospitalization event. Taken together, tafamidis prevented 2.62 CV-related hospitalization days per patient per year (4.0969 vs. 6.7177 days) in the total population (Fig. 1). When translating these findings to the real-world US setting, tafamidis could potentially reduce on average a total of ~27,518 CV-related hospitalization days per year if the approximately 10,500 real-life patients followed the trend of trial participants.

According to data from the ATTR-ACT trial, tafamidis also had an expectedly larger impact on the burden of hospitalization in the subgroup analysis assuming treatment initiation in NYHA classes I and II. Tafamidis had less than half the annual number of CV-related hospitalizations compared to placebo in these patients (relative risk reduction 0.48; 0.3378 vs. 0.7091, $p < 0.0001$). Tafamidis was also associated with shorter duration of CV-related hospitalization episode than placebo (8.5039 days vs. 9.6410 days, respectively) among NYHA class I/II patients. Therefore, with 1.14 fewer days per hospitalization, tafamidis reduced the annual number of CV-related hospitalization days from 6.84 to 2.87, which is a 3.96-day reduction per NYHA class I/II patient (Fig. 1).

4 Discussion

Through this analysis, we illustrate the benefit of tafamidis as a disease-modifying treatment compared to placebo on CV-related hospitalization outcomes. On average, tafamidis was associated with a lower rate of CV-related hospitalizations as well as a shorter length of stay per hospitalization among all treated patients. We show that 2.62 CV-related hospitalization days could be prevented per year with tafamidis in the total population, and that number increases to 3.96 days if tafamidis is initiated in patients at less advanced disease stages (NYHA class I/II). This is in line with recent national scientific statements and the observation that diagnosing patients earlier in the disease process is paramount

Table 1 Summary of CV-related hospitalization rate and length of stay from ATTR-ACT, by treatment arm and by population

Model parameter	Mean (95% CI) annual rate of CV-related hospitalizations per patient	Mean (95% CI) LOS (days) per CV-related hospitalization
Total population		
Tafamidis ($n = 264$)	0.4750 (0.4181–0.5396)	8.6250 (7.5727–9.6773)
Placebo ($n = 177$)	0.7025 (0.6174–0.7993)	9.5625 (8.3807–10.7443)
Baseline NYHA I/II subpopulation		
Tafamidis ($n = 186$)	0.3378 (0.2857–0.3994)	8.5039 (7.1216–9.8861)
Placebo ($n = 114$)	0.7091 (0.6078–0.8274)	9.6410 (8.1482–11.1339)

ATTR-ACT Transthyretin Amyloidosis Cardiomyopathy Clinical Trial, *CI* confidence interval, *CV* cardiovascular, *LOS* length of stay, *NYHA* New York Heart Association Functional Classification

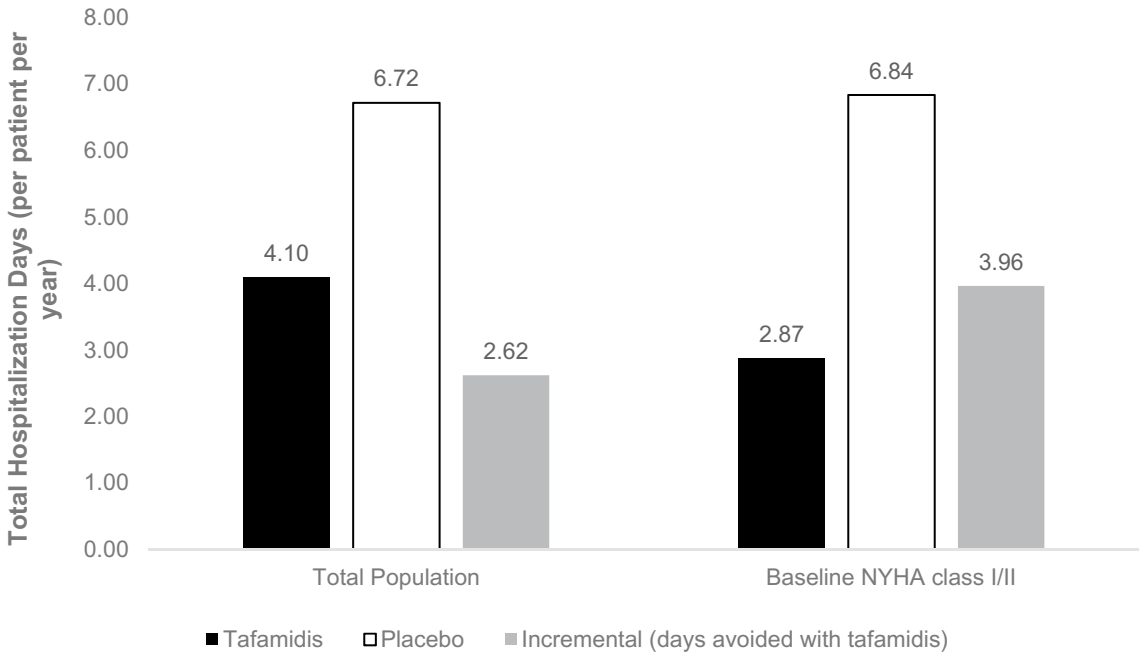

Fig. 1 Tafamidis is associated with lower total mean CV-related hospitalization days compared with placebo in the total population and baseline NYHA class I/II subpopulation. *CV* cardiovascular, *NYHA* New York Heart Association Functional Classification

for slowing disease progression and increasing the benefit that patients can derive from treatment [12–15]. Clinicians should consider the early identification of affected individuals with widely available non-invasive diagnostic techniques. Real-world observations suggest that the increased awareness and availability of minimally invasive diagnostic tools, such as bone scintigraphy in the absence of a monoclonal protein, have contributed to a greater proportion of patients being diagnosed in NYHA class I or II over time, highlighting a shift to earlier diagnosis and the growing importance of these patients [16, 17].

Although not shown in this study, the trial found that tafamidis was associated with a lower rate of CV-related hospitalization and shorter duration per hospitalization than placebo in both subgroups of wild-type ATTR-CM and variant ATTR-CM, and therefore, a tafamidis benefit would be expected regardless of transthyretin genotype and the study conclusions would be unchanged. In support, additional published analyses from ATTR-ACT also concluded that tafamidis is an effective treatment for all patients with ATTR-CM, regardless of subtype [18]. The effect of tafamidis on the frequency and duration of CV-related hospitalizations was numerically more favorable in patients with wild-type ATTR-CM. Considering that a recent publication reported that wild-type patients made up the vast majority of diagnoses over the past decade, particularly in the USA, the results of our study could be considered a conservative estimate of the reduction in hospitalization burden for the real-world ATTR-CM population [16]. Likewise, there was a similar effect in frequency and duration of CV-related hospitalizations in both tafamidis doses (80 mg and 20 mg). A study by Vong and colleagues also explored the hospitalization effect of tafamidis using ATTR-ACT data and determined that outcomes were not estimable for each tafamidis dose within the duration of the trial because ATTR-ACT was designed to assess the comparative efficacy of the pooled doses of tafamidis with placebo, rather than the individual doses [19, 20]. For these reasons, our analysis focused on the total population and the pooled tafamidis dose to align with the comparisons in the primary ATTR-ACT analysis.

Other subgroup analyses beyond NYHA class I/II were not explored further. Despite seeing a larger incremental difference than placebo in total hospital days in the baseline NYHA class I patients who received tafamidis compared with patients in baseline NYHA class II, it would not have been possible to determine the meaningfulness of this difference with any certainty given the very low number of patients with baseline NYHA class I enrolled in ATTR-ACT (24 [9.1%] patients in the tafamidis arm and 13 [7.3%] patients in the placebo arm) [11]. In addition, a recent study found that, given the high mortality (with placebo) in the NYHA class III subgroup and the longer survival with tafamidis, there is a confounding effect of death on CV-related hospitalizations that underestimates the hospitalization effect of tafamidis [21]. Due to this confounding survivor bias, an NYHA class III-specific analysis was not conducted.

A potential shortcoming of our analysis is that we could not adjust for global variability in disease management in

the data from ATTR-ACT for hospitalizations. Although variability in overall disease management can influence hospital admission and discharge patterns occurring with standard of care, the present analysis can still be viewed as an approximation of the number of avoidable CV-related hospitalization days with tafamidis in patients with ATTR-CM. In reality, the number of hospitalization days that could be avoided in any given patient treated with tafamidis might vary from this analysis, which is an average estimate using hospitalization data from all treated patients in ATTR-ACT, rather than only hospitalized patients. We present our results on a per-treated patient per-year basis to facilitate generalizing our analysis to any country's setting. For example, we translated our findings to a real-life setting and predicted that tafamidis could potentially reduce on average a total of ~27,518 CV-related hospitalization days per year in the USA. As more patients initiate treatment with tafamidis, especially if treatment is initiated early on in their disease, the number of CV-related hospitalization days avoided per year is expected to increase in parallel.

5 Conclusions

Our study results confirm that tafamidis prevents more CV-related hospitalization events and hospitalization days per year of treatment, supporting the benefit of treatment with tafamidis compared to placebo in both the total population and the baseline NYHA class I/II subpopulation. This benefit would be magnified as more patients add tafamidis to their treatment regimen for ATTR-CM, a chronic disease with recurrent hospitalizations. Importantly, this study addresses an evidence gap in the literature related to hospitalization length of stay from ATTR-ACT, and this is the first time the tafamidis benefit on frequency and duration of hospitalization outcomes are reported for the NYHA class I/II subgroup. This analysis underscores the importance of earlier diagnosis and treatment when therapies for ATTR-CM may be most effective. The hospitalization data from ATTR-ACT suggest that timely diagnosis and treatment with tafamidis in the NYHA class I/II patients could lead to further decreases in the total number of CV-related hospitalization days.

Declarations

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Conflict of interest Mark Rozenbaum and Rahul Bhambri are employees of Pfizer and hold Pfizer stock and/or stock options. Editorial/medical writing support and data analysis were provided by Diana Tran at EVERSANA and was funded by Pfizer Inc. Jose Nativi-Nicolau received funding for clinical trials from Pfizer, Akcea, and Eidos and Educational Grants from Pfizer and has been a consultant for Pfizer, Eidos, Akcea, and Alnylam.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material All data generated or analyzed during this study are included in this article.

Code availability Not applicable.

Author contributions All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. MHR and DT designed the study. DT conducted the analyses and drafted the manuscript. All authors critically reviewed the manuscript for intellectual content and approved the final version of the manuscript.

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