JACC: CARDIOONCOLOGY VOL. 3, NO. 4, 2021

EDITORIAL COMMENT

Monitoring Tafamidis, The Most Expensive Cardiac Medication

Are Serum Transthyretin Levels the Answer?*

Ian C. Chang, MD,[a] Eli Muchtar, MD,[b] Martha Grogan, MD[a]

Once considered a rare condition, transthyretin (TTR) cardiac amyloidosis (ATTR-CM) is now increasingly diagnosed as a result of heightened awareness and improved diagnostics. The TTR stabilizer tafamidis is the only medication currently approved by the Food and Drug Administration (FDA) for ATTR-CM. The pivotal ATTR-ACT (Tafamidis in Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) demonstrated that tafamidis treatment slowed progression of disease and was associated with reduced mortality and cardiovascular hospitalization (1). Another TTR stabilizer, AG10 (acoramidis), is being studied in a phase 3 clinical trial of ATTR-CM, as are several RNA-silencer therapies. Tafamidis is a small molecule that binds to the thyroxine-binding site of the TTR tetramer, thereby slowing the process of dissociation into amyloidogenic monomer (2). In the ATTR-ACT study, tafamidis was found to be well tolerated, with a similar incidence of adverse events between those receiving tafamidis and placebo. No drug-specific safety monitoring was recommended by the FDA. However, with a list price of $225,000 per year, tafamidis treatment results in a significant financial burden for many patients, even with insurance coverage (3). Therefore, with an expensive treatment that has relatively few side effects in this slowly progressive disease, patients and providers commonly wonder whether tafamidis is working and naturally seek measures of efficacy.

TTR, or prealbumin, is a homotetrameric protein produced by the liver and choroidal plexus that transports thyroxine and retinol-binding protein (4). Serum TTR concentration is influenced by factors affecting its production, stability, and metabolism (5), and some studies suggest prognostic implications. In untreated patients with wild-type TTR cardiomyopathy (ATTRwt), a serum TTR level <18 mg/dL was associated with shorter survival (6). In nonamyloid patients, lower serum TTR levels predicted increased mortality in patients with heart failure (7). In 2 Danish prospective general population cohorts, a TTR level at or lower than the 5th percentile was associated with a higher risk of incident heart failure. Normal values vary on the basis of age, sex, and race, with a higher TTR level in younger, male, and White patients. In addition, the hepatic regulation is affected by nutritional status and acts as a negative acute phase reactant (5,8). Because serum TTR has a short half-life and is affected by various factors, its interpretation needs careful assessment, potentially with repeat testing for confirmation.

In this issue of *JACC: CardioOncology*, Falk et al (9) report on their retrospective review of serum TTR levels in 72 patients before and within 3 to 12 months after starting tafamidis. Given that assays of TTR stabilization are not currently clinically available and are performed under nonphysiological conditions, Falk et al (9) postulated that serum TTR levels may serve as a surrogate for TTR stability testing. Falk et al (9) found that serum TTR levels increased significantly after tafamidis initiation, with a mean increase of 31.1% in patients with ATTRwt. Only 3 patients did not demonstrate increased TTR levels; the reason was thought to be the result of systemic illness in

*Editorials published in *JACC: CardioOncology* reflect the views of the author and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

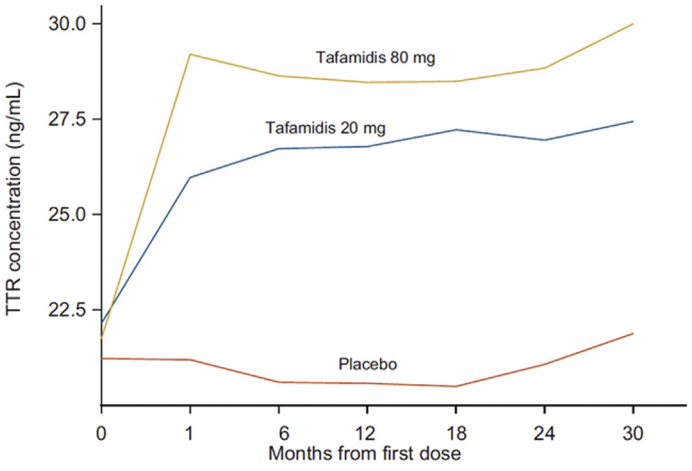
From the [a]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA; and the [b]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA.

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.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2021.09.007

JACC: CARDIOONCOLOGY, VOL. 3, NO. 4, 2021
OCTOBER 2021:587–589

FIGURE 1 Serum TTR Levels in ATTR-ACT



Serum transthyretin (TTR) concentration in tafamidis-treated patients enrolled in ATTR-ACT (Tafamidis in Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) (1). Reproduced with permission from Damy et al (10). © 2020 The Authors. *European Journal of Heart Failure*, published by John Wiley and Sons Ltd on behalf of European Society of Cardiology. This is an open access article under the terms of the Creative Commons. Attribution-NonCommercial-NoDerivs License (CC BY-NC-ND 4.0), which permits use and distribution in any medium, provided the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

1 patient, noncompliance in the second, and unknown in the third. In a subset of patients with sequential testing, TTR levels were sustained. The other report of serum TTR levels in tafamidis treated ATTR-CM patients published in manuscript form was in an online supplement of a study of safety and efficacy of different tafamidis dosages in ATTR-ACT and the long-term extension study (10). The supplemental figure in that report (10) demonstrated a sustained increase in serum TTR levels from onset of therapy for both the 20-mg dose and the 80-mg dose compared with flat levels in patients receiving placebo (**Figure 1**). The current study by Falk et al (9) adds to the published work showing that tafamidis increases serum TTR as reported with other stabilizers (6,11). Falk et al (9) speculate that the degree of change in TTR levels, although an indirect indicator, may provide a better assessment of drug effect than in vitro stabilization assays. In addition, although stabilizers vary in potency at fixed plasma concentrations, these investigators note that the reduction in TTR tetramer dissociation is similar between AG10 and tafamidis in clinically used doses. Falk et al (9) also question whether any clinically significant difference will be found between AG10 and tafamidis and recognize that a trial comparing these 2 agents is unlikely to be performed. Interestingly, Falk et al (9) mention studies of TTR levels in diflunisal-treated patients in their discussion. The TTR levels reported in these small studies are similar or even somewhat higher than with tafamidis. Thus, if Falk et al (9) are correct that TTR levels are a good indicator of stabilization and drug efficacy, diflunisal may remain an option, especially for early stage and appropriately selected patients with ATTR-CM who are burdened by the financial toxicity of tafamidis.

Despite the important observation and thoughtful discussion, this retrospective study has several limitations, including limited inclusion to patients with follow-up visits and a relatively small sample size. Although 18 patients were excluded because of treatment with diflunisal immediately before initiation of tafamidis, Falk et al (9) do not provide data regarding TTR levels on diflunisal as a comparison. Even though it was reasonable to exclude patients receiving TTR-silencing therapy, clinicians should recognize that these drugs lower serum TTR levels, and thus the results of this study are not applicable to patients receiving combination therapy. This study does not provide information on the correlation of the change in serum TTR level with outcomes in tafamidis-treated patients. However, the results do provide some "real-world" data demonstrating an increase in serum TTR levels during treatment with tafamidis, an indirect reassurance of TTR stability and potential treatment efficacy. A larger limitation of current published reports is the lack of a detailed analysis of TTR levels in the ATTR-ACT trial, including correlation with clinical outcomes.

Beyond the scope of this observational study, a clinical question is whether we need to test TTR levels for therapeutic monitoring at all or more than once. From the available data, the stabilizing effect of tafamidis appears almost universal. Barring a low TTR level from a secondary cause, the data suggest that TTR levels would increase in almost all patients. ATTR-CM is a life-threatening condition with a poor prognosis if untreated; coupled with the astronomical cost of therapy, patients, providers, and insurers are understandably eager to assess response to therapy. However, treatment response in ATTR-CM is challenging for multiple reasons (12). Given that tafamidis *slows* the progression of disease, how does one determine whether an individual patient's trajectory represents an adequate response to therapy? Natural history studies, biomarker staging systems, and clinical experience provide perspective but not objective data to determine efficacy in an individual patient. Even therapies that may reverse disease will likely be hampered by the very slowly progressive nature of

ATTR-CM. Because this disease likely develops over decades, it may take years to detect clinically significant changes in cardiac imaging parameters. Patients and providers, especially those less familiar with ATTR-CM, will benefit from the virtue of watchful waiting and avoidance of tests that will not change management. In the future, as treatment options are likely to expand beyond TTR stabilizers, perhaps TTR levels will be used to guide therapy. For now, in the absence of proven testing for tafamidis efficacy, close monitoring for heart failure symptoms, disease progression, and eligibility for organ transplantation remain the mainstays of clinical follow-up.

In summary, Falk et al (9) report the observation that serum TTR levels increased with tafamidis use and speculate that TTR levels may provide insight into TTR stability and drug efficacy. There is an ongoing need for more data from both clinical trials and postapproval use to help inform clinical decision making as it pertains to the use of serum TTR levels in monitoring the treatment of patients with ATTR-CM.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Muchtar has received a consulting fee (funds to the institution; no personal compensation) from Protego. Dr Grogan has received clinical trial and/or consulting fees (funds to the institution; no personal compensation) from Akcea, Alnylam, Eidos, Pfizer, and Prothena. Dr Chang has reported that he has no relationships relevant to the content of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Martha Grogan, Department of Cardiovascular Diseases, Mayo Clinic, 200 Southwest First Street, Rochester, Minnesota 55905, USA. E-mail: grogan.martha@mayo.edu. Twitter: @MarthaGrogan1.

REFERENCES

1. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007–1016.

2. Zhou S, Ge S, Zhang W, et al. Conventional molecular dynamics and metadynamics simulation studies of the binding and unbinding mechanism of TTR stabilizers AG10 and tafamidis. *ACS Chem Neurosci*. 2020;11:3025–3035.

3. Masri A, Chen H, Wong C, et al. Initial experience prescribing commercial tafamidis, the most expensive cardiac medication in history. *JAMA Cardiol*. 2020;5:1066–1067.

4. Vieira M, Saraiva MJ. Transthyretin: a multifaceted protein. *Biomol Concepts*. 2014;5:45–54.

5. Ranasinghe RN, Biswas M, Vincent RP. Prealbumin: the clinical utility and analytical methodologies. *Ann Clin Biochem*. Published online June 11, 2020. https://doi.org/10.1177/0004563220931885

6. Hanson JLS, Arvanitis M, Koch CM, et al. Use of serum transthyretin as a prognostic indicator and predictor of outcome in cardiac amyloid disease associated with wild-type transthyretin. *Circ Heart Fail*. 2018;11:e004000.

7. Lourenco P, Silva S, Frioes F, et al. Low prealbumin is strongly associated with adverse outcome in heart failure. *Heart*. 2014;100:1780–1785.

8. Buxbaum J, Koziol J, Connors LH. Serum transthyretin levels in senile systemic amyloidosis: effects of age, gender and ethnicity. *Amyloid*. 2008;15:255–261.

9. Falk RH, Haddad M, Walker CR, Dorbala S, Cuddy SAM. Effect of tafamidis on serum transthyretin levels in non-trial patients with transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol CardioOnc*. 2021;3:580–586.

10. Damy T, Garcia-Pavia P, Hanna M, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail*. 2021;23:277–285.

11. Judge DP, Heitner SB, Falk RH, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2019;74:285–295.

12. Grogan M. The incremental value of diuretic dose in staging systems for transthyretin cardiac amyloid: keep it simple. *J Am Coll Cardiol CardioOnc*. 2020;2:425–427.

KEY WORDS amyloidosis, prealbumin, transthyretin