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INTERMEDIATE

CASE REPORT: CLINICAL CASE

Rhabdomyolysis in the Setting of Concomitant Use of Tafamidis, Atorvastatin, and Amiodarone

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ABSTRACT

An 85-year-old women with transthyretin cardiac amyloidosis presented with generalized weakness, elevated liver function test levels, and creatinine kinase consistent with rhabdomyolysis 1 week after starting tafamidis. She was already taking atorvastatin and amiodarone, raising the possibility of a drug-drug interaction inhibiting the breakdown and excretion of atorvastatin, causing drug-induced rhabdomyolysis. (**Level of Difficulty: Intermediate.**)
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HISTORY OF PRESENTATION

An 85-year-old woman presented to the emergency department after a fall; she had generalized weakness and difficulty walking, which had preceded her fall by at least 1 day. Her physical examination was unremarkable apart from an unsteady gait, and she had no overt evidence of fluid overload.

LEARNING OBJECTIVES

- To understand the potential role of tafamidis in the development of rhabdomyolysis.
- To understand the complexities in management of older people with cardiac amyloidosis, with multiple comorbidities and polypharmacy.

MEDICAL HISTORY

The patient had a history of coronary artery disease with prior revascularization, atrial flutter, a permanent pacemaker insertion for sick sinus syndrome, diet-controlled diabetes mellitus, and chronic kidney disease. She had had multiple hospitalizations for decompensated heart failure over a 12-month period, leading to a diagnosis of transthyretin amyloidosis (ATTR) cardiomyopathy due to the V122I mutation. Her medications included atorvastatin 80 mg once daily and amiodarone 200 mg once daily (the former she been taking for 5 years, the later for 4 months); apixaban 2.5 mg twice daily; and torsemide 20 mg once daily. Tafamidis 61 mg daily was started as an outpatient 1 week before presentation.

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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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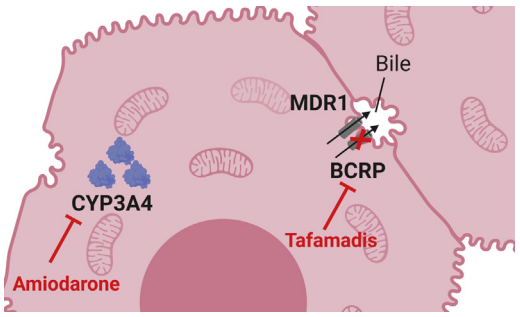
FIGURE 1 Hepatocytes



Tafamidis is known to inhibit breast cancer resistance protein (BCPR or ABCG2), an efflux transporter active in the hepatocyte, intestinal enterocyte, and kidney proximal tubule, which may increase exposure of substrates of this transporter. Statins are substrates of this transporter; they are also metabolized by cytochrome P450 3A4 (CYP3A4), which is inhibited by amiodarone. A synergistic effect between BCRP and CYP3A4 has been postulated; this is based on the synergy between P-glycoprotein (also known as multidrug resistance-1 [MDR1]) and BCRP, and substrates these transporters share with CYP3A4. It may be that the combination of a weak CYP3A4 inhibitor (amiodarone) with a BCRP inhibitor (tafamidis) increased atorvastatin exposure in this high-risk patient, resulting in statin-induced rhabdomyolysis.

DIFFERENTIAL DIAGNOSIS

Given the history of ATTR cardiomyopathy with frequent heart failure admissions and longstanding poor mobility, the patient's presentation was attributed to disease progression. The priority was to exclude a cerebrovascular event.

INVESTIGATIONS

Laboratory studies revealed liver function test (LFT) results elevated from baseline: alanine aminotransferase (ALT) 264 U/l (reference range 10 to 50 U/l) and aspartate aminotransferase (AST) 590 U/l (reference range 10 to 50 U/l). LFTs from 1 year prior varied between ALT 72 to 138 U/l and AST 90 to 220 U/l, largely dependent on volume status. After starting amiodarone, in addition to atorvastatin, ALT was 85 U/l and AST was 113 U/l. Creatinine kinase (CK) levels were not measured.

The patient underwent magnetic resonance imaging of her brain and magnetic resonance imaging angiography of her brain and neck, which were normal. Her LFT abnormalities were attributed to hepatic congestion in the setting of amyloid cardiomyopathy. She was discharged to rehabilitation, where she continued to report generalized weakness and fatigue.

LFTs were rechecked, and serum transaminase levels had increased from 1 week prior: ALT 473 U/l and AST 762 U/l. CK levels were 18,569 U/l (reference range 26 to 192 U/l), consistent with rhabdomyolysis. N-terminal pro-B-type natriuretic peptide levels were 4619 pg/ml (reference range <1,800 pg/ml), similar to the patient's baseline value. Fifth-generation high-sensitivity troponin T levels were elevated to 285 ng/l from her baseline level of 135 ng/l (reference range 0 to 9 ng/l). She had no leukocytosis or significant anemia. Creatinine levels at baseline were 1.4 mg/dl (reference range 0.5 to 1.2 mg/dl).

The patient had had no recent trauma/injuries, no excessive exercise or seizures, no signs of an infection, and no alcohol or drug use that may have caused rhabdomyolysis; results of thyroid studies were normal. Physical examination was largely unchanged from 1 week prior; the most notable finding was difficulty mobilizing without assistance. There were no physical examination findings consistent with an inflammatory myopathy. An electrocardiogram showed sinus rhythm with first-degree atrioventricular block at a ventricular rate of 60 beats/min.

MANAGEMENT

Tafamidis, amiodarone, and atorvastatin were held. Over the course of her admission, the patient was given intravenous fluid, which was discontinued when CK levels were <10,000 U/l; CK and AST/ALT levels decreased, and creatinine remained at baseline levels. Amiodarone was reintroduced with no change in CK or AST/ALT levels.

DISCUSSION

Transthyretin (ATTR) cardiac amyloidosis is caused by amyloid fibrils depositing in the myocardium, which can be wild type or variant; the latter is associated with >100 pathologic mutations in the transthyretin gene (1). The most common mutation in the United States is valine-to-isoleucine at amino acid position 122 (V122I), found in 3.4% of individuals of African descent (2,3). Patients who develop ATTR cardiomyopathy have progressive congestive heart failure, often complicated by atrial arrhythmias. Choice of antiarrhythmic therapy in this group is limited, and amiodarone is probably the most commonly used.

ABBREVIATIONS AND ACRONYMS

ALT = alanine aminotransferase

AST = aspartate aminotransferase

ATTR = transthyretin amyloidosis

BCRP = breast cancer receptor protein

CK = creatinine kinase

CYP3A4 = cytochrome P-450 3A4 pathway

LFT = liver function test

TABLE 1 Pharmacological Properties of Tafamidis, Atorvastatin, Amiodarone, and Apixaban

	Tafamidis	Atorvastatin	Amiodarone	Apixaban
Bioavailability	NA	14%	50%	50%
T_{max}, h	1.75–4	1–2	3–7	3–4
$t_{1/2}$	49 h	14 h	40-55 days	12 h
Major CYP enzyme	NA Induces CYP2B6 and CYP3A4	CYP3A4	CYP3A and CYP2C8 Inhibits CYP3A4	CYP3A4
Protein binding	>99%	>98%	96%	87%
Renal elimination	22%	<2%	Negligible	27%
Efflux transporter	NA Inhibits BCRP	P-glycoprotein BCRP	NA Inhibits P-glycoprotein	P-glycoprotein, BCRP

P-glycoprotein is also known as multidrug resistance protein 1. Source: Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: UpToDate, Inc., 2020; May 6, 2020.

BCRP = breast cancer receptor protein; CYP = cytochrome P-450; NA = not applicable; $t_{1/2}$ = time from maximum concentration to half maximum concentration; T_{max} = time to maximum plasma concentration.

Based on the positive outcome of the ATTR-ACT (*Tafamidis in Transthyretin Cardiomyopathy Clinical Trial*), the TTR stabilizer tafamidis was approved for use in the United States and Europe in early 2019 to treat wild-type ATTR and variant ATTR cardiomyopathy (4). Tafamidis was associated with decreases in all-cause mortality and cardiovascular-related hospitalizations, and it reduced the decline in functional capacity and quality of life. Notably, the safety profile for tafamidis was excellent, with adverse events no greater than those with placebo.

To the best of our knowledge, this case is the first reported of rhabdomyolysis in a patient receiving tafamidis therapy. Drug-induced rhabdomyolysis is the most likely explanation, in the absence of other etiologic explanations for the sudden development of rhabdomyolysis and the recent initiation of tafamidis. Amiodarone alone may rarely cause this effect, but reintroduction did not cause recurrence. An amiodarone-statin interaction may have been a cause, although the patient had tolerated the 2 drugs without problems for several months and had developed symptoms shortly after starting tafamidis; this scenario suggests that this agent was the culprit or the precipitant of rhabdomyolysis, in the setting of a high-dose statin and amiodarone use.

Tafamidis is known to inhibit breast cancer resistance protein (BCPR or ABCG2), an efflux transporter, which may increase exposure of substrates of this transporter; a potential interaction with rosuvastatin is listed in the package insert (**Figure 1**) (5). Statin-induced rhabdomyolysis is a relatively rare phenomenon, which more readily occurs as a dose-related side effect in the presence of a drug interaction (**Table 1**). Pharmacologic studies have shown that breast cancer receptor protein (BCRP) inhibition or BCRP polymorphisms can increase blood levels of several statins, including atorvastatin (6). There have been case reports of rhabdomyolysis after concomitant use of cyclosporine, another BCRP inhibitor, and simvastatin (7). Apixaban is also a substrate of BCRP; although it is not a likely culprit in the drug-drug interaction, its pharmacokinetic profile may also be altered (8).

Advanced age, female sex, and multisystem disease are all risk factors for statin-induced myopathy, as is polypharmacy. It may be that the combination of a weak cytochrome P-450 3A4 pathway (CYP3A4) inhibitor (amiodarone) with a BCRP inhibitor (tafamidis) increased atorvastatin exposure in this high-risk patient, resulting in statin-induced rhabdomyolysis. A synergistic effect between BCRP and CYP3A4 has been postulated; this is based on the synergy between P-glycoprotein and BCRP, and substrates these transporters share with CYP3A4 (9).

The patient's predominant symptom was generalized weakness, common in ATTR and often attributed to progression of the disease. Given the nonspecific symptoms that patients with rhabdomyolysis may present with, it is essential not to attribute these symptoms to the patient's heart failure and amyloidosis without further investigation. This patient faced a dangerous delay in diagnosis because her elevated serum transaminase levels were initially attributed to hepatic congestion. With increasing diagnosis of ATTR cardiomyopathy and use of tafamidis, this case suggests that caution needs to be used in this cohort of patients in whom statins are commonly co-administered, and in whom amiodarone may have been used to control the atrial arrhythmias frequently occurring in ATTR. We believe that this was likely a dose-related side effect related to the amiodarone-statin interaction, in which the addition of tafamidis altered the excretory pathway of the statin, resulting in a further increase in statin levels. This may warrant a

statin dose reduction before initiation of a TTR stabilizer.

FOLLOW-UP

With physical therapy, the patient's strength and gait improved during hospitalization. CK levels at discharge were 905 U/l with ALT/AST levels of 177/160 U/l. Three weeks' post-discharge, a follow-up CK level was 235 U/l and ALT/AST was 39/47 U/l. She declined reintroduction of tafamidis or atorvastatin. Of the 108 patients currently prescribed tafamidis at our academic medical center, a majority (53.7%) are on statin therapy of any intensity, 21.2% are on high-intensity statin therapy, and 27.8% are on amiodarone. Of this cohort, 19.4% are concurrently on statin therapy, amiodarone, and tafamidis, with 5.6% on high-intensity statin therapy, amiodarone, and tafamidis. No other patients have developed this serious adverse event thus far; the main reported adverse event is fatigue.

CONCLUSIONS

This case highlights the complexities often encountered in the management of patients with ATTR; they are elderly with multiple co-morbidities, on multiple medications. Although we cannot be certain this was simply not an interaction between amiodarone and atorvastatin, the known inhibitory effect of atorvastatin on BCRP likely increased the statin levels further, in addition to the rapidity of symptom development with starting tafamidis. We still have more to learn about novel transthyretin therapies and their potential drug-drug interactions and resultant side effects as they are prescribed in larger numbers. Our experience underscores the importance of a thorough evaluation of new symptoms and laboratory abnormalities in such patients, with a heightened awareness for potential drug-drug interaction in this high-risk cohort.

AUTHOR DISCLOSURES

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REFERENCES

1. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641–54.

2. Buxbaum J, Jacobson DR, Tagoe C, et al. Transthyretin V122I in African Americans with congestive heart failure. J Am Coll Cardiol 2006;47:1724–5.

3. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. Genet Med 2017;19:733–42.

4. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16.

5. Vyndaqel® or Vyndamax™ (tafamidis meglumine or tafamidis) Drug Interactions. Pfizer Medical Information, US. Available at: https://www.pfizermedicalinformation.com/en-us/vyndaqel-or-vyndamax/drug-interactions. Accessed January 30, 2020.

6. Keskitalo JE, Zolk O, Fromm MF, Kurkinen KJ, Neuvonen PJ, Niemi M. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2009;86:197–203.

7. Tong J, Laport G, Lowsky R. Rhabdomyolysis after concomitant use of cyclosporine and simvastatin in a patient transplanted for multiple myeloma. Bone Marrow Transplant 2005;36:739–40.

8. Wiggins BS, Dixon DL, Neyens RR, Page RL, Gluckman TJ. Select drug-drug interactions with direct oral anticoagulants: JACC Review Topic of the Week. J Am Coll Cardiol 2020;75:1341–50.

9. Kodaira H, Kusuhara H, Ushiki J, Fuse E, Sugiyama Y. Kinetic analysis of the cooperation of P-glycoprotein (P-gp/Abcb1) and breast cancer resistance protein (Bcrp/Abcg2) in limiting the brain and testis penetration of erlotinib, flavopiridol, and mitoxantrone. J Pharmacol Exp Ther 2010;333:788–96.

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