CASE IN POINT

Rosuvastatin-Induced Rhabdomyolysis, Pancreatitis, Transaminitis, and Acute Kidney Injury

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Changing medications within a drug class requires considering the indication and dosage, possible adverse effects, and drug-drug interactions.

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Fed Pract. 2021;38(suppl 4). Published online November 12. doi:10.12788/fp.0199

Attention should be paid to changing a tolerated medication to another within its class. Many drugs approved by the US Food and Drug Administration (FDA), have equivalent therapeutic properties as existing drugs. Rarely do such medications share the same potency and adverse effect (AE) profile.

CASE PRESENTATION

A 77-year-old man presented to the emergency department (ED) at the Raymond G. Murphy Medical Center in Albuquerque, New Mexico, with a 1-month history of progressive muscle weakness, which was so severe that he required assistance rising from chairs. The symptoms began when he switched from atorvastatin 40 mg daily to rosuvastatin 40 mg daily. A nephrology consultation was requested for an elevated plasma creatinine.

The patient reported strict adherence to his prescribed medications. In the days following the switch to rosuvastatin, he noticed that his urine turned black. He described the color as "like burnt coffee." The color gradually cleared before his ED presentation. The patient stopped taking rosuvastatin the day prior to presentation and noted improvement of his symptoms. Review of symptoms was significant for lower extremity paresthesia and numbness the day he started rosuvastatin. He had no symptoms of decompensated heart failure and no recent exacerbations requiring alteration of his diuretic regimen.

The patient's medical history was significant for traumatic brain injury with complex partial seizures, carpal tunnel syndrome, dyslipidemia, coronary artery disease with percutaneous intervention to the right coronary artery in the late 1990s, atrial fibrillation and ventricular tachycardia, status post implantable cardioverter defibrillator, heart failure with reduced ejection fraction (25%) attributed to ischemic cardiomyopathy, hypertension, lower urinary tract symptoms/prostatism, and previous bladder cancer. In the mid-1960s, the patient served in the US Army and had been deployed to South Korea. After the service, he worked for the local city government. He was retired for about 15 years. He reported no tobacco, alcohol, or recreational drug use and no tattoos. He did not require prior blood or blood product transfusions. None of his family members—parents, siblings, or children—had any history of kidney disease.

The patient's outpatient medications included levetiracetam 750 mg twice daily, melatonin 9 mg at night, menthol 16%/methyl salicylate 30% topically up to 4 times per day as needed, aspirin 81 mg once daily, fish oil 1000 mg twice daily, amiodarone 400 mg twice daily, hydralazine 20 mg 3 times daily, isosorbide mononitrate 60 mg daily, metoprolol succinate 100 mg daily, and tamsulosin 0.4 mg at night. His vital signs were stable: afebrile (97.5 ºF), normocardic (74 beats per minute), normotensive (118/78 mm Hg), and normoxic (98% on room air). On examination, he appeared elderly, somewhat frail, and chronically ill but in no acute distress. Affect was pleasant and appropriate, attention was high, and his thought process was logical. He had sparse, grey scalp hair. Extraocular movements were intact. Oral mucosa was pink and moist. His back was nontender, and there was no costovertebral tenderness bilaterally. The patient was in no respiratory distress, with a slightly hyperresonant chest to percussion bilaterally, very faint inspiratory basilar crepitant rales (that cleared with repeat inspiration), and was otherwise clear to auscultation

throughout. An outline of an implanted pacemaker was evident on the chest under his left clavicle, with a laterally displaced apical impulse. The rate was normal and the rhythm was regular. Upper extremities demonstrated papyraceous skin but without cyanosis, clubbing, or edema. Radial pulses were slightly diminished. He had no lower extremity edema.

His laboratory values are provided in Table 1. Kidney function was stable months prior to admission. Of note, the blood urea nitrogen and plasma creatinine were increased from his baseline up to 47 and 5.89 mg/dL, respectively. The serum glutamic-oxaloacetic transaminase and serum glutamic pyruvic transaminase were 1051 U/L and 408 U/L, respectively. Plasma amylase and lipase levels also were elevated, 230 U/L and 892 U/L, respectively. Creatine kinase was 41,099 U/L. Urinalysis demonstrated a specific gravity of 1.017, pH of 5, and a large amount of blood (92 red blood cells/high power field).

A 12-lead electrocardiogram demonstrated a sinus rhythm, PR interval of 0.20 ms, narrow QRS with a leftward frontal axis deviation, R-transition between precordial leads V1 and V2, and flattening of the ST segments in III, V1-V3 (Figure 1). A portable chest X-ray demonstrated clear lung fields, no evidence of effusion in the costophrenic area. Ultrasonography was conducted at the time of the examination (Figure 2). The kidneys were smoothly contoured, each measuring > 10 cm; there was an exophytic cyst on the left. Otherwise, the cortices, perhaps slightly echogenic, did not appear diminished. The bladder was not abnormally enlarged.

Rosuvastatin-induced rhabdomyolysis, pancreatitis, transaminitis, and drug-induced acute kidney injury were considered high among the diagnostic differentials. The 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor was stopped, and he was prescribed an acute renal insufficiency diet. All laboratory parameters improved with this change (Figure 3). Two months after presentation (and with rosuvastatin added to his list of adverse reactions), all symptoms resolved and his plasma creatinine reached a nadir of 1.22 mg/dL.

TABLE 1 Patient's Laboratory Results

Characteristics	Reference Range, Adults[a]	Most Recent Results Before Presentation	Results at Initial Consultation
Hemoglobin, g/dL	13.5-17.7	12.0	11.5
Hematocrit, %	42.0-53.0	36.4	37.1
White-cell count, µL	4.0-11.0	5.9	7.8
Platelet count, K/mm^3	150-400	232	166
Sodium, mmol/L	137-145	138	138
Potassium, mmol/L	3.4-4.8	4.5	4.3
Chloride, mmol/L	98-107	108	106
Carbon dioxide, mmol/L	20-31	21	23
Urea nitrogen, mg/dL[b]	9-20	27	41
Creatinine, mg/dL[b]	0.66-1.25	1.87	5.22
Glucose, mg/dL[b]	74-99	83	83
Calcium, mg/dL	8.4-10.2	8.8	9.1
Phosphorus, mg/dL	2.5-4.5	3.5	not available
Magnesium, mg/dL	1.6-2.3	2.1	2.1
Protein, g/dL	6.3-8.5	6.8	6.7
Albumin, g/dL	3.5-5.0	3.6	3.7
Bilirubin, total, mg/dL	0.2-1.3	0.7	1.2
Bilirubin, direct, mg/dL)	0.0-0.4	0.0	0.3
Serum glutamic-oxaloacetic transaminase, U/L	17-59	45	1318
Serum glutamic pyruvic transaminase, U/L	≤ 50	32	454
Amylase, U/L	30-130	not available	230
Lipase, U/L	23-100	30	892

[a]Specific to Raymond G. Murphy Veterans Affairs Medical Center in Albuquerque, New Mexico; determined by the patient population and the laboratory methods used.
[b]Conversion: urea nitrogen units to mM × 0.357; creatinine units to µM × 88.4; glucose units to mM × 0.05551.

DISCUSSION

Statin-class drugs inhibit the HMG-CoA reductase (Table 2). Upregulation of low-density lipoprotein cholesterol (LDL-C) receptors in the liver result in increased LDL-C uptake and cholesterol catabolism.[1] Prescribed inhibitors of the HMG-CoA reductase—statins—are known to reduce mortality due to cardiovascular disease (CVD). Much like any other pharmaceutical agent with any measurable potency, HMG-CoA inhibitors can have AEs. Statin therapy has been associated with pancreatitis.[2] Muscle toxicity is a complication of HMG-CoA reductase inhibitors, and statin-associated symptoms are a leading cause of nonadherence.[3] Rosuvastatin

FIGURE 1 12-Lead Electrocardiogram Showing Frontal Left-Axis Deviation and R Transition After V1

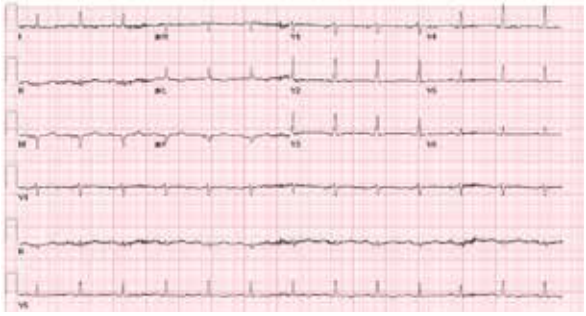
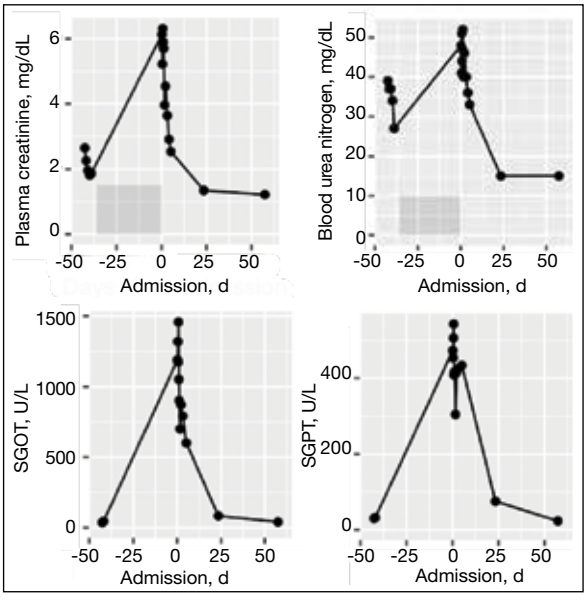
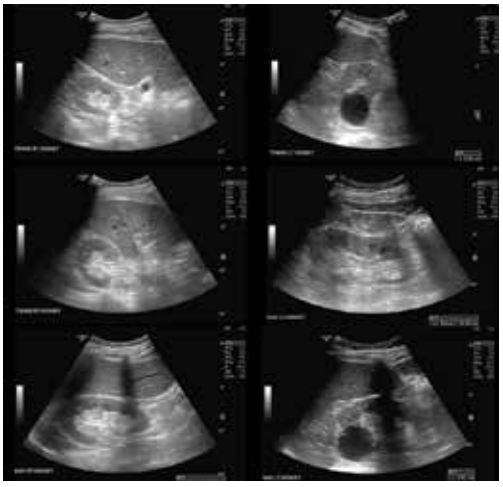


FIGURE 3 Improved Laboratory Results Following Rosuvastatin Discontinuation



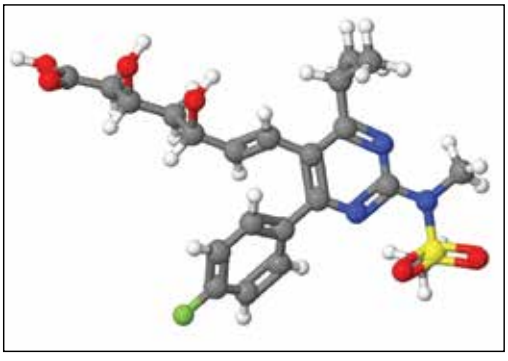
Abbreviations: SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

FIGURE 2 Bedside Kidney Ultrasonography



Both kidneys were > 10 cm in length and generally smoothly contoured without diminishment of cortical sizes. Of note, cysts (1 partially exophytic) in the left kidney; radiology noted normal liver size.

FIGURE 4 Rosuvastatin Chemical Structure



Source: Jmol, an open-source Java viewer for chemical structures in 3D (http://www.jmol.org).

had higher AE and drug reactions compared with that of atorvastatin and pitavastatin (35.6%, 8.7%, and 22.2%, respectively) in clinical trials for approval.[4] We have reported concomitant adermatopathic dermatomyositis with statin-induced myopathy in a 48-year-old man from simvastatin (40 to 80 mg daily).[1]

Toxin-induced myopathy should be considered early in the differential diagnosis of weakness.[5] All HMG-CoA inhibitors have been associated with acute kidney injury, particularly at high doses and also are known to induce myopathies, sometimes with inclusion bodies.[1] Muscle-related AEs correlate with the potency of an HMG-CoA reductase inhibitor according to an analysis using the FDA AE Reporting System (AERS).[6] Myalgia and rhabdomyolysis are well-known AEs of this class of medications. Furthermore, type II muscle atrophy—particularly in the proximal limb muscles—has been reported.[5] Patients may have difficulty rising from chairs.[1] Rosuvastatin had the strongest signal for muscular AEs (eg, myalgia, rhabdomyolysis, increased creatine phosphokinase level) from an FDA analysis of AERS.[7]

Rosuvastatin is the only HMG-CoA reductase inhibitor that causes dose-dependent increases in proteinuria and hematuria (Figure 4).[8] Rosuvastatin at a 5-mg dose may induce 4 times the proteinuria as a placebo. Typically, other statins potentially reduce proteinuria

(without hematuria). Proteinuria may be induced by rosuvastatin even at low doses.[8] Proteinuria is attributed to how rosuvastatin impacts proximal tubular function.[9] The drug is transported into the proximal tubule by the organic anion transporter-3. Acute kidney injury has been associated with several statins, including rosuvastatin.[7,10] This may be associated with denuded tubular epithelia, active urinary sediment, acute tubular toxicity, vacuolated epithelial cells, and tubular cell casts. Unlike atorvastatin, the increase in proteinuria and hematuria also is dose dependent.

In patients with renal insufficiency (short of end-stage renal disease [ESRD]), most statins other than rosuvastatin are well tolerated and recommended for reduction of overall and CVD mortality risk. However, these benefits seem to diminish once ESRD is reached. Atorvastatin did not impact CVD mortality in patients with type 2 diabetes mellitus (T2DM) and ESRD (despite decreasing LDL-C).[11] The AURORA study randomized 10 mg of statin vs placebo in 2776 maintenance dialysis patients aged 50 to 80 years. Rosuvastatin lowered the LDL-C but did not affect all-cause mortality (13.5 vs 14.0 events per 100 patient-years). Patients randomized to rosuvastatin had more than twice as many unclassified strokes (9 vs 4). Rosuvastatin, although efficacious in reducing LDL-C, had no impact on CVD mortality, nonfatal myocardial infarction, or nonfatal stroke.[12] Post hoc analysis demonstrated that in patients with T2DM with ESRD the hazard ratio for hemorrhagic stroke was 5.2.[13]

Rosuvastatin ranked lower than lovastatin, pravastatin, simvastatin, atorvastatin, and fluvastatin with respect to reduction of all-cause mortality in trials of participants with or without prior coronary artery disease.[14] AEs, such as rhabdomyolysis, proteinuria, nephropathy, renal failure, liver, and muscle toxicity are higher with rosuvastatin than other medications in its class.[15]

CONCLUSIONS

For patients with existing CVD, standard clinical practice is to encourage increased and regular physical activity, cholesterol-lowering diets, weight loss, and smoking cessation. Hypertension should be treated. Glycemia should be well controlled in the setting of T2DM. β-blockers may be beneficial in those with histories of myocardial infarction or heart failure with reduced systolic function. Statins are a valuable tool in the treatment of dyslipidemia.

TABLE 2 Pharmacokinetic Parameters for HMG-CoA Reductase Inhibitors

Statins (mg)	Protein Binding, %	Elimination Half-Life, h	LDL Cholesterol Reduction
Atorvastatin (10-80)	≥ 98	14.0	38-54
Fluvastatin (20-80)[a]	98	3.0	17-33
Lovastatin (20-80)	> 95	1.1–1.7	29-48
Pitavastatin (1-4)	> 99	12.0	31-41
Pravastatin (10-40)	50	1.8	19-40
Rosuvastatin (10-40)	88	19.0	52-63
Simvastatin (10-40)	95	4.9	28-41

Abbreviations: HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL, low-density lipoprotein (plasma).
[a]Immediate release, twice daily.

Statin-induced muscle symptoms are a major reason for discontinuation and nonadherence.[16] Statin-induced myalgia, myositis, and myopathy have been used interchangeably.[17] Rhabdomyolysis, myalgia, increased creatine kinase, statin myopathy, and immune-mediated necrotizing myopathy are among the clinical phenotypes caused by statins.[17] There are 33,695 serious cases—1808 deaths—reported with rosuvastatin in the FDA AERS as of June 30, 2021. Myalgia, pain in extremity, muscle spasms, pain, and arthralgia top the list of AEs. When statin-induced symptoms occur, adherence is rarely improved by dismissive clinicians.[18]

Drugs in the same class often have common therapeutic properties. Potencies and AE profiles are seldom uniform. The decision to add or change the brand of medication within a class should be balanced with considerations for the indication, duplications, simplification, AEs, appropriate dosage, and drug-drug interactions.

Acknowledgments

Brent Wagner is funded by a US Department of Veterans Affairs Merit Award (I01 BX001958), a National Institutes of Health R01 grant (DK-102085), Dialysis Clinic, Inc., and partially supported by the University of New Mexico Brain and Behavioral Health Institute (BBHI 2018-1008, 2020-21-002) and in part by the University of New Mexico's Signature Program in Cardiovascular and Metabolic Disease (CVMD); and the University of New Mexico School of Medicine Research Allocation Committee (C-2459-RAC, New Mexico

Medical Trust). Brent Wagner is an Associate Member to the University of New Mexico Health Sciences Center Autophagy, Inflammation, and Metabolism Center of Biomedical Research Excellence (AIM CoBRE) supported by NIH grant P20GM121176.

Funding

National Institutes of Health Grant R01 DK-102085, Dialysis Clinic Inc., VA Merit Award I01 BX001958, Center for Integrated Nanotechnologies User Agreement 2019AU0120, Brain & Behavioral Health Institute (grants 2018-1008, 2020-21-002), University of New Mexico's Signature Program in Cardiovascular and Metabolic Disease (CVMD), the University of New Mexico School of Medicine Research Allocation Committee (C-2459-RAC, New Mexico Medical Trust) and a metabolomics voucher from the AIM Center (NIH P20GM121176).

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The authors report no actual or potential conflicts of interest with regard to this article.

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