Case Report

Rosuvastatin-Induced Rhabdomyolysis: A Case Report

Ravindra Nikalji, Suvadeep Sen[1]

Departments of Nephrology and [1]Critical Care, Apollo Hospital, Navi Mumbai, Maharashtra, India

Abstract

Rosuvastatin is a recently approved statin and used widely across the globe for primary and secondary prevention of atherosclerotic cardiovascular heart disease. It has the highest lipid-lowering property among all statins and relatively well tolerated. Rhabdomyolysis is a rare but potentially serious adverse effect. The present report highlights the case of a patient admitted with proximal myopathy with severe rhabdomyolysis and acute kidney injury associated with life-threatening hyperkalemia. The symptoms appeared within 1 month of starting rosuvastatin. He required temporary dialysis to overcome the crisis. His myopathy and kidney injury were completely reversible after a few months of stopping the drug. In this report, we have also discussed the various risk factors for developing myopathy with statins and the importance of strict pharmacovigilance, and a greater caution among physicians while using this drug.

Keywords: *Acute kidney injury, rhabdomyolysis, rosuvastatin*

Background

Atherosclerotic cardiovascular disease is one of the leading causes of mortality and morbidity across the globe. Statins are a competitive inhibitor of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase in the pathway of lipid metabolism and have a powerful effect on lowering of harmful low-density lipoprotein (LDL) cholesterol. Rosuvastatin, the newest agent in the armamentarium, are often called super-statin due to its highest potency and efficacy in terms of lipid-lowering ability. But it can have a serious side effect in the form of myopathy and renal injury. In this article, we have report a patient developing severe myopathy and rhabdomyolysis after starting rosuvastatin within the recommended dose and without having reported risk factors.

Case Description

A 69-year-old male was admitted to our hospital with a history of pain in the back and progressive muscle weakness of lower limbs for the last 1 week and decreased urine output for the past 3 days and breathlessness for 1 day. He did not have any history of fever, rash, joint pain, altered sensorium, chest pain, or cough and expectoration. His ongoing medication included, aspirin 75 mg, clopidogrel 75 mg, and rosuvastatin 40 mg once daily each. These medications were started a month back when he was admitted to a different hospital and diagnosed with ischemic heart disease with left ventricular failure. His previous known renal function was normal, with creatinine being 0.8 mg/dL. There was no history of addiction or substance abuse and allergy to any medication or substance. He was otherwise healthy with activities appropriate for his age before this episode of illness with no history of trauma and strenuous exertion in the recent past.

On admission, he was hemodynamically unstable, tachypneic (respiratory rate of 32/min), tachycardia, but was conscious, oriented with warm extremities. Systemic examination revealed normal vesicular breath sounds in the chest without any crackles and rhonchi, normal heart sounds without any murmur and other adventitious sounds. On neurological evaluation, he had bilateral paraparesis with proximal muscle involvement more than distal muscle, power at the hip joint was 1/5, and at knee and ankle was 3/5, plantar reflex flexor, bilateral knee jerks, and ankle jerks absent, with no upper limb involvement. Sensory function, cranial nerve, and higher function were within normal limits. There was no band like sensation complained by the patient. His oxygen saturation at room air

How to cite this article: Nikalji R, Sen S. Rosuvastatin-induced rhabdomyolysis: A case report. Indian J Nephrol 2021;31:190-3.

Received: 29-11-2019
Accepted: 16-02-2020
Published: 27-03-2021

Address for correspondence:
Dr. Suvadeep Sen,
Department of Critical Care,
Apollo Hospital, Plot No- 23,
CBD Belapur,
Navi Mumbai, - 400 614,
Maharashtra, India.
E-mail: s.sen2011@hotmail.com

Access this article online

Website: www.indianjnephrol.org

DOI: 10.4103/ijn.IJN_388_19

Quick Response Code:

was 100%. The abdomen was soft without any tenderness and organomegaly.

Laboratory tests revealed to have high anion-gap metabolic acidosis with normal lactate level and PaO_2 103 mmHg at room air. He was found to have renal impairment. Serum potassium was significantly high. Liver enzymes were slightly elevated. He was oliguric with dark-colored urine. Routine urine analysis showed positive dipstick for blood with no RBC in microscopic examination. Serum total creatinine kinase and urine myoglobin were significantly high confirming the diagnosis of rhabdomyolysis (all laboratory values shown in Table 1). His ECG found to have junctional rhythm, in echocardiography, there was normal left ventricular systolic function with grade II diastolic dysfunction, congested inferior vena cava (IVC) with normal right ventricle and valvular structure. There was no pericardial effusion. A chest radiogram showed congested hilum, no effusion or consolidation. Human immunodeficiency virus (HIV) serology was nonreactive. Ultrasonography of the abdomen revealed to have normal kidney size and echotexture, normal liver size and echotexture, no evidence of free fluid in the abdomen, and no lymphadenopathy. Blood and urine cultures were sterile. Serology for leptospira and dengue were negative.

He was initially started with nor-adrenaline support for low blood pressure. Hemodialysis was initiated as he was oliguric, had evidence of metabolic acidosis and hyperkalemia with ECG changes. His hemodynamic parameters improved gradually after the correction of acidosis. ECG converted to normal sinus rhythm. He was weaned from vasopressor support within the next 24 h. Rosuvastatin was stopped. Post stabilization, nerve conduction velocity (NCV) study was conducted with median superficial radial, ulnar, bilateral common peroneal tibial and sural nerves including motor and sensory conduction study. It showed preserved distal latency with reduced compound muscle action potential (CMAP) amplitude and conduction velocity in bilateral tibial and common peroneal nerve. Sensory testing revealed to have reduced sensory nerve action potential (SNAP) amplitude with preserved distal latency and conduction velocity in the sural nerve. F waves were normal in latency and persistence. The rest of the nerves tested were normal. Electromyography (EMG) study in the right vastus muscle showed normal insertional activity with the absence of spontaneous activity. On volitional testing, observed motor unit action potential was polyphasic with short duration and amplitude, interference pattern was complete with early recruitment. He was diagnosed to have statin-induced myopathy with rhabdomyolysis and acute kidney injury.

Table 1: On-admission biochemical laboratory values for our patient

Parameter	Value	Parameters	Value
Hemoglobin	96 g/L	Bilirubin	5.81 µmol/L
Leucocyte	9.8×10^9/L	AST	477 IU/L
Platelet	274×10^9/L	ALT	251 IU/L
ESR	85 mm/h	Serum albumin	18 g/L
Lactate	1.95 mmol/L	Alkaline phosphate	147 IU/L
CRP	441 µg/L	Blood urea nitrogen	15.71 mmol/L
Procalcitonin	0.96 µg/L	Creatinine	521.68 µmol/L
hs-Trop I	86.6 ng/L	Sodium	128 mmol/L
CPK (total)	>10000 IU/L	Potassium	6.9 mmol/L
CPK-MB	1969 IU/L	Chloride	97 mmol/L
TSH	0.66 mIU/L	Total calcium	1.32 mmol/L
Urine myoglobin	710.2 µg/L	Phosphorus	1.57 mmol/L

L: Liter; ESR: Erythrocyte sedimentation rate; hs-Trop I: High-sensitivity troponin-I; CPK: Creatinine phosphokinase; AST: Aspartate aminotransferase; ALT: Alanine amino-transferase; CRP: C-reactive protein; TSH: Thyroid-stimulating hormone

Post stabilization, he was started with physiotherapy for lower limb weakness. He was discharged on day 5 of hospital admission, with instruction for periodic follow-up. His kidney functions gradually recovered over the next 3 weeks, and creatinine normalized after 6 weeks post-admission. His power in the lower limbs also improved gradually with complete motor recovery at 6 weeks.

Discussion

Statins are very commonly used drugs as lipid-lowering agents. All statins decrease LDL and very-low-density lipoprotein (VLDL) cholesterol and triglyceride and increase HDL cholesterol to a variable degree. LDL cholesterol is one of the major risk predictors of atherosclerotic cardiovascular disease (ASCVD). Roughly it is said that reduction of LDL cholesterol by 1% approximately reduces ASCVD risk by 1%.[1] Studies and controlled trials have shown that statins are overall well-tolerated and have fewer drug-drug interactions and overall good patient acceptance. They are one of the mainstay agents used currently in primary and secondary prevention of atherosclerotic cardiovascular heart disease. Notable adverse effects are 1) statin-associated muscle symptoms (SAMS), 2) acute kidney injury (AKI), 3) hepatitis and fulminant hepatic failure, and 4) new-onset diabetes mellitus.

Statin-associated muscle symptoms (SAMS) has a wide range of the clinical spectrum. It can be from subjective myalgia without elevation of muscle enzymes, serious myopathy with muscle pain and weakness along with elevation of muscle enzymes (myositis) to the severest form of rhabdomyolysis with AKI. Incidence of rhabdomyolysis with currently available statins is reported to be in the ranges from 0.6 to 1.2 per 10,000 person-years.[2] The risk factor of developing SAMS include female gender, advanced age (especially more than 80 years), small body frame and frailty, chronic kidney disease, hepatic insufficiency, physical disability, perioperative period, and polypharmacy.[3] The myositis happens more commonly in patients with concomitant use of drugs like cyclosporin, azole antifungals, macrolide antibiotics, HIV protease

inhibitors, alcohol abuse, verapamil, consumption of grapefruit juice in large quantities, and other lipid-lowering agents like niacin and fibrates.

All statins are associated with SAMS. Fluvastatin and pravastatin are least likely to be associated with myopathy followed by rosuvastatin. Atorvastatin, lovastatin, and simvastatin in order with the increasing association of myopathy (https://www.pogoe.org/ask/statins). The differential effect on myopathy maybe because of some pharmacokinetic differences related to potency, drug metabolism, protein binding capacity, and drug interaction.

Rosuvastatin is a relatively newer generation of statin approved by the Food and Drug Administration (FDA) in 2003. Rosuvastatin is the most potent statin and has the longest half-life (20.8 h) [3]. It is relatively hydrophilic.[4] Its oral bioavailability is 20%. It has relatively low drug-drug interaction as compared to other statins (less metabolism with CYP 3A4 system). Only 10% of rosuvastatin requires active drug metabolism (CYP 2C9) with clearance predominantly by the fecal route. Advancing age has no clinically meaningful pharmacokinetic effect on rosuvastatin metabolism. Concomitant administration of ciclosporin and gemfibrozil increases rosuvastatin concentration. Dose modification is required in a patient with severe renal impairment (in GFR <30 mL/min/1.73 m^2, the dose should not exceed 10 mg once daily).[3] There are case reports of rosuvastatin-induced rhabdomyolysis when prescribed with ticagrelor.[5] Comparative studies revealed that rosuvastatin has higher LDL-C lowering property[6,7] and may have higher atherosclerosis reducing effect when compared to other commonly used statins.[8,9]

Nevertheless, there are controversies regarding its safety we should not overlook. Soon after its approval by the FDA (July 9th, 2003), its safety became disputed. A petition was filed by public citizens, a US advocacy group, to ban this drug because of seven cases of severe rhabdomyolysis in the United States, Canada, and the United Kingdom, within a few months post-launch.[10] Another post-marketing analysis published in 2005 revealed that adverse events (rhabdomyolysis, proteinuria/nephropathy, or renal failure) associated with per million prescriptions of rosuvastatin were significantly higher than those seen with atorvastatin, pravastatin, and simvastatin.[11] On the basis of the above mentioned facts, FDA conducted a detailed study of all the cases cited in the petition and found out that the incidence of rhabdomyolysis in those cases was either due to prescription at higher than the recommended dose or due to associated drug interaction. They finally cleared rosuvastatin off accusations and directed marketing with minor labeling changes.[12] Another recent population-based study also showed a higher risk of abnormally raised muscle enzymes[13] and higher hazard ratio for rhabdomyolysis[14] for rosuvastatin when compared to atorvastatin. It may also cause non-rhabdomyolysis acute kidney injury[15] (proteinuria, hematuria, and renal tubular toxicity). In a randomized study (PLANET-I), comparing rosuvastatin 40 mg with atorvastatin 80 mg in the diabetic patient with nephropathy, atorvastatin was found to be a superior reno-protective agent than rosuvastatin.[16] Despite the reported incidence of higher renal toxicity by rosuvastatin, in the present era of "statin war," it holds a major market across the globe, the main reason being higher cholesterol-lowering potency when compared mg to mg basis.[17]

In the present case only positive causal association for rhabdomyolysis was the initiation of rosuvastatin within the last 1 month. The gentleman had no known risk factors for the development of rhabdomyolysis (preexisting renal impairment, concomitant drugs, and higher than the recommended dose). Though the case was successfully treated with hemodialysis, and withholding the culprit drug, and the patient recovered muscle power completely after few weeks of stopping the offending drug, it added to significant morbidity and health care cost.

Conclusion

Stains are a widely prescribed drug for primary and secondary prevention of atherosclerotic cardiovascular diseases. Rosuvastatin, although pharmacologically safe, can have serious side effects like rhabdomyolysis. The present case report adds to the already existent safety controversies associated with rosuvastatin and warrants greater pharmacovigilance while prescribing this drug, especially in the older population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Acknowledgments

Apollo Hospital, Navi Mumbai.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cholesterol Treatment Trialists (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, *et al*. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

2. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol 2016;67:2395-410.
3. Jacobson TA. Overcoming 'ageism' bias in the treatment of hypercholesterolaemia: A review of safety issues with statins in the elderly. Drug Saf 2006;29:421-48.
4. Davidson MH. Rosuvastatin in elderly patients. Drugs Aging 2007;24:933-44.
5. Vrkić Kirhmajer M, Macolić Šarinić V, Šimičević L, Ladić I, Putarek K, Banfić L, *et al*. Rosuvastatin-induced rhabdomyolysis-possible role of ticagrelor and patients' pharmacogenetic profile. Basic Clin Pharmacol Toxicol 2018;123:509-18.
6. Schuster H, Barter PJ, Stender S, Cheung RC, Bonnet J, Morrell JM, *et al*. Effective Reductions in Cholesterol Using Rosuvastatin Therapy I Study Group. Effects of switching statins on achievement of lipid goals: Measuring effective reductions in cholesterol using rosuvastatin therapy (MERCURY I) study. Am Heart J 2004;147:705-13.
7. Gandhi SK, Järbrink K, Fox KM, Brandrup-Wognsen G. Effectiveness of rosuvastatin in reducing LDL-C and target LDL-C goal attainment in real-world clinical practice. Curr Med Res Opin 2009;25:2817-28.
8. Pitt B, Loscalzo J, Monyak J, Miller E, Raichlen J. Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study). Am J Cardiol 2012;109:1239-46.
9. Qian C, Wei B, Ding J, Wu H, Cai X, Li B, *et al*. Meta-analysis comparing the effects of rosuvastatin versus atorvastatin on regression of coronary atherosclerotic plaques. Am J Cardiol 2015;116:1521-6.
10. Petition to Ban Cholesterol-Lowering Drug Rosuvastatin (Crestor) - Public Citizen. Available from: https://www.citizen.org/article/petition-to-ban-cholesterol-lowering-drug-rosuvastatin-crestor/. [Last accessed on 2020 Jul 05].
11. Alsheikh-Ali A, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: A postmarketing analysis. Circulation 2005;111:3051-7.
12. Regulations.gov-Docket Browser. Available from: https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&D=FDA-2004-P-0009. [Last accessed on 2020 Jul 05].
13. Van Staa TP, Carr DF, O'Meara H, McCann G, Pirmohamed M. Predictors and outcomes of increases in creatine phosphokinase concentrations or rhabdomyolysis risk during statin treatment. Br J Clin Pharmacol 2014;78:649-59.
14. Coste J, Billionnet C, Rudnichi A, Pouchot J, Dray-Spira R, Giral P, *et al*. Statins for primary prevention and rhabdomyolysis: A nationwide cohort study in France. Eur J Prev Cardiol 2019;26:512-21.
15. Ward FL, John R, Bargman JM, McQuillan RF. Renal tubular toxicity associated with rosuvastatin therapy. Am J Kidney Dis 2017;69:473-6.
16. De Zeeuw D, Anzalone DA, Cain VA, Cressman MD, Heerspink HJ, *et al*. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): A randomised clinical trial. Lancet Diabetes Endocrinol 2015;3:181-90.
17. Wolfe S. Rosuvastatin: Winner in the statin wars, patients' health notwithstanding. BMJ 2015;350:h1388.