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Kidney Biopsy Teaching Case

Renal Tubular Toxicity Associated With Rosuvastatin Therapy

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Preapproval clinical trials examining the safety and efficacy of rosuvastatin demonstrated an increased incidence of proteinuria, hematuria, rhabdomyolysis, and other acute kidney injury of unknown cause at high doses. The latter cases manifested with urine sediment findings and in some cases, renal histology, indicating renal tubular injury in the absence of rhabdomyolysis. Despite these provocative findings, there have been very few reports in the literature regarding non−rhabdomyolysis-mediated acute kidney injury associated with high-dose rosuvastatin since its widespread introduction more than a decade ago, suggesting that it is either a rare entity or systematically underdiagnosed and under-reported. We present a case of renal tubular toxicity attributable to the initiation of rosuvastatin treatment at a dose of 40 mg in a patient with no prior evidence of kidney disease. Tubular toxicity should be considered in cases of unexplained kidney injury in the setting of exposure to a potent statin such as rosuvastatin, particularly at high dose. The limited evidence suggests a good kidney prognosis following withdrawal of the agent in these cases.

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INDEX WORDS: Acute kidney injury (AKI); statin; rosuvastatin; tubular toxicity; acute tubular necrosis.

INTRODUCTION

The advent of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition, hereafter referred to as "statin therapy," has led to significant benefits in the primary and secondary prevention of coronary artery disease and stroke.[1-3] In patients with chronic kidney disease (CKD), statin therapy significantly reduces major cardiovascular events.[4] In kidney transplant recipients, these agents reduce cardiovascular mortality and can lower the incidence of nonfatal myocardial infarction.[5] Statins act by lowering plasma low-density lipoprotein (LDL) cholesterol levels through increased hepatic LDL receptor expression and reduced de novo biosynthesis by inhibiting mevalonate synthesis.[6] Statins can also improve endothelial function and have anti-inflammatory effects on the vasculature.[7-9]

The primary clinically relevant adverse effect encountered with statin use is myopathy, and although still rare, it is seen with increased frequency at higher prescribed statin doses and with concomitant administration of certain drugs, particularly fibrates, niacin, and inhibitors of the enzyme cytochrome P450 3A4, such as cyclosporine, azoles, macrolides, and protease inhibitors. Postmarketing reviews of the first year of rosuvastatin use in clinical practice demonstrated that it was more likely to be associated with a composite kidney adverse end point of rhabdomyolysis, proteinuria, nephropathy, or kidney failure when compared with both concurrent users of other statins (atorvastatin, simvastatin, and pravastatin) and the first postmarketing year of these other statins.[10] Acute kidney injury (AKI) in association with statin use is predominantly caused by rhabdomyolysis leading to acute tubular necrosis, often in the setting of concurrent fibrate use or with another interacting medication.[11-13] Statin-associated acute interstitial nephritis has also rarely been reported.[14,15] We report a case of AKI attributable to direct tubular toxicity associated with initiation of high-dose rosuvastatin treatment, in the absence of rhabdomyolysis.

CASE REPORT

Clinical History and Initial Laboratory Data

A 53-year-old woman with non−insulin-dependent diabetes and hypertension presented with a subacute increase in serum creatinine level and new-onset proteinuria. The patient was asymptomatic and clinically well, with no myalgia or myopathy. There was no history of diabetic retinopathy, and recent screening for microalbuminuria in the past year had negative results. Long-term medications included telmisartan, linagliptin, metformin, and amlodipine. Rosuvastatin was the only recent additional prescription, started 14 months earlier at 40 mg daily, for primary prevention of ischemic heart disease. There was no exposure to nonsteroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast agents, or other nephrotoxic agents. The family history was significant for ischemic heart disease, diabetes, and hypertension. On examination, the office blood pressure was 130/80 mm Hg. Body mass index was calculated at 46 kg/m^2. Systemic examination was otherwise noncontributory.

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On presentation, serum creatinine level was 1.86 (reference range, 0.5-1.2) mg/dL, corresponding to estimated glomerular filtration rate (eGFR; calculated with the CKD-EPI [CKD Epidemiology Collaboration] creatinine equation) of 35 mL/min/1.73 m^2. Creatinine level was recorded at 1.42 mg/dL (eGFR, 48 mL/min/1.73 m^2) 6 months earlier and at 0.76 mg/dL (eGFR, 104 mL/min/1.73 m^2) 18 months earlier (Fig 1). Serum electrolyte levels and routine hematology panel results were within normal ranges. Hemoglobin A_{1c} level was 7.1%, and total cholesterol was 169 (LDL cholesterol, 92) mg/dL. Serum creatine kinase level was only mildly elevated at 301 (reference range, <195) U/L. The ultrasound showed normal appearance of both kidneys. Urinalysis demonstrated moderate microscopic hematuria and albuminuria with albumin excretion of 1 g/L. Urine protein-creatinine ratio was elevated at 1.8 (reference range, <0.2) mg/mg. Urine microscopy demonstrated innumerable granular and hemegranular casts, with isomorphic red blood cells and white blood cells present.

Kidney Biopsy

Light microscopy demonstrated 18 glomeruli, and none was globally sclerosed. Glomeruli showed mild capillary wall wrinkling without an increase in mesangial matrix or mesangial cellularity, and no endocapillary hypercellularity. There were no segmental scars. Proximal tubular toxicity was evident by luminal ectasia, simplification, loss of brush border, and variegated cytoplasmic staining. There was mild interstitial edema and inflammation without tubulitis (Fig 2A and B). No crystals were seen, including under polarized light. There was mild interstitial fibrosis (10%-15%). Direct immunofluorescence showed no staining for immunoglobulin G (IgG), IgA, IgM, C3, C1q, or κ or λ light chains. Electron microscopy showed no glomerular electron-dense deposits, and basement membranes had a mean thickness of 304 nm. Proximal tubules showed denudation without specific mitochondrial changes (Fig 2C).

Diagnosis

Histologic findings were consistent with ongoing renal tubular injury with mild chronic changes, possibly related to a drug. In the absence of another plausible cause and given that the only recently introduced medication was a high-dose potent statin, we suspected rosuvastatin-induced direct tubular toxicity.

Clinical Follow-up

Rosuvastatin treatment was discontinued at the initial presentation based on concerns of a drug-induced AKI, with no changes to other medications. By the time of kidney biopsy 2 weeks later, serum creatinine level had already improved to 1.13 mg/dL (eGFR, 64 mL/min/1.73 m^2). This was in keeping with the suspected diagnosis of a statin-induced nephrotoxicity. Three months later, serum creatinine level was 1.06 mg/dL (eGFR, 69 mL/min/1.73 m^2) and urinalysis was negative for both hematuria and proteinuria. Total cholesterol level was now elevated at 239 mg/dL, and treatment with atorvastatin, 40 mg daily, was initiated. The patient soon developed severe myalgia requiring discontinuation of atorvastatin treatment. Fifteen months after presentation, with no statin therapy, serum creatinine level was 0.89 mg/dL (eGFR, 85 mL/min/1.73 m^2) with no proteinuria (protein-creatinine ratio, <0.2 mg/mg). This may represent a decline in the patient's baseline kidney function following this episode of AKI.

DISCUSSION

Statin-induced direct tubular toxicity is an infrequently reported cause of AKI. Tubular toxicity was evident in this case based on urine microscopy and histologic findings on kidney biopsy. Except for the preceding introduction of rosuvastatin at a high dose, there was no other plausible cause for these findings. Discontinuation of treatment with the drug was associated with kidney recovery. The pre-existing conditions of diabetes and hypertension may have also increased the patient's susceptibility to developing AKI.[16] Van Zyl-Smit et al[17] previously reported a case of direct renal tubular toxicity, which was associated with escalation of a patient's rosuvastatin dose to 80 mg daily and subsequently resolved completely with discontinuation of treatment with the drug. Upon rechallenging with both rosuvastatin and subsequently atorvastatin, urinary abnormalities suggestive of tubular toxicity reappeared.

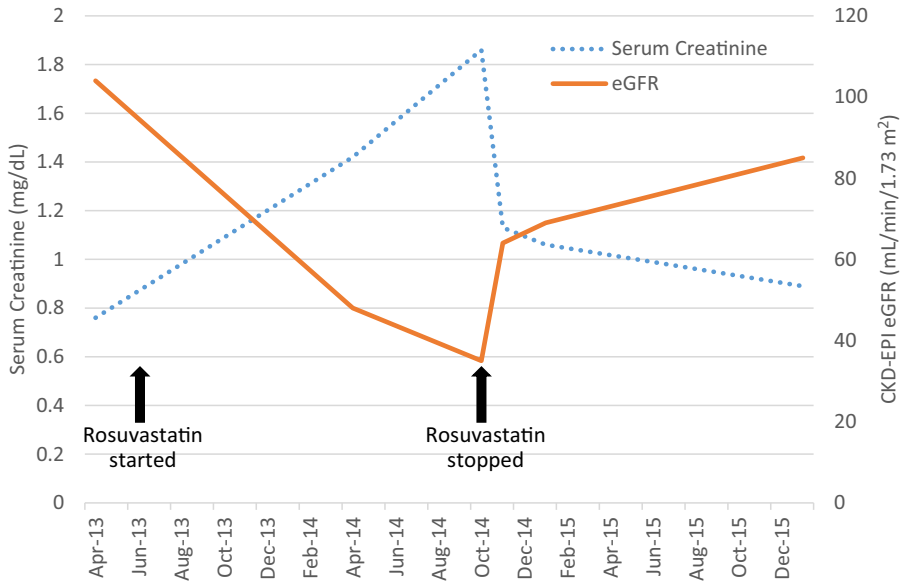

Figure 1. Trend in serum creatinine levels and estimated glomerular filtration rates (eGFRs) over time. Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.