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CASE REPORT

INTERMEDIATE

CLINICAL CASE

Acute Tubular Injury in a Patient on a Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor

June K. Pickett, MD,[a] Maulin Shah, MD,[a,b,c] Michael Gillette, PharmD,[b] Peter Jones, MD,[a] Salim Virani, MD, PhD,[a,b] Christie Ballantyne, MD,[a] Vijay Nambi, MD, PhD[a,b,d]

ABSTRACT

A 72-year-old man with coronary artery disease, statin intolerance, and chronic kidney disease stage IIIa was initiated on alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, and developed acute kidney injury. A kidney biopsy was performed and suggested acute tubular injury. The serum creatinine returned to baseline after discontinuation of alirocumab. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:1042–5) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 72-year-old man with a past medical history of coronary artery disease (CAD), atrial fibrillation, diabetes mellitus, chronic kidney disease (CKD) IIIa, esophageal cancer in remission, hyperlipidemia, and statin intolerance was seen in the cardiology clinic for his CAD. The patient was asymptomatic and, overall, doing well. His medications included losartan, aspirin, ezetimibe, apixaban, diltiazem, furosemide, omeprazole, and gabapentin. He was a nonsmoker.

LEARNING OBJECTIVE

- To consider acute kidney injury as a potential rare side effect of PCSK9-I.

Physical examination demonstrated a blood pressure of 125/75 mm Hg and normal cardiovascular, respiratory, abdominal, and neurological examination. Laboratory examination was significant for a

From the [a]Department of Medicine, Baylor College of Medicine, Houston, Texas; [b]Michael E DeBakey Veterans Affairs Hospital, Houston, Texas; [c]Section of Nephrology, Baylor College of Medicine, Houston, Texas; and the [d]Division of Atherosclerosis and Vascular Medicine, Methodist DeBakey Heart and Vascular Center, Methodist Hospital, Houston, Texas. Dr. Shah has served as principal investigator for a Leonard-Meron Biosciences, Inc-sponsored trial. Dr. Jones has served as a scientific advisory consultant for Esperion and Amarin. Dr. Virani has received research support from the Department of Veterans Affairs, World Heart Federation, Jooma and Tahir Family Honorarium, and serves as Associate Editor for *Innovations,* acc.org, American College of Cardiology; and is a Steering Committee member, Patient and Provider Assessment of Lipid Management (PALM registry) at the Duke Clinical Research Institute, for which he receives no financial remuneration. Dr. Ballantyne has received grant and research support paid to Baylor Medical College; has received support from Abbott Diagnostic, Akcea, Amgen, Esperion, Novartis, Regeneron, Roche Diagnostic, NIH, AHA, and ADA; and has served as consultant for Abbott Diagnostics, Akcea, Amarin, Amgen, Arrowhead, Astra Zeneca, Boehringer Ingelheim, Corvidia, Denka Seiken, Esperion, Gilead, Janssen, Matinas BioPharma Inc., Merck, Novartis, Novo Nordisk, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. Dr. Nambi has received VA MERIT grant 1I01CX001112-01; and is named on provisional patent no. 61721475 Biomarkers to Improve Prediction of Heart Failure Risk, filed by Baylor College of Medicine and Roche; and is the site principal investigator for a study sponsored by Merck and Amgen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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 *JACC: Case Reports* author instructions page.

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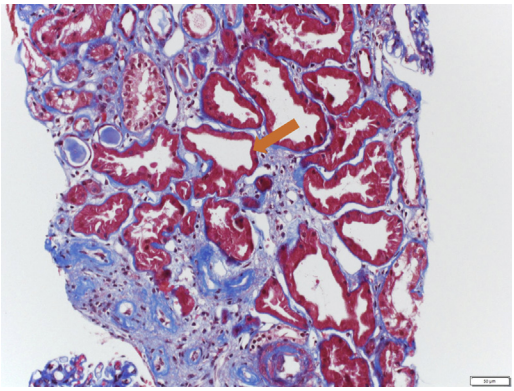
FIGURE 1 Light Microscopy With Trichrome Staining



The **orange arrow** shows tubular injury as evidenced by dilated tubules, flattened epithelium due to loss of brush border. **Blue staining** in the interstitium indicated interstitial fibrosis and atrophy (IFTA). In this biopsy, there is moderate IFTA of approximately 20% to 50%.

low-density lipoprotein-cholesterol (LDL-C) of 163 mg/dl on ezetimibe therapy. Patient noted he had been on simvastatin and atorvastatin previously; however, he did not tolerate these medications because of severe leg weakness and subsequent functional limitation and did not want to initiate any statin at any dose. Given his CAD and poorly controlled hyperlipidemia in the setting of statin intolerance, he was initiated on alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9-I). Two months after being on alirocumab 150 mg every 2 weeks, he had a decline in renal function, with his baseline serum creatinine (SCr) of approximately 1.3 mg/dl (estimated glomerular filtration rate [eGFR] ~55 ml/min/1.73 m^2), increasing to 2.3 mg/dl. Upon outpatient evaluation, the patient noted that he was in his usual state of health and had no new complaints or interval events. He had received no iodinated contrast material and had no known medication changes other than addition of alirocumab. He was referred to nephrology for further assessment.

PAST MEDICAL HISTORY

The patient has a history of stable CAD, permanent atrial fibrillation, diabetes mellitus, familial hypercholesterolemia (LDL- C had been as high as 217 mg/dl in the past), CKDIIIa, and esophageal cancer in remission. Last coronary angiography done for symptoms of exertional dyspnea in 2018 revealed 50% stenosis of left anterior descending (LAD) artery with a fractional flow reserve of 0.91 as well as 70% mid-vessel stenosis of a small right coronary artery.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the acute kidney injury (AKI) in this patient after initial physical examination and preliminary laboratory data (see the following) included urate nephropathy, glomerulonephritis, interstitial nephritis, or toxic mediated acute tubular injury.

INVESTIGATIONS

Urinalysis revealed subnephrotic proteinuria (urine protein 30 mg/dl), microscopic hematuria (3 red blood cells per high power field) and pyuria (1 white blood cell per high power field). Additional work-up revealed an elevated serum uric acid of 20 mg/dl. Allopurinol was started, and uric acid improved to 9.0 mg/dl within 1 month. However, the SCr did not improve after reduction and stabilization of uric acid and discontinuation of losartan; therefore, the patient's nephrologist recommended a kidney biopsy. The kidney biopsy (Figures 1 and 2) revealed dilated tubules and flattened epithelium from loss of proximal tubular cell brush border, consistent with acute tubular injury. There was no evidence of uric acid crystals on biopsy. There were also thickened glomerular basement membranes, nodular mesangial matrix expansion, and hyaline material within arteriole vessel walls, which are features consistent with a background of diabetic nephropathy.

MANAGEMENT

Given the time course and no other clear explanation of persistent AKI after discontinuation of medications and improvement in uric acid, it was suspected that alirocumab may be contributing to the cause of the acute tubular injury. Alirocumab was discontinued, and the serum creatinine subsequently improved and returned to a baseline creatinine of 1.3 mg/dl in approximately 3 months (Figure 3).

DISCUSSION

The American Heart Association/American College of Cardiology Multisociety 2018 Cholesterol Guidelines have recommended as a Class I indication the initiation of high -intensity or maximal statin therapy for those with atherosclerotic cardiovascular disease (ASCVD). They also recommend that if LDL-C is

ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury

ASCVD = atherosclerotic cardiovascular disease

CAD = coronary artery disease

CKD = chronic kidney disease

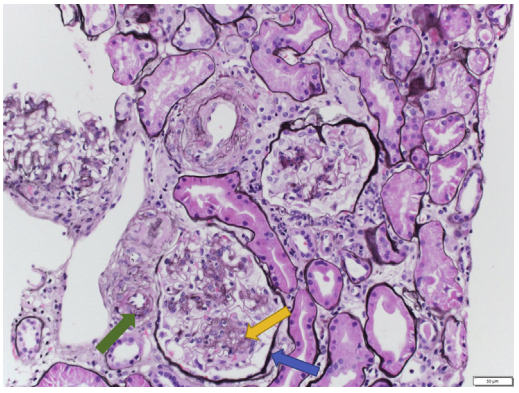
IFTA = interstitial fibrosis and atrophy

LDL-C = low-density lipoprotein-cholesterol

PCSK9-I = proprotein convertase subtilisin/kexin type 9 inhibitor

SCr = serum creatinine

FIGURE 2 Light Microscopy With Methenamine Silver-Periodic Acid-Schiff (Jones) Stain



The **blue arrow** shows glomeruli have thickened glomerular basement membrane. The **yellow arrow** shows evidence of mesangial matrix expansion. The **green arrow** shows hyaline material within arteriole vessel walls.

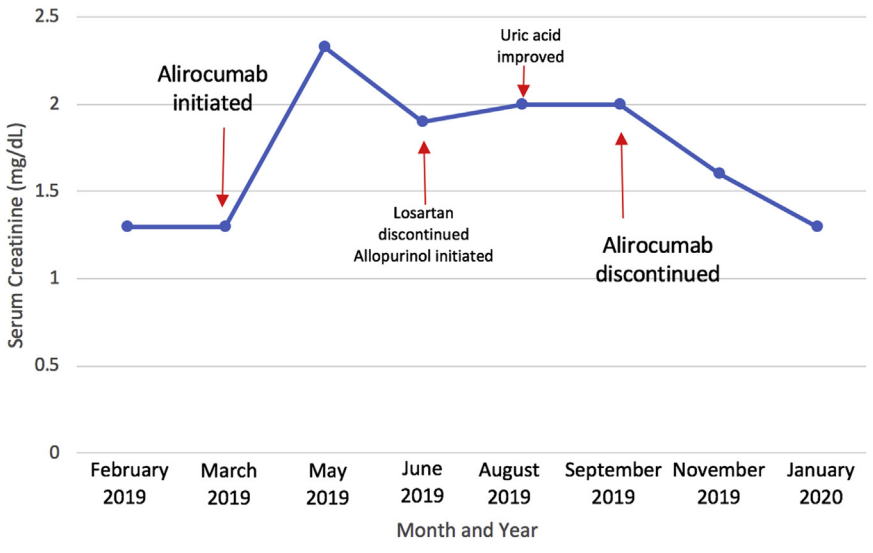
>70 mg/dl on maximally tolerated statin, it is appropriate to initiate ezetimibe in very high-risk patients with ASCVD. If, after this patient is still in need of LDL-C reduction, it is a Class IIa indication to initiate PCSK9-I, as was done in our patient (LDL-C of 163 mg/dl) (1).

In our review of literature, there has been only 1 other report of alirocumab-induced kidney injury in a patient with stage IV CKD as well as a report of a patient with normal renal function who developed AKI after receiving an experimental drug SPC5001, an antisense oligonucleotide directed against PCSK9 (2,3). The mechanisms of kidney injury were unclear in these cases, and both were managed conservatively. In the clinical trials that have evaluated alirocumab and evolocumab, they have been well tolerated, in general, with the most common reported adverse events leading to discontinuation being injection-site reactions, myalgias, neurocognitive events, and ophthalmologic events. Additional side-effects include nasopharyngitis, hypersensitivity vasculitis, and influenza-like symptoms. There are no reports of AKI in the alirocumab safety trials, although subjects with GFRs of <30 ml/min/m^2, HbA1c >10.0% were excluded (4). It is unclear if the mechanism of AKI with alirocumab in our case is direct toxicity or if the patient was predisposed to AKI from another cause (5). However, in general, patients at risk for drug-induced nephrotoxicity include those with CKD, diabetes, intravascular volume depletion, congestive heart failure, and sepsis (5).

FOLLOW-UP

The SCr slowly returned to baseline 3 months after discontinuation of alirocumab, and his LDL-C was 118 mg/dl. The LDL-C after 8 doses (approximately 16 weeks) of alirocumab was 94 mg/dl. Thus, we believe that the LDL-C of 118 mg/dl after discontinuation of alirocumab was likely reflective of the residual effect of medication and that the LDL-C will continue to increase. The patient is hesitant to

FIGURE 3 Time Frame of Kidney Injury Related to Alirocumab Initiation



initiate a statin, even at lower doses, given previous symptoms of severe leg weakness, and he continues to take ezetimibe. We will consider the addition of bempedoic acid when it is available. Alternatively, after discussion with nephrology, we have considered initiating evolocumab instead of alirocumab, with the consideration that some idiosyncratic reactions related to other constituents that make up alirocumab may have played a role in the renal injury that may not be related to the PCSK9-I. If he is started on evolocumab, we would monitor kidney function earlier in treatment and more frequently. However, we are waiting 3 months after stabilization of renal function before considering evolocumab.

CONCLUSIONS

This case highlights the temporal development of AKI—specifically, acute tubular injury—after initiation of the PCSK9-I alirocumab. The time course and resolution of AKI after stopping alirocumab suggested the AKI might have been associated with the PCSK9-I, although the mechanism is unclear. Given the more frequent use of the PCSK9-I, clinicians should be aware of this rare possible side effect in patients at high risk for AKI, especially as the effects will be longer term. Subsequent management strategies for hyperlipidemia will need to involve clinician-patient discussion with consideration of alternate therapies. Additional studies should be considered to study the efficacy and safety of PCSK9-I in patients with more advanced CKD.

ADDRESS FOR CORRESPONDENCE: Dr. Vijay Nambi, Baylor College of Medicine, 6565 Fannin Street, MS A601/STE B160, Houston, Texas 77030. E-mail: vnambi@bcm.edu.

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:3168–209.

2. Jhaveri KD, Barta VS, Pullman J. Praluent (alirocumab)-induced renal injury. J Pharm Pract 2017;30:7–8.

3. Van Poelgeest EP, Swart RM, Betjes MG, et al. Acute kidney injury during therapy with an antisense oligonucleotide directed against PCSK9. Am J Kidney Dis 2013;62:796–800.

4. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489–99.

5. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev 2016;37:85–98.

KEY WORDS cardiovascular disease, hypercholesterolemia, secondary prevention