

[CASE REPORT]

Acute Tubular Necrosis Associated with Angiotensin Receptor-neprilysin Inhibitor

Moo Jun Kim¹, Ha Nee Jang², Haa-Na Song³, Jong Sil Lee⁴ and Min Gyu Kang⁵

Abstract:

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), significantly reduces mortality and morbidity in patients with chronic heart failure with a reduced ejection fraction (HFrEF). However, a considerable number of patients treated with sacubitril/valsartan experience hypotension, oliguria, progressive azotemia, and renal failure as adverse events. These issues have been linked to significant gaps in the usage and dosing of guideline-directed medical therapy with ARNI in patients with HFrEF. We herein report a relevant case of pathologically proven acute tubular necrosis after the first dose of sacubitril/valsartan, highlighting the importance of optimizing the medical therapy in an outpatient with HFrEF.

Key words: angiotensin receptor-neprilysin inhibitor, heart failure with reduced ejection fraction, acute tubular necrosis, HFrEF

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Introduction

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), reportedly reduces the risk of cardiovascular death or heart failure hospitalization in patients with chronic heart failure with a reduced ejection fraction (HFrEF). Combination of neurohormonal modulators is superior to angiotensin-converting-enzyme inhibitor (ACEI), even at a suboptimal dose (1). Sacubitril/valsartan was shown to be associated with a significant reduction in blood pressure and less renal impairment than enalapril. However, there is limited information available on renal hemodynamics; therefore, sacubitril/valsartan should be given cautiously due to the risk of acute or chronic adverse effects.

We herein report a relevant case of acute tubular necrosis (ATN) induced by a conventional dose of sacubitril/valsartan in an outpatient of HFrEF.

Case Report

A 58-year-old man with exertional dyspnea presented to the outpatient department. He had a history of myocardial infarction treated with percutaneous coronary intervention 20 years previously and received guideline-directed medical therapy, including aspirin (100 mg once daily), valsartan (80 mg once daily), bisoprolol (2.5 mg once daily), and atorvastatin (10 mg once daily). Hypertension and smoking (more than 20 pack years) were risk factors of earlier myocardial infarction. He had a blood pressure of 108/70 mmHg and a regular heart rate of 66 beats per minute.

On a physical examination, generalized edema and weight gain were absent. Electrocardiography showed Q waves in the precordial leads. The electrolyte balance, albumin level, and renal function were normal (sodium 138.9 mmol/L, potassium 3.8 mmol/L, chloride 102.4 mmol/L, total CO₂ 23 mmol/L, albumin 4.6 g/dL, blood urea nitrogen 10.1 mg/dL,

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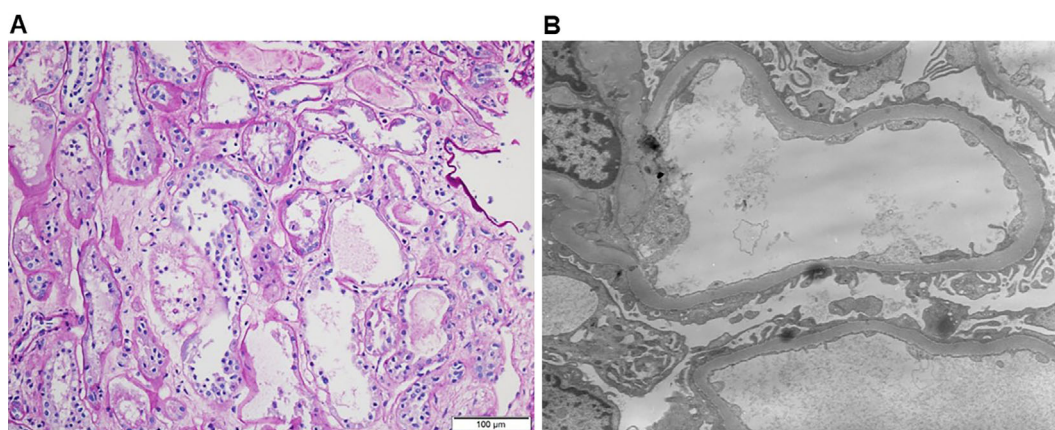


Figure 1. (A) A kidney biopsy revealed the features of ischemic acute tubular injury on PAS stain: coarse vacuolization, flattened epithelium, necrosis, cellular cast and reduction of brush borders ($\times 200$). (B) Ultrathin section of a glomerulus shows focal areas of epithelial foot process fusion and segmental mesangial expansion. Electron-dense deposits are not found ($\times 4,000$).

and creatinine 0.84 mg/dL). Urine chemistry was following; sodium 136.4 mmol/L, potassium 52.9 mmol/L, chloride 128.5 mmol/L, osmolality 808 mosm/kg, and creatinine 234.5 mg/dL.

Echocardiography was used to assess the severely reduced ejection fraction (EF) with dilated left ventricle (LV) dimensions (LVEF 34%, LV end-diastolic dimension 60 mm). The patient's valsartan (80 mg once daily) was replaced with sacubitril/valsartan (50 mg twice daily). Based on the home blood pressure recorded a month after sacubitril/valsartan use, we noted that his ambulatory systolic blood pressure was typically in the low range of 90-100 mmHg.

Six weeks later, the patient was admitted to the emergency room due to oliguria and generalized edema. On a physical examination, his initial blood pressure was 100/60 mmHg, with a peripheral pulse rate of 62 beats per minute. A blood test revealed that the creatinine level had surged from 0.88 to 18.64, and his blood urea nitrogen level was 107.0 mg/dL. His electrolytes were imbalanced and the albumin level was decreased (sodium 127.9 mmol/L, potassium 4.8 mmol/L, chloride 87 mmol/L, total CO₂ 14 mmol/L, albumin 3.1 g/dL). An arterial blood gas analysis revealed the following: pH 7.35, bicarbonate 14.6 mmol/L, and pCO₂ 26.5 mmHg. Urine examination was following; sodium 48.4 mmol/L, potassium 16.9 mmol/L, chloride 32.3 mmol/L, osmolality 302 mosm/kg, creatinine 129.3 mg/dL, and protein/creatinine 0.4. Fractional excretion of sodium was 6.67%, suggesting ATN or intrinsic renal failure. Anemia was significant (hemoglobin 8.0 g/dL, hematocrit 27%, iron 30 μ g/dL, total iron binding capacity (TIBC) 208 μ g/dL, transferrin saturation 14%, ferritin 206.6 ng/mL, normocytic normochromic anemia with anisocytosis in peripheral blood smear).

Emergency hemodialysis was initiated. A renal ultrasound examination demonstrated normal-sized kidneys without hydronephrosis, but the renal resistive indices were between 0.75 and 0.85. Echocardiography showed an improved

LVEF compared with 6 weeks earlier (38% to 43%). Five days after admission, a renal biopsy confirmed extensive ischemic damage to the tubules, including coarse vacuoles, flattened epithelial, cellular casts, thinning and loss of apical cytoplasm, and reduced brush borders, strongly indicating ATN (Fig. 1A). Electron microscopy revealed apparent epithelial cell foot process effacement (Fig. 1B). An ultrathin section of a glomerulus showed focal areas of epithelial foot process fusion and segmental mesangial expansion, which are non-specific changes excluding nephrotic syndrome. Seven days after admission, duodenofiberscopy revealed a duodenal ulcer that had likely caused iron deficiency anemia. He was therefore diagnosed with renal anemia due to pre-existing iron deficiency anemia.

The development of impaired renal hemodynamics, influenced by systemic hypotension after sacubitril/valsartan treatment, was thought to be a main pathogenesis of ATN. The acute kidney injury (AKI) might have been induced by pre-existing anemia that had exacerbated the oxygen demand-supply mismatch in the renal vasculature. The patient's urine output and renal function improved after discontinuation of sacubitril/valsartan and the performance of hemodialysis four times (Fig. 2).

During the 1-month follow-up, his blood pressure was 126/80 mmHg, and his heart rate was 60 beats per minute. Electrolyte balance and renal function were normalized. Valsartan (80 mg once daily), an angiotensin receptor blocker (ARB), was added, but the use of an ARNI or mineralocorticoid receptor antagonist (MRA) was limited due to the substantial risk of hypotension. The patient was followed up for blood pressure and blood tests every eight weeks. After 12 months, the anemia was corrected (hemoglobin, 13.7 g/dL; hematocrit, 43%) following treatment of duodenal ulcer. The individualized medical therapy for maintaining ARB and beta-blockers did not complicate the patient's renal function or heart failure for 18 months after discharge.

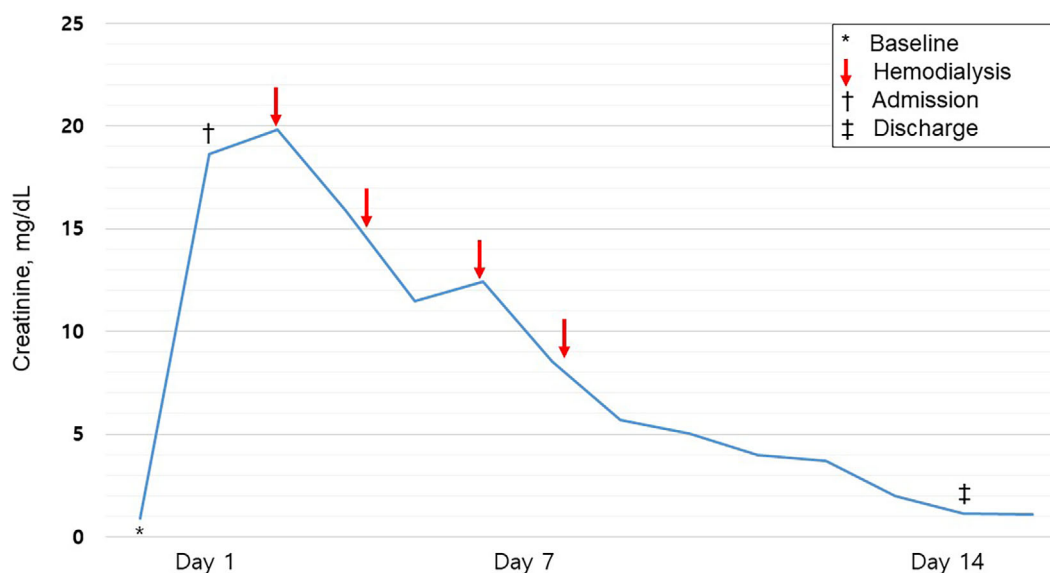


Figure 2. Serial changes in the serum creatinine level during hospitalization.

Discussion

We reported a case of ATN induced by a conventional dose of sacubitril/valsartan in an outpatient setting. To our knowledge, this is the first case of pathologically proven ATN associated with sacubitril/valsartan. In this case, pre-existing anemia might have an influence on progression of AKI.

ARNI is the first-line drug for HF treatment, and ACEI or ARB is recommended only when it is ARNI is difficult to administer (2). Recent data from clinical studies suggested that directly initiating ARNI, rather than conducting a pre-treatment period of ACEI or ARB therapy, was safe and effective (3). The two largest studies of sacubitril/valsartan in patients with HF, the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trials, achieved more favorable renal outcomes with sacubitril/valsartan than with an ACEI or ARB (1, 4).

The complex interconnections between the heart and kidneys in regulating fluids and electrolytes are markedly imbalanced in HF (5, 6). Optimal HF therapies allow the kidney to maintain its glomerular and tubular function. Data from PARADIGM-HF confirmed that sacubitril/valsartan was superior in terms of renal protection in HFrEF patients with chronic kidney disease and diabetic patients (7). However, a considerable proportion (approximately 5%) of patients treated with sacubitril/valsartan experienced hypotension, oliguria, progressive azotemia, and renal failure as adverse events in real-world practice, especially among East Asians (8). These issues of symptomatic hypotension and the risk of renal impairment were linked to significant gaps in the usage and dosing of guideline-directed medical ther-

apy for ARNI among patients with HFrEF (9, 10). Severe blood pressure drop caused by sacubitril/valsartan can aggravate renal ischemia (11, 12), resulting in progression of AKI, especially under conditions of oxygen demand-supply mismatch.

To our knowledge, this is the first biopsy-proven case of ATN after the use of sacubitril/valsartan. Clinical evidence, including the patient's history of drug use, the timing of AKI occurrence, a low range of blood pressure after sacubitril/valsartan, and histologic findings, supported the explanation of our report. Our case emphasizes the need for close blood pressure and renal function monitoring after ARNI administration. Furthermore, histologic confirmation in our case report provided the pathomechanism of AKI and help a management of ATN. The present findings suggest that strategies that is guideline-oriented and reflects the patient's realistic condition are required in management of chronic HFrEF.

In conclusion, when aiming for low blood pressure levels in the treatment of patients with HF, attention should be paid to ATN arising from ischemic AKI, even during treatment with an ARNI, which has a lower risk of AKI than monotherapy with RAS inhibitors.

The authors state that they have no Conflict of Interest (COI).

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