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【 CASE REPORT 】

Optimal Therapeutic Strategy Using Sacubitril/Valsartan in a Patient with Systolic Heart Failure and Chronic Kidney Disease - An Initial Case Report in Japan

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Abstract:
Sacubitril/valsartan has demonstrated its prognostic advantageousness over enalapril in patients with heart failure with a reduced ejection fraction. However, the optimal therapeutic strategy using sacubitril/valsartan in real-world practice, particularly among a Japanee cohort, remains uncertain. A 75-year-old man with systolic heart failure and chronic kidney disease was administered sacubitril/valsartan. Plasma B-type natriuretic peptide transiently increased, accompanied by an increase in the urine volume, which allowed us to terminate loop diuretics. The estimated glomerular filtration rate as well as heart failure symptom improved at the one-month follow-up. Sacubitril/valsartan might be a promising option to preserve the renal function and improve clinical outcomes when the dose of concomitant diuretics can be decreased, although further large-scale studies are warranted to validate our hypothesis.

Key words: hemodynamics, angiotensin receptor neprilysin inhibitor (ARNI), renal function

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Introduction

The clinical outcomes in patients with heart failure with a reduced ejection fraction have not yet been satisfactorily high despite the recent establishment of guideline-directed medical therapy, including beta-blockers, angiotensin-converting enzyme inhibitors, and mineralcorticoid antagonists (1).

In the PARADIGM-HF study (2), sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor, has demonstrated its advantageousness over enalapril, an angiotensin-converting enzyme inhibitor, in preventing cardiovascular death or heart failure readmissions in patients with heart failure with reduced ejection fraction. Sacubitril/valsartan has been approved by the Japanese National Health Insurance Program since August 2020. However, the practical therapeutic strategy using sacubitril/valsartan and patients' detailed response in real-world daily practice remains to be elucidated.

Care Report

On admission

A 75-year-old man with medical histories of hypertension and paroxysmal supraventricular tachycardia was admitted to our institute complaining of dyspnea on effort (New York Heart Association class III) due to the dilated phase of hypertrophic cardiomyopathy, which was previously diagnosed by an endo-myocardial biopsy. He had twice been hospitalized previously due to a worsening heart failure for the past two years.

Medication on admission was 2.5 mg/day of carvedilol, 2.5 mg/day of enalapril, and 4 mg/day of torasemide. He was intolerant to the further up-titration of carvedilol due to dizziness. His blood pressure was 141/92 mmHg and his heart rate was 86 bpm. His chest X-ray showed cardiomegaly and bilateral mild congestion. Saturation with 2 L of nasal cannula oxygenation support was 97%. Transthoracic echocardiography showed 64 mm of left ventricular

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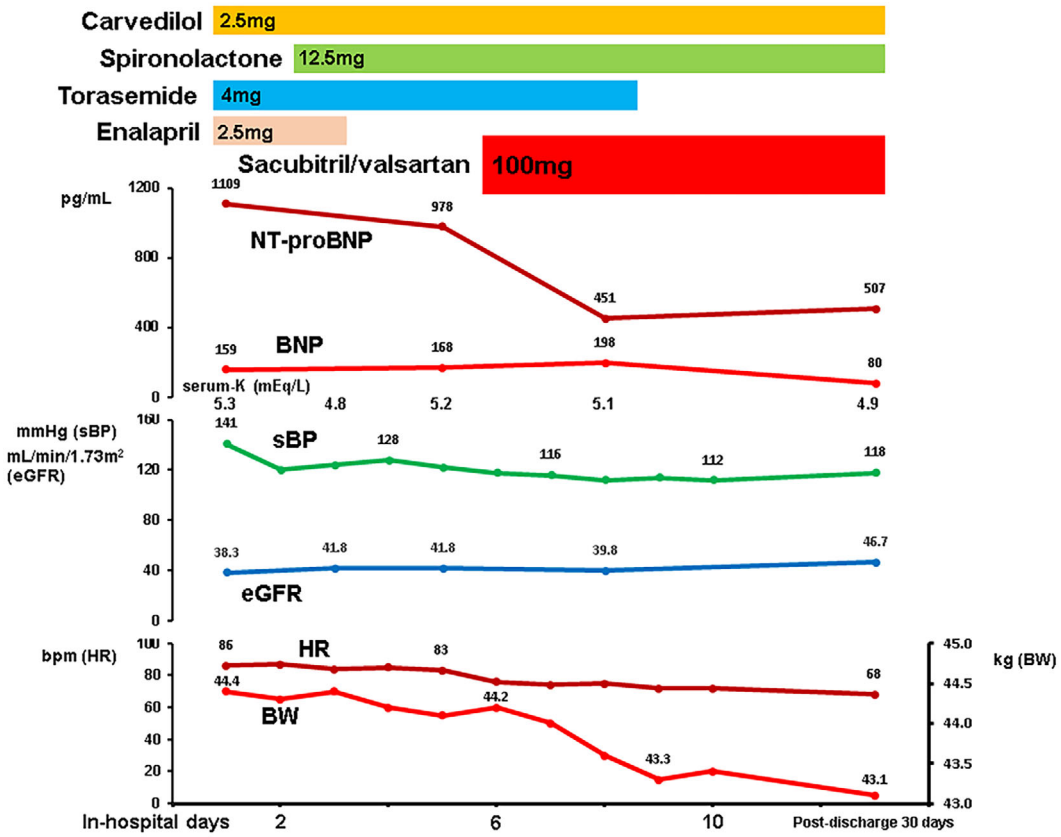

Figure. **Time course. After admission, we initiated 100 mg/day of sacubitril/valsartan to treat heart failure refractory to guideline-directed medical therapy. BNP: B-type natriuretic peptide, serum-K: serum potassium, sBP: systolic blood pressure, eGFR: estimated glomerular filtration rate, HR: heart rate, BW: body weight**

end-diastolic diameter, 26% of left ventricular ejection fraction (calculated by the modified Simpson's method), and mild mitral regurgitation. Plasma B-type natriuretic peptide (BNP) was 159 pg/mL, NT-proBNP was 1,109 pg/mL, and estimated glomerular filtration ratio (eGFR) was 38.3 mL/min/1.73 m^2.

In-hospital course

Following the administration of 12.5 mg/day of spironolactone on day 2, his systolic blood pressure remained 120-130 mmHg, serum potassium level remained around 5.0 mEq/L, and eGFR remained around 40 mL/min/1.73 m^2 (Figure). After 2 days following the termination of enalapril (day 4 and 5), we initiated 100 mg/day of sacubitril/valsartan for his refractory heart failure on day 6.

Following the initiation of sacubitril/valsartan

His systolic blood pressure slightly decreased down to 110-120 mmHg and serum potassium level remained around 5.0 mEq/L. The plasma level of BNP slightly increased from 168 pg/mL to 198 pg/mL transiently, whereas plasma level of NT-proBNP decreased from 978 pg/mL to 451 pg/mL. Given that daily urine volume relatively increased (no data are shown) and body weight decreased approximately 1 kg after 2 days, we terminated 4 mg/day of torasemide. He was discharged with an optimized heart failure symptom on day 10.

Post-discharge course

At 30 days following the index discharge, the plasma level of NT-proBNP remained unchanged and BNP slightly decreased from 198 pg/mL to 80 pg/mL. Of note, eGFR improved from 39.8 to 46.7 mL/min/1.73 m^2.

Discussion

Indications for sacubitril/valsartan

Our patient had worsening heart failure refractory to guideline-directed medical therapy (1). We confirmed the tolerability to enalapril beforehand. This would be a key to avoid unplanned withdrawal of sacubitril/valsartan, which might rather cause hemodynamic deterioration and an increase in the plasma NT-proBNP level, as observed in the enalapril arm of the PARADIGM-HF study (3).

Appropriate patients selection

Given the sub-analysis of the PARADIGM-HF study (2), our patient might have a favorable profile for the sacubitril/valsartan therapy, i.e., New York Heart Association func-

tional class <III and left ventricular ejection fraction <35%. However, the impact of sacubitril/valsartan on the Asian population remains controversial (2, 4). We confirmed a relatively well preserved blood pressure and renal function to prevent adverse events before the start of sacubitril/valsartan administration.

Reaction to sacubitril/valsartan

Following the administration of sacubitril/valsartan, the plasma BNP level increased slightly probably due to the inhibition of neprilysin, and plasma NT-proBNP level decreased significantly, indicating an improvement in heart failure. The plasma BNP level also decreased 30 days later, probably due to a further improvement in heart failure.

The blood pressure did not decrease considerably (within 10 mmHg), which would indicate a favorable clinical outcome (5). An immediate decrease in body weight would probably have been driven by the increased urine volume. Increased active BNP might have facilitated natriuresis as a visible acute effect of sacubitril/valsartan. As a result, we could terminate torasemide, which might have resulted in the observed improvement of the renal function (6).

Long-term outcomes

Natriuresis would be one of the visible acute effects of sacubitril/valsartan. We believe that a decrease in the dose of concomitant diuretics might have a potential to improve renal function. We demonstrated a similar finding in the meta-analysis of tolvaptan, a vasopressin type-2 receptor antagonist (7). Patients who achieved a decrease in the diuretics dose following the administration of tolvaptan tended to have a better long-term prognosis. To the best of our knowledge, this is the first case report of sacubitril/valsartan administration in Japan. Further large-scale observational studies are warranted to validate our proposed therapeutic strategy.

We continued to administer 100 mg/day of sacubitril/valsartan given relatively lower blood pressure. Given the results of PIONEER-HF study (8), dose up-titration might not necessarily be essential. Instead, we should avoid too much hypotension and unplanned termination of sacubitril/valsartan, which might cause a deterioration of the hemodynamics due to the acute the re-activation of neprilysin (3).

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