Effect of add-on sacubitril/valsartan on the left ventricular hypertrophy of a patient with hypertension

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Abstract
The combination of sacubitril and valsartan has recently become eligible for reimbursement in Japan for the treatment of hypertension. However, the real-world clinical efficacy of sacubitril/valsartan in patients with hypertension who are taking multiple anti-hypertensive medications remains to be characterized. We treated a man in his late 40s who had undergone a percutaneous coronary intervention and had hypertension that was refractory to multiple anti-hypertensive medications. We initiated sacubitril/valsartan 200 mg/day as an add-on therapy, and 3 months later, his blood pressure had decreased from 154/78 mmHg to 134/70 mmHg, in the absence of any drug-related adverse events. Furthermore, his left ventricular mass index had improved from 135 g/m² to 112 g/m². Thus, sacubitril/valsartan might ameliorate hypertrophy in patients with hypertension.

Keywords
Case report, heart failure, reverse remodeling, hemodynamics, sacubitril, valsartan, hypertension, left ventricular mass, anti-hypertensive medication

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Introduction
The combination of sacubitril and valsartan has been shown to improve the mortality and morbidity of patients with systolic heart failure. In addition, it may also be beneficial in patients with heart failure but preserved ejection fraction. Recently,
sacubitril/valsartan for the treatment of hypertension has become eligible for reimbursement in several countries, including Japan. However, most of the patients who were enrolled in the phase II and III trials had mild-to-moderate hypertension, and sacubitril/valsartan was administered alone, without concomitant administration of any other anti-hypertensive medications. Therefore, the clinical implications of the use of sacubitril/valsartan in patients with hypertension when administered on an add-on basis are unknown. Furthermore, the effects of sacubitril/valsartan on atherosclerotic parameters, including left ventricular mass index, remain to be investigated.

We treated a patient who was taking multiple anti-hypertensive medications, and found that 3 months of sacubitril/valsartan as an add-on therapy ameliorated his hypertension and caused the regression of his left ventricular hypertrophy.

**Case report**

**Before referral**

A man in his late 40s who had undergone a percutaneous coronary intervention in his left anterior descending artery for the treatment of acute coronary syndrome 6 months previously was referred to our outpatient clinic for follow-up. He had comorbidities of dyslipidemia and hypertension, and he had been taking bisoprolol 1.25 mg and enalapril 2.5 mg for the hypertension and rosuvastatin 5.0 mg for the dyslipidemia. In addition, as secondary means of prevention of ischemic heart disease, he had been taking aspirin 100 mg, prasugrel 3.75 mg, and vonoprazan 10 mg.

**On referral**

The patients did not report any symptoms, including angina, following his initial discharge. He was 165 cm tall and weighed 55 kg. His blood pressure was 158/88 mmHg and his pulse rate was 79 bpm. Chest X-rays showed a cardiothoracic ratio of 0.48 and no pulmonary congestion. Electrocardiography showed normal sinus rhythm and a heart rate of 70 bpm. His estimated glomerular filtration ratio was 105 mL/minute/1.73 m² and there was no proteinuria. His plasma N-terminal-proB-type natriuretic peptide concentration was 227 pg/mL.

We initiated treatment with indapamide 1 mg and esaxerenone 2.5 mg for the persistent hypertension, in addition to the bisoprolol and enalapril. However, the patient’s systolic blood pressure remained ~150 mmHg, despite medical therapy for several months following discharge. Therefore, we decided to initiate sacubitril/valsartan treatment.

The presentation of this case report conforms to the CARE guidelines.

**Initiation of sacubitril/valsartan**

Prior to the initiation of sacubitril/valsartan, the patient’s blood pressure was 154/92 mmHg and his heart rate was 78 bpm (Figure 1). Transthoracic echocardiography revealed a left ventricular end-diastolic diameter of 45 mm and a left ventricular ejection fraction of 57%, but no significant valve diseases (Figure 2a). His left ventricular mass index was 135 g/m².

We stopped the enalapril 2.5 mg and initiated sacubitril/valsartan 200 mg once daily. During the 3-month period of administration of sacubitril/valsartan as an add-on therapy, such that the patient was taking four anti-hypertensive medications, he did not have any drug-related adverse events, such as dizziness, thirst, or hypotension. His blood pressure and plasma N-terminal-proB-type natriuretic peptide concentration decreased gradually to 134/70 mmHg and 146 pg/mL, respectively (Figure 1). Transthoracic echocardiography
Figure 1. Clinical course of the patient.
SBP, systolic blood pressure; HR, heart rate; DBP, diastolic blood pressure.

Figure 2. M-mode transthoracic echocardiographic images at baseline (a) and 3 months after the initiation of sacubitril/valsartan administration (b).
LVDD, left ventricular end-diastolic diameter; IVS, interventricular septal thickness; PW, posterior wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction.
showed a left ventricular end-diastolic diameter of 47 mm and a left ventricular ejection fraction of 63%. In addition, the thickness of his interventricular septum/posterior wall decreased from 12/13 mm to 10/10 mm, and his left ventricular mass index decreased to 112 g/m² (Figure 2b) over this period.

Discussion

Sacubitril/valsartan monotherapy

Sacubitril/valsartan has become eligible for reimbursement recently, but its efficacy in real-world daily practice remains uncertain. In a phase II clinical trial, sacubitril/valsartan was found to be superior to placebo or valsartan in its effect to reduce blood pressure in patients with mild-to-moderate hypertension.3,4 In addition, in the phase III trial, sacubitril/valsartan was found to be superior to olmesartan in its effect to reduce blood pressure.5 Finally, in a single-arm phase III trial of patients with severe hypertension, defined using a systolic blood pressure ≥180 mmHg or a diastolic blood pressure ≥110 mmHg, sacubitril/valsartan was shown to be safe and effective.6

Taking these findings together, sacubitril/valsartan has been demonstrated to be as safe and effective as other angiotensin receptor II antagonists. However, its clinical efficacy and safety when concomitantly administered with other anti-hypertensive medications, as in the present patient, remains uncertain.

Sacubitril/valsartan as an add-on therapy

Few previous studies have evaluated the anti-hypertension effects of sacubitril/valsartan as an add-on therapy. A phase III trial demonstrated that the addition of sacubitril/valsartan to amlodipine reduced blood pressure versus amlodipine alone.9 In the present patient, sacubitril/valsartan further reduced systolic blood pressure by approximately 20 mmHg when concomitantly administered with bisoprolol, esaxerenone, and indapamide.

The mechanism of the anti-hypertensive effect of sacubitril/valsartan is unique. In addition to the suppression of renin–angiotensin–aldosterone system by valsartan, the neprilysin inhibitor sacubitril stimulates the activity of natriuretic peptides, thereby increasing natriuresis, suppressing sympathetic nerve activity, and facilitating cardiac reverse remodeling.10 These multiple effects might synergistically ameliorate hypertension that is refractory to other medications.

Further studies

Few studies have investigated the effects of sacubitril/valsartan on atherosclerotic parameters. A phase II trial demonstrated that it is more effective than olmesartan at improving left ventricular mass as a secondary endpoint,7 but in addition to the resulting reduction in afterload, the multiple effects of sacubitril/valsartan described above might directly facilitate cardiac reverse remodeling, consistent with its results in the present patient.

The N-terminal-proB-type natriuretic peptide concentration of the patient decreased during 3 months of sacubitril/valsartan therapy. Even a slight increase in N-terminal-proB-type natriuretic peptide concentration has been shown to be associated with an incremental risk of cardiovascular disease in Japanese patients,11 but whether anti-hypertensive therapy using sacubitril/valsartan prevents cardiovascular events in patients with hypertension remains an open question.

A number of limitations to the present study should be mentioned. Given the multiple drugs being taken by the present patient, other medications may have affected the changes in the parameters measured. Of note, we did not have a control arm in the present study. Furthermore, we did not
monitor ambulatory blood pressure, and therefore the blood pressure data presented here should be interpreted with caution.

**Author Contributions**
Conceptualization, TI; methodology, TI; software, KK; validation, KK; investigation, TI; resources, KK; data curation, TI; original draft preparation, TI; review and edition, KK; visualization, TI; supervision, KK. All the authors have read and agree with the text of the final draft.

**Data availability**
Data are available upon reasonable requests from the corresponding author.

**Declaration of conflicting interests**
The authors declare no conflicting interests in preparing this article.

**Ethics statement**
Written informed consent was obtained from the patient for his treatment and the publication of his case. The publication of this case report was approved by the ethics committee of University of Toyama (R2015154, April 11 2016).

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