Secure Combination Therapy With Low-Dose Bosentan and Ambrisentan to Treat Portopulmonary Hypertension Minimizing Each Adverse Effect

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Summary

Although endothelin receptor antagonists (ERAs) including bosentan and ambrisentan are essential tools for the treatment of pulmonary arterial hypertension (PAH), each agent has a specific adverse effect with non-negligible frequency, ie, liver dysfunction for bosentan and peripheral edema for ambrisentan. These adverse effects often hinder the titration of the doses of ERAs up to the therapeutic levels. Portopulmonary hypertension, which is complicated with liver cirrhosis and successive portal hypertension, is one of the PAHs refractory to general anti-PAH agents because of the underlying progressing liver dysfunction and poor systemic condition. We here present a patient with portopulmonary hypertension, which was treated safely by combination therapy that included low-dose bosentan and ambrisentan, minimizing the adverse effects of each ERA. Combination therapy including different types of ERAs at each optimal dose may become a breakthrough to overcome portopulmonary hypertension in the future. (Int Heart J 2015; 56: 471-473)

Key words: Pulmonary artery hypertension, Endothelin receptor antagonist, Liver cirrhosis

Although portopulmonary hypertension (PoPH), which is complicated with liver cirrhosis and successive portal hypertension, is one form of pulmonary arterial hypertension (PAH), its precise mechanism remains unknown thus far.1-3 It is speculated that excessive pulmonary blood flow via portosystemic shunts exerts shear stress on the PA owing to portal hypertension, which leads to proliferation and hyperplasia of PA intima and media, and then raises pulmonary vascular resistance (PVR).2-4 While the therapeutic strategy of PoPH conforms to that of idiopathic PAH (IPAH), there is no established strategy to treat PoPH. Clinical management of PoPH is difficult because of the underlying liver dysfunction and fluid retention.

Specific attention should be paid to patients with PoPH when an endothelin receptor antagonist (ERA), one of the essential tools to treat PAH,5-7 is administered, since its adverse effects, such as liver dysfunction or peripheral edema,8-9 are also problematic in patients with PoPH.1

We here present a patient with PoPH refractory to tadalafil and beraprost, which was managed safely by the addition of 2 types of ERAs, low dose bosentan and ambrisentan, thus minimizing the adverse effects of each agent.

Case Report

A 57-year-old man, who had been followed at another hospital for liver cirrhosis (Child-Pugh A) with a history of ruptured esophageal varices 10 years previously was admitted to our hospital on December 2011 complaining of dyspnea on effort (WHO functional class III). Chest X-rays showed dilated bilateral PA, and an electrocardiogram (ECG) indicated right heart overload (Figure 1A and B). Elevated right ventricular systolic pressure (RVSP, 124 mmHg) was estimated along with enlargement of the RV cavity by transthoracic echocardiography (Figure 2A). His plasma level of B-type natriuretic peptide (BNP) was 664 pg/mL.

We performed the first hemodynamic study at a month after the admission,10,11 and found elevated mean PA pressure (mPAP, 62 mmHg) and decreased cardiac index (CI, 1.76 L/minute/m²). Other differential diagnoses including connective tissue disease, adult congenital heart disease, respiratory disease, or chronic thromboembolic pulmonary hypertension were excluded by systemic inspection with blood examination, computed tomography, lung perfusion scintigraphy, and transthoracic echocardiography, and finally he was diagnosed as PoPH.12

Next, 125 mg of bosentan was administered as the first ERA rather than ambrisentan, considering severe bilateral leg edema and relatively reserved hepatic function. Both 180 μg of beraprost as a prostanooid and 40 mg of tadalafil as a phosphodiesterase type 5 (PDE-5) inhibitor were initiated as a 3-drug combination therapy (Figure 3).

The second hemodynamic study showed persistent eleva-
tion of mPAP (62 versus 57 mmHg) after 2-month treatment. We could not increase the dose of bosentan up to the standard dose because of potential worsening of liver dysfunction as a side effect of bosentan.

After ambrisentan was added as the second ERA at a half dose of 2.5 mg, hemodynamic study showed a significant decrease in mPAP down to 42 mmHg while maintaining the CI level. Peak oxygen consumption increased from 10.9 to 17.8 mL/kg/minute accompanied by improved WHO functional class (from III to II). No side effect such as liver dysfunction or worsening of leg edema was observed during the treatment period.

He was then followed as an ambulatory patient and he had no complaints. After 17 months, a follow-up hemodynamic study showed a significant decrease in PVR, although mPAP increased relatively accompanied by elevated CI probably due to increased preload. Transthoracic echocardiography demonstrated amelioration of both RV dilatation and a left-side shift of the ventricular septum (Figure 2B).

**DISCUSSION**

Although PoPH is one form of secondary PAH, there is no established strategy to manage it, probably because of underlying liver dysfunction and fluid retention. The prognosis of PoPH is very poor, and there are few reports describing the treatment of PoPH.1)

![Figure 1. Chest X-ray (A) and electrocardiogram (B) obtained on admission.](image)

![Figure 2. Transthoracic echocardiography on admission (A) and at 3 months after the initiation of treatment (B). Dilatation of the RV and left-side intraventricular septum were improved by the treatment.](image)

![Figure 3. Time course of the treatment.](image)
We intended from the beginning to initiate “3-drug combination therapy” consisting of (I) ERA, (II) a prostanoid, and (III) a PDE-5 inhibitor, considering the refractoriness of PoPH to any anti-PH treatments and the recently cumulating evidence supporting sequential combination therapy.3-10

However, we could not increase the dose of bosentan up to the standard range because of the emergence of liver dysfunction. Bosentan is accompanied by liver dysfunction with increased transaminase enzymes in 5-10% of patients, while fluid retention rarely occurs.10,17 On the other hand, the commercially available other ERA ambrisentan frequently facilitates fluid retention while maintaining liver function,14,19 and we could not administer the standard dose of ambrisentan instead of bosentan after taking into consideration his peripheral edema. Although little has been reported,20 combination therapy including the 2-ERAs bosentan and ambrisentan was successfully performed by decreasing the dose of each agent within a safe range and preventing the adverse effects of the 2 drugs. Low-dose 2-ERA combination therapy may be safe, especially in patients with PAH and who are suffering from liver dysfunction or fluid retention.

Endothelin binds two opposite-effect receptors, ie, ETₐR and ET₄R. Although the precise mechanism remains unknown, ETₐR stimulation seems to cause vasoconstriction, whereas ET₄R stimulation seems to lead to vasodilation. Both receptors interact together intricately, and how this “cross-talk” contributes to the development of PAH remains unknown.20

Bosentan antagonizes both ETₐR and ET₄R, whereas ambrisentan antagonizes only ET₄R selectively.20 Although there is no experimental or clinical evidence, combination therapy with the above 2 different-type antagonists may have had a synergistic vasodilative effect in the present patient.

The PAP level was probably not normalized because of the underlying untreatable portal hypertension. The establishment of combination therapy consisting of optimal doses of bosentan and ambrisentan, or including macitentan, the next generation ERA,20 would be a future concern.

References