Safety and Efficacy of Ambrisentan–Phosphodiesterase Type 5 (PDE5) Inhibitor Combination Therapy for Japanese Pulmonary Arterial Hypertension Patients in Real-World Clinical Practice

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Background: This retrospective study was conducted to evaluate the safety and efficacy of ambrisentan combination therapy with phosphodiesterase type 5 (PDE5) inhibitors in Japanese patients with pulmonary arterial hypertension (PAH).

Methods and Results: PAH patients who received ambrisentan for the first time in combination with a PDE5 inhibitor between January 2013 and the end of August 2015 were included in this study. Adverse drug reaction (ADR) safety analysis, as well as the efficacy analysis focusing on changes in clinical parameters, were investigated for overall cases and cases stratified by patient background. Forty-eight consecutive patients (n=21, 43.8% with idiopathic PAH; male/female, 18/30; average age, 43.3±17.4 years; World Health Organization functional class III/IV, n=22, 45.8%) who were treated with ambrisentan and a PDE5 inhibitor in Japan underwent the safety analysis. A total of 14 ADR occurred in 10 patients (20.8%). ADR included headache (8.3%), face edema (4.2%), angina pectoris (2.1%), hyperemia (2.1%), dyspnea (2.1%), pulmonary hypertension (i.e., worsening of PAH, 2.1%), nausea (2.1%), hepatic function abnormal (2.1%), edema (2.1%), and sudden death (2.1%). On analysis of hemodynamics parameters, there was a significant improvement in the mean pulmonary arterial pressure (−13.5 mmHg, P=0.0001) and pulmonary vascular resistance (−563.53 dyn·s·cm^{-5}, P=0.0033).

Conclusions: Ambrisentan combination therapy is safe and effective in hemodynamics improvement.

Key Words: Ambrisentan; Combination therapy; Hemodynamics; Phosphodiesterase type 5 inhibitor; Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a progressive and multifactorial disorder that leads to right ventricular overload associated with right-sided heart failure. PAH is associated with significant morbidity and mortality, with a 5-year survival rate of 34% in untreated patients, according to a historic national registry in the USA.[1] Meanwhile, the 5-year survival rate in idiopathic/heritable PAH patients was 96% according to the latest report in a Japanese PAH expert center.[2] This remarkable improvement was brought about by aggressive use of PAH-targeted drugs including combination therapy with i.v. epoprostenol.[3] Due to the progressive nature and severity of the disease, the trend in the treatment strategy for PAH has evolved from monotherapy to combination

therapy to improve prognosis. The usefulness of combination therapy has been corroborated by multiple randomized controlled trials (RCT) as well as by a meta-analysis showing that combination therapy was associated with a significant 38% reduction of risk of combined clinical worsening events (15 RCT: n=3,906; risk ratio [RR], 0.62; 95% CI: 0.50–0.77).[4–7] Combination therapy was also associated with improvement in 6-min walking distance (10 RCT: n=1,553; weighted mean difference [WMD], +23.0 m; 95% CI: 15.9–30.1), improved functional class (9 RCT: n=1,737; RR, 1.26; 95% CI: 1.05–1.51), and beneficial effects on pulmonary hemodynamics such as cardiac index (WMD, +0.35 L/min/m; 95% CI: 0.14–0.56).[7]
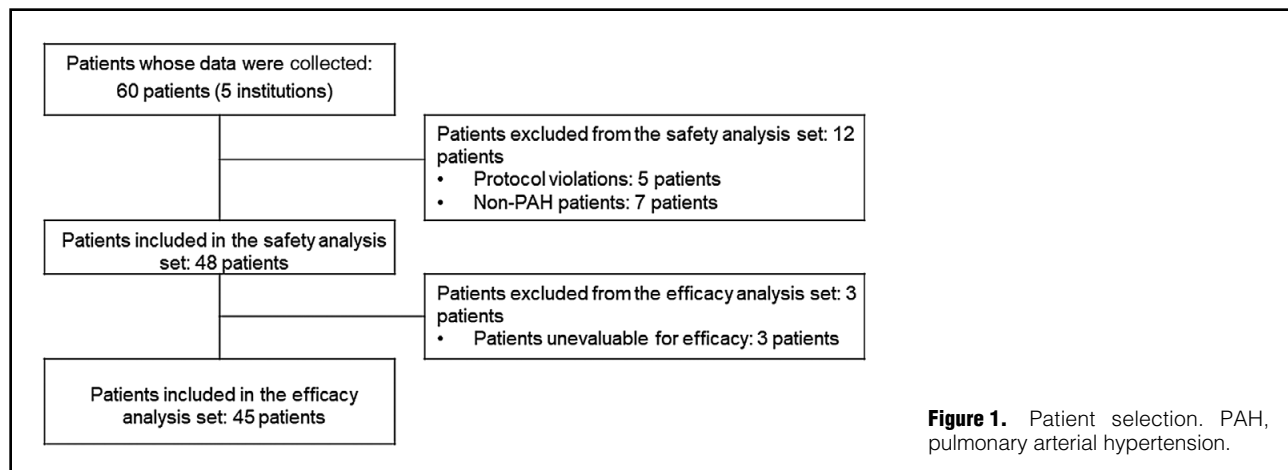
Initial combination therapy with ambrisentan (an

Figure 1. Patient selection. PAH, pulmonary arterial hypertension.

endothelin receptor antagonist [ERA]) and tadalafil (a phosphodiesterase type 5 [PDE5] inhibitor) resulted in a significantly lower risk of clinical failure events than that for ambrisentan or tadalafil monotherapy in the large event-driven AMBITION study.[4] The latest European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines recommend that the concurrent use of 2 drugs beginning in the initial stage in naïve and adult patients with PAH should be considered.[8]

Information on the safety and effectiveness of these combination therapies in Japanese patients, however, is limited. Therefore, we conducted a retrospective survey in Japanese patients to gather information on the safety and efficacy of ambrisentan combination therapy with PDE5 inhibitor (i.e., tadalafil and sildenafil).

Methods

This investigation was initiated to assess the long-term safety and efficacy and clinical course in patients using ambrisentan and a PDE5 inhibitor in real-world clinical practice as a special drug use investigation. This investigation was conducted in accordance with the Japanese Good Post-Marketing Study Practice (GPSP; Ordinance of Ministry of Health, Labour and Welfare No. 171 of December 20, 2004), and the study protocol was reviewed and approved by each site's institutional review board before the study began. Informed consent was not required from the individual participants included in this survey according to the GPSP. A written contract was concluded with the institution before the initiation of the survey and an agreement for the publication of this survey was obtained from all participating institutions. The subjects of this survey were PAH patients who received ambrisentan for the first time in combination with PDE5 inhibitors as an initial combination therapy or sequential combination therapy between January 2013 and the end of August 2015. Initial combination therapy was defined as treatment with ambrisentan and approved PDE5 inhibitors (tadalafil or sildenafil) concomitantly, or treatment with ambrisentan ≤30 days after PDE5 inhibitors, and sequential combination therapy was defined as addition of ambrisentan after suboptimal response to background PDE5 inhibitors. This survey was conducted using the continuous survey system to consecutively select patients from the participating

institutions so that no bias occurred during the patient selection process. The clinical classification of PAH was carried out with an old version used in a Japanese phase 3 clinical trial.[9] The rules of personal data confidentiality were fully respected.

Subjects
In this survey, data on PAH patients aged ≥15 years who were treated with ambrisentan and a PDE5 inhibitor at 5 institutions specializing in the treatment of PAH where both drugs are adopted and to which they are supplied, were collected. The institutions were Keio University Hospital, Kyorin University Hospital, Okayama Medical Center, Nagoya City University Hospital, or Japanese Red Cross Osaka Hospital in Japan. In Japan, pediatric use is generally defined as use in patients aged <15 years old.

Observation Period
The patients were observed for ≥1 year and this was extended up to 3 years, with patient cooperation.

Collected Information
Items of investigation included patient characteristics, patient data before and during combination treatment (laboratory test data, patient status, cardiopulmonary hemodynamics), and PAH treatment history before and during the combination treatment. For safety and efficacy analysis, the following data were obtained at baseline; 1 month after the initiation of combination therapy; and every 3 months in the follow-up period: incidence of adverse events (AE), type of AE, occurrence date, outcomes, severity, causal relationship with ambrisentan, cause of the AE, World Health Organization (WHO) pulmonary hypertension functional class (WHO-FC), 6-min walk distance (6MWD), B-type natriuretic peptide (BNP), N-terminal prohormone BNP (NT-proBNP), tricuspid regurgitant pressure gradient (TRPG), and diameters of the inferior vena cava on echocardiography. Cardiopulmonary hemodynamics parameters determined on right heart catheterization included mean right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), mean pulmonary artery wedge pressure (PAWP), cardiac output (CO), pulmonary vascular resistance (PVR), and oxygen saturation (SaO_2). The clinical parameters, especially hemodynamics, were measured at the investigator's discretion depending on

Table 1. Safety Analysis: Patient Characteristics (n=48)

	All patients	Initial combination treatment	Sequential combination treatment
No. patients	48 (100)	20 (41.7)	28 (58.3)
Follow-up period (days)	335.9±215.1	319.9±246.5	347.3±193.6
Female	30 (62.5)	13 (65.0)	17 (60.7)
Age (years)	43.3±17.4	41.5±11.8	44.5±20.6
PAH classification			
Primary	25 (52.1)	11 (55.0)	14 (50.0)
IPAH	21 (43.8)	8 (40.0)	13 (46.4)
FPAH	4 (8.3)	3 (15.0)	1 (3.6)
Secondary	23 (47.9)	9 (45.0)	14 (50.0)
CHD with a shunt	7 (14.6)	0	7 (25.0)
CTD	8 (16.7)	3 (15.0)	5 (17.9)
Portal hypertension	7 (14.6)	5 (25.0)	2 (7.1)
Others	6 (12.5)	1 (5.0)	5 (17.9)
6MWD (m)	300.7±185.9 (n=11)	271.2±184.7 (n=9)	433.5±171.8 (n=2)
WHO-FC			
I	2 (4.2)	2 (10.0)	0
II	22 (45.8)	7 (35.0)	15 (53.6)
III	19 (39.6)	9 (45.0)	10 (35.7)
IV	3 (6.3)	1 (5.0)	2 (7.1)
Unknown or unlisted	2 (4.2)	1 (5.0)	1 (3.6)
PAWP (mmHg)	8.9±3.6 (n=33)	8.1±3.3 (n=18)	9.8±3.8 (n=15)
mPAP (mmHg)	42.5±18.0 (n=35)	50.2±19.3 (n=19)	33.3±10.9 (n=16)
CO (L/min)	4.5±2.1 (n=32)	4.0±2.1 (n=18)	5.2±1.8 (n=14)
PVR (dyn·s·cm^{-5})	809.6±630.9 (n=32)	1,054.3±665.4 (n=19)	452.0±361.8 (n=13)
TRPG (mmHg)	63.0±22.7 (n=32)	73.5±25.5 (n=16)	52.4±13.4 (n=16)

Data given as mean±SD or n (%). 6MWD, 6-min walk distance; CHD, congenital heart disease; CO, cardiac output; CTD, connective tissue disease; FC, function class; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, mean pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; TRPG, tricuspid regurgitant pressure gradient; WHO, World Health Organization.

Table 2. Concomitant Medication

PDE5i[†]	
Tadalafil	34 (70.8)
Sildenafil	21 (43.8)
PGI2	
Beraprost	17 (35.4)
Epoprostenol	12 (25.0)
Anticoagulants	
Warfarin	5 (10.4)
Diuretics	
Furosemide	27 (56.3)
Spironolactone	12 (25.0)
Torasemide	6 (12.5)
Tolvaptan	3 (6.3)
Azosemide	2 (4.2)
Trichlormethiazide	1 (2.1)

Data given as n (%) including overlapping. [†]Some patients switched to another PDE5i. PDE5i, phosphodiesterase type 5 inhibitor; PGI2, prostaglandin I2.

local clinical settings.

Data Analysis

For safety analysis, data from all AE that occurred after the beginning of treatment with ambrisentan were collected, regardless of whether they were considered related to ambrisentan. When a relationship with ambrisentan was judged by the physician to be present based on clinical evaluation and according to the reference safety information, the AE was treated as an adverse drug reaction (ADR) during the acquisition of safety information. In the safety analysis, the incidence rate for AE and ADR was calculated by dividing the number of patients with an AE or ADR by the total number of patients included in the safety analysis. MedDRA version 20.1 was used for the coding of ADR, and the ADR were reported to the regulatory authority. The efficacy analysis included patients in whom each parameter was examined at least once before and after ambrisentan treatment. Variations in parameters before and after treatment with ambrisentan were analyzed in all evaluable patients by comparing the baseline values (values obtained before treatment) and post-treatment test values (values obtained in the final test conducted during the observation period). Differences between baseline and post-treatment parameters were tested for statistical significance using the paired Wilcoxon test.

Results

Patient Selection

Patient selection is shown in **Figure 1**. Of 60 patients assessed in this study, 48 patients, excluding those who violated the

Table 3. Safety Analysis Set: ADR

	All patients	Initial combination treatment	Sequential combination treatment
No. patients	48	20	28
No. patients with onset of ADR	10 (20.8)	5 (25.0)	5 (17.9)
No. ADR	14	6	8
No. events by type of ADR			
Headache	4 (8.3)	2 (10.0)	2 (7.1)
Face edema	2 (4.2)	1 (5.0)	1 (3.6)
Angina pectoris	1 (2.1)	1 (5.0)	0
Hyperemia	1 (2.1)	0	1 (3.6)
Dyspnea	1 (2.1)	1 (5.0)	0
Pulmonary hypertension	1 (2.1)	0	1 (3.6)
Nausea	1 (2.1)	0	1 (3.6)
Hepatic function abnormal	1 (2.1)	1 (5.0)	0
Edema	1 (2.1)	0	1 (3.6)
Sudden death	1 (2.1)	0	1 (3.6)

Data given as n (%). MedDRA version 20.1 was used for the coding of ADR, and the ADR were reported to the regulatory authority and used for the present analysis. ADR, adverse drug reaction.

study protocol (e.g., patients who have already been treated with ambrisentan at other institutions) and those who were recognized as having non-PAH from comorbidity information, underwent safety analysis. Of the subjects included in the safety analysis, 3 were excluded from the efficacy analysis because of unavailable results. Thus, 45 patients were included in the efficacy analysis.

The diagnoses in the non-PAH patients were: pulmonary hypertension associated with pulmonary venous obstruction in 3 patients, pulmonary hypertension associated with chronic obstructive pulmonary disease in 1 patient, pulmonary hypertension associated with hypoxemia in 1 patient, pulmonary hypertension associated with chronic pulmonary thromboembolism in 1 patient, and pulmonary hypertension associated with idiopathic pulmonary fibrosis in 1 patient.

Patient Characteristics

The characteristics of the 48 patients in the safety analysis are listed in **Table 1**. There were 30 female patients (62.5%), and the overall mean patient age was 43.3±17.4 years old. Of those with primary PAH, idiopathic PAH was found in 21 patients (43.8%). Mean baseline 6MWD was 300.7±185.9 m. In total, 85.4% of the patients were categorized in WHO-FC II–III. Concomitant medications are listed in **Table 2**. The background of patients who underwent the initial combination therapy was more severe than that of those who underwent sequential combination therapy in mPAP, PVR, 6MWD, and TRPG (e.g., baseline mPAP: 50.2±19.3 mmHg for initial combination therapy vs. 33.3±10.9 mmHg for sequential combination therapy). As noted, the clinical classification of PAH in this survey was carried out according to that used in a Japanese phase 3 clinical trial.[9]

Safety

A total of 14 ADR occurred in 10 patients (20.8%). Common ADR included headache (8.3%), face edema (4.2%), angina pectoris (2.1%), hyperemia (2.1%), dyspnea (2.1%), pulmonary hypertension (2.1%), nausea (2.1%), hepatic function abnormal (2.1%), edema (2.1%), and sudden death (2.1%).

Table 4. Outcomes of Serious ADR

Serious ADR	n (%)	Outcome
Angina pectoris	1 (2.1)	Remission
Hepatic function abnormal	1 (2.1)	Recovery
Pulmonary hypertension	1 (2.1)	Death
Sudden death	1 (2.1)	Death

ADR, adverse drug reaction.

There were no differences in the incidence and types of ADR in relation to the initial or sequential combination treatments (**Table 3**). A safety analysis by presence/absence of connective tissue disease associated with PAH (CTD-PAH) is given in **Supplementary Table 1**. A higher incidence rate of headache (10.0%) and face edema (5.0%) was observed in non-CTD-PAH patients, but the reason for this could not be identified because of the small sample size of non-CTD-PAH patients. Serious ADR were found in 4 patients (8.3%): 1 each with angina pectoris (2.1%), hepatic function abnormal (2.1%), pulmonary hypertension (2.1%), and sudden death (2.1%; **Table 4**). Of the 4 patients who had serious ADR, the 2 who died (i.e., the pulmonary hypertension patient and the patient who had sudden death) had both received the sequential combination therapy. In the patient who had pulmonary hypertension (male, 18 years old), this was regarded as worsening of PAH. In the case of the sudden death, this occurred at 469 days after ambrisentan treatment, and that patient (male, 73 years old) had complications of epilepsy, primary biliary cirrhosis, chronic kidney disease, mixed CTD, constipation, anemia, and heart failure. The angina pectoris occurred at 20 days after ambrisentan treatment and that patient (female, 34 years old) had known angina pectoris. And the hepatic function abnormal occurred at 44 days after ambrisentan treatment in a female patient (44 years old) with the complications of heart failure, heart aneurysm and stomach polyps. Of the 6 patients with non-serious ADR, in 4 patients the ADR completely resolved, and in 2 patients the ADR were lessened in severity.

Table 5. Type and Timing of 14 ADR

Type of ADR	≤1 M	1–3 M	3–6 M	6–9 M	9–12 M	12–24 M	24–36 M	>36 M	Unknown	No. ADR
Headache	1	0	1	0	0	0	0	0	2	4 (8.3)
Angina pectoris	1	0	0	0	0	0	0	0	0	1 (2.1)
Hyperemia	0	0	0	0	0	0	0	0	1	1 (2.1)
Dyspnea	1	0	0	0	0	0	0	0	0	1 (2.1)
Pulmonary hypertension	0	0	0	0	0	0	0	0	1	1 (2.1)
Nausea	0	0	0	0	0	0	0	0	1	1 (2.1)
Hepatic function abnormal	0	1	0	0	0	0	0	0	0	1 (2.1)
Face edema	1	0	0	0	0	0	0	0	1	2 (4.2)
Edema	0	0	0	0	0	0	0	0	1	1 (2.1)
Sudden death	0	0	0	0	0	1	0	0	0	1 (2.1)

Data given as n (%). ADR, adverse drug reaction; M, month(s).

Of 7 ADR for which the incidence time could be confirmed, 4 ADR occurred ≤1 month after the initiation of combination therapy, although the date of occurrence was not identified for another 7 ADR (**Table 5**). Therefore, careful observation in the early treatment period is required to detect ADR as early as possible. Headache and edema are the major ADR of drugs such as ambrisentan with vasodilating effects. In this study, headache (4 events), edema (1 event), and face edema (2 events) either resolved or lessened in severity after discontinuation of the ambrisentan. The estimated 1-year survival rate from initiation of ambrisentan was 97.4%.

Efficacy
Change in PAH-Related Parameters Change in PAH-related parameters after combination treatment is given in **Table 6**. In this study, the final hemodynamic test was performed at a mean of 220.4±123.2 days (median, 255 days) after the initiation of combination therapy. A significant improvement in mPAP (−13.5 mmHg, decreased by 26%, P=0.0001) and in PVR (−563.5 dyn·s·cm^{-5}, decreased by 23.8%, P=0.0033) was seen after treatment with ambrisentan. The change in parameters in patients receiving i.v. epoprostenol combination therapy, and according to CTD-PAH status, and according to type of combination therapy, is given in **Supplementary Table 2**. Similar reductions in hemodynamics were observed with concomitant use of epoprostenol.

Change in WHO-FC After Combination Therapy The changes in WHO-FC from baseline to 12 months after treatment are shown in **Figure 2**. The proportion of patients classified as WHO-FC III decreased. Patients classified as WHO-FC II accounted for 42.1% at baseline, whereas the corresponding rates were 63.6% and 66.7% at 6 and 12 months, respectively. The rate of improvement of WHO-FC by at least 1 grade was 36.4% and 33.3% at 6 and 12 months, respectively.
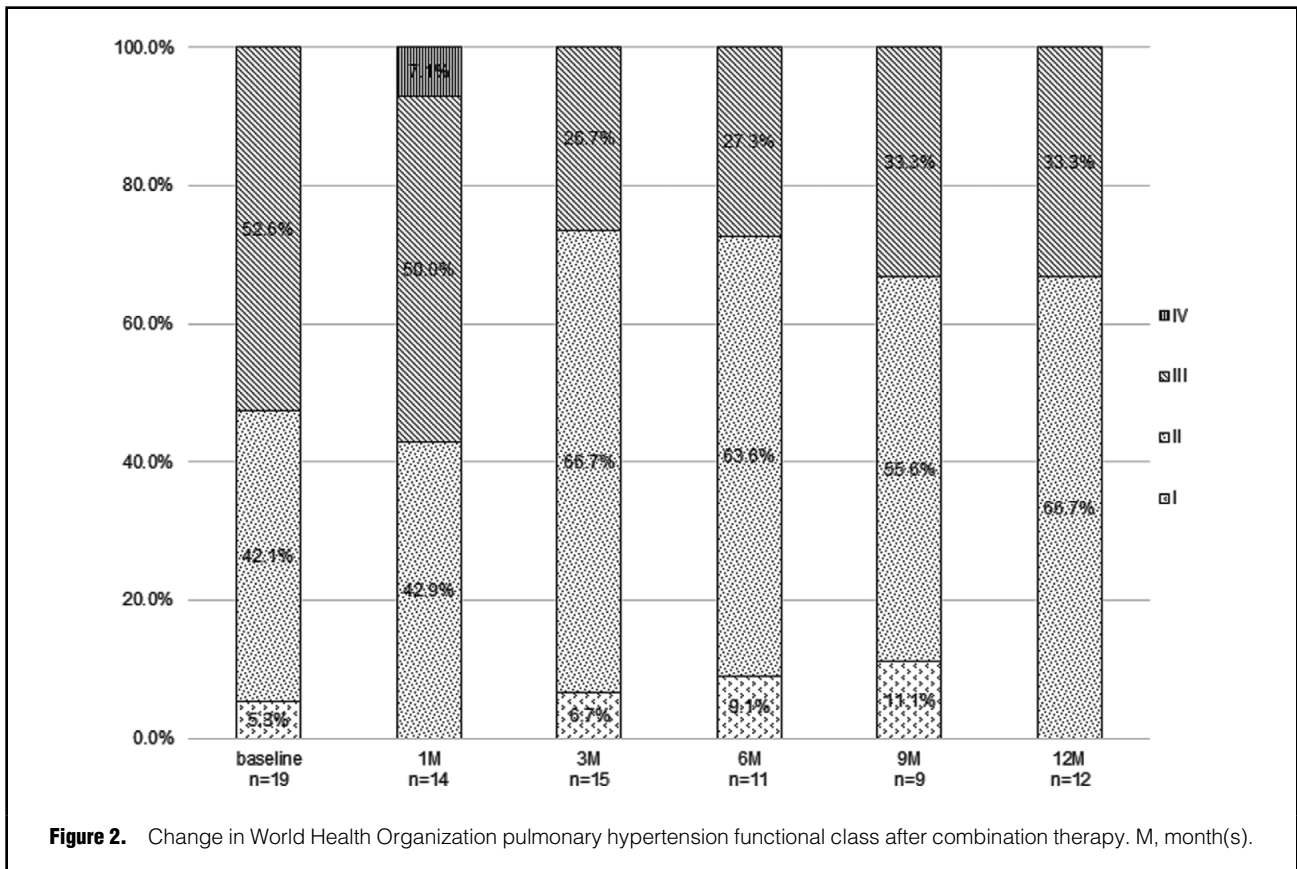
Discussion

In the present study, significant improvement was seen in mPAP (−13.5 mmHg, decreased by 26%, P=0.0001) and in PVR (−563.5 dyn·s·cm^{-5}, decreased by 23.8%, P=0.0033), and the safety profile was consistent with previous clinical trials in Japan, and globally in Japanese PAH patients treated with ambrisentan and a PDE5 inhibitor. The benefit of combination therapy with ambrisentan and a PDE5 inhibitor was corroborated in Japanese PAH patients in a real-world clinical practice setting.

This study was conducted as post-marketing surveillance (PMS) to evaluate the safety and efficacy of ambrisentan and a PDE5 inhibitor, focusing on ERA and PDE5 inhibitor combination therapy, which is frequently used in real-world clinical practice. An interim PMS analysis of the safety and efficacy of ambrisentan in 702 patients with PAH noted an ADR rate of 29.1% (204 patients, 324 events).[10] Common ADR (≥2%) included anemia (4.6%), peripheral edema (4.1%), headache (3.6%), edema and face edema (2.6% each), abnormal hepatic function (2.3%), and epistaxis (2.1%). A total of 82 serious ADR occurred in 44 patients (6.3%, 44/702), although these interim PMS data included patients who underwent only ambrisentan monotherapy.[10] There was no difference in safety with regard to the presence/absence of CTD-PAH.[10] Furthermore, in the interim PMS analysis, the incidence of ADR for the ambrisentan combination with tadalafil and sildenafil was consistent with that for all patients as a whole.[10] The safety evaluations for the initial combination or sequential combination with PDE5 inhibitors in the PMS interim analysis were difficult because the detailed treatment period of the concomitant drugs specific to PAH, including PDE5 inhibitors, was not obtained in the case report form.[10] The present study is the first in which the treatment period of the combination therapy with PDE5 inhibitors was closely investigated, and the subjects were limited to Japanese patients receiving initial or sequential combination therapy at expert centers where PAH specialists were available. The present results are consistent with the AMBITION study, which investigated the efficacy and safety of initial combination therapy,[4] although we need to keep in mind that the AMBITION study evaluated the combination of ambrisentan with tadalafil as a PDE5 inhibitor. Based on the AMBITION results, along with some other smaller mostly uncontrolled studies, the ESC/ERS guidelines and Japanese guidelines for the diagnosis and treatment of pulmonary hypertension (revised 2017 edition) were specified, and for the first time, the concurrent use of PAH drugs in the initial stage should be considered for treatment-naïve PAH patients.[8,11] Currently, combination therapy is considered to be a core treatment strategy for PAH, aimed at further improvement of treatment. Regarding safety, in the AMBITION study, peripheral edema (45%) and headache (42%) were more common AE in the combination therapy group than in the monotherapy group.[4] Frequent ADR in

Table 6. Change in Functional Parameters After Combination Treatment

		n	Mean±SD	Mean of variation (95% CI)
Pulmonary function				
FVC (%)	Baseline	14	82.6±19.6	–
	After treatment	14	88.0±14.4	5.35 (–0.04 to 10.74)
	P-value[†]	0.0651		
TLC (%)	Baseline	10	86.3±21.4	–
	After treatment	10	86.2±19.0	–0.13 (–9.38 to 9.12)
	P-value[†]	0.9219		
FEV_1 (%)	Baseline	16	81.5±17.8	–
	After treatment	16	82.8±12.8	1.31 (–4.55 to 7.17)
	P-value[†]	0.7436		
SpO_2 (%)	Baseline	8	86.7±15.7	–
	After treatment	8	90.6±10.4	3.86 (–4.55 to 12.28)
	P-value[†]	0.9453		
SaO_2 (%)	Baseline	7	95.3±2.0	–
	After treatment	7	95.8±1.0	0.46 (–1.64 to 2.56)
	P-value[†]	0.8125		
DLco (mL/min/mmHg)	Baseline	12	36.9±19.0	–
	After treatment	12	46.4±27.9	9.51 (–7.07 to 26.09)
	P-value[†]	0.1763		
Hemodynamics				
RAP (mmHg)	Baseline	17	8.0±4.7	–
	After treatment	17	5.4±2.2	–2.65 (–5.61 to 0.31)
	P-value[†]	0.1225		
PAWP (mmHg)	Baseline	18	8.2±2.8	–
	After treatment	18	9.2±2.8	1.06 (–1 to 3.11)
	P-value[†]	0.3107		
mPAP (mmHg)	Baseline	20	44.9±14.2	–
	After treatment	20	31.4±8.6	–13.5 (–19.27 to –7.73)
	P-value[†]	0.0001		
CO (L/min)	Baseline	18	4.1±2.2	–
	After treatment	18	5.3±1.7	1.23 (–.044 to 2.9)
	P-value[†]	0.0335		
PVR (dyn·s·cm^{-5})	Baseline	19	949.2±694.5	–
	After treatment	19	385.7±247.7	–563.53 (–917.31 to –209.74)
	P-value[†]	0.0033		
Saturation (%)	Baseline	8	91.1±14.9	–
	After treatment	8	95.3±1.7	4.25 (–8.27 to 16.77)
	P-value[†]	1.0000		
Cardiac index (L/min/m^2)	Baseline	20	2.5±1.0	–
	After treatment	20	4.3±3.6	1.82 (–0.02 to 3.66)
	P-value[†]	0.0019		
SvO_2 (%)	Baseline	13	68.0±13.7	–
	After treatment	13	74.5±6.3	6.55 (–3.31 to 16.42)
	P-value[†]	0.2439		
Echocardiography				
TRPG (mmHg)	Baseline	22	62.3±25.1	–
	After treatment	22	46.9±22.2	–15.41 (–24.18 to –6.63)
	P-value[†]	0.0006		
Clinical status				
6MWD (m)	Baseline	5	324.6±187.1	–
	After treatment	5	434.8±105.6	110.2 (–30.67 to 251.07)
	P-value[†]	0.0625		
BNP (pg/mL)	Baseline	16	353.9±339.0	–
	After treatment	16	145.2±187.7	–208.63 (–357.74 to –59.51)
	P-value[†]	0.0182		

Data given as mean±SD. [†]Paired Wilcoxon test. BNP, brain natriuretic peptide; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SaO_2, blood oxygen saturation; SpO_2, percutaneous oxygen saturation; SvO_2, mixed venous oxygen saturation; TLC, total lung capacity. Other abbreviations as in Table 1.

Figure 2. Change in World Health Organization pulmonary hypertension functional class after combination therapy. M, month(s).

the present study were headache (8.3%) and face edema (4.2%). Headache and edema also tended to be more common in Japanese patients with vasodilator combination therapy. From these results, ambrisentan and PDE5 inhibitor combination therapy is tolerated by the majority of Japanese patients, and new AE were not seen. Thus, this combination therapy is a reasonable therapeutic option for Japanese patients.

In the present efficacy analysis, 6MWD, WHO-FC, BNP, TRPG and hemodynamic parameters were examined at baseline and after treatment in all patients and in relation to the presence and absence of CTD, to follow changes in symptoms after treatment. In particular, mPAP was decreased by 13.5mmHg from baseline to post-treatment assessment. A single-center blinded evaluation of patients enrolled in the AMBITION study showed that initial combination therapy in 19 patients significantly changed mPAP from 55±11mmHg to 37±11mmHg after 6 months of treatment.[12] In a retrospective study, Ogawa et al reported an association between high survival rate (96% at 5 years) in 56 Japanese patients with idiopathic/heritable PAH and improvement due to PAH-targeted drugs in hemodynamics parameters such as mPAP, PVR, and cardiac index after treatment.[2,3] The Japan PH Registry (JAPHR), the first organized multicenter registry for PAH in Japan, noted an excellent survival rate (i.e., 95.7% at 3 years) and an improvement in hemodynamics parameters by initial combination therapy; and an AMBITION post-hoc analysis showed survival improvement due to initial combination therapy.[13,14] Thus, the initial combination therapy might be associated with a survival advantage and

the treatment strategy of initial combination therapy and the follow-up based on the improvement in hemodynamic status are important. A prospective investigation is needed to demonstrate the beneficial effect of improvement of hemodynamic parameters for favorable long-term outcome in PAH patients.

Study Limitations
There was a limitation of the efficacy data under this surveillance because each clinical parameter was not measured consistently; that is, data were collected at each investigator's discretion. The appropriateness of combination therapy in each case (e.g., initial combination therapy for patients with WHO-FC I) was not considered because this surveillance reflected the actual clinical practice in a real-world setting compared with the registration trial. We collected case records for 60 patients from 5 expert centers as a special drug use investigation. The generalization of obtained results should be carefully interpreted because of the small sample size and lack of control group (i.e., monotherapy), although 3 expert centers among the participating institutions were regarded as nationwide representative institutions, and in their epidemiologic study the 1-, 3-, 5-, and 10-year survival rates of Japanese patients were 97.9%, 92.1%, 85.8%, and 69.5%, respectively.[3] Furthermore, this study could not assess fully the influence of the combination itself compared with monotherapy and combination type (i.e., initial or sequential combination) and concomitant medications, except for PDE5 inhibitors or changes in concomitant drugs. Thus, the improvement of clinical parameters by initial or sequential combination

therapy should be evaluated in a large-scale prospective trial or Japanese registry such as JAPHR.[14] Sitbon et al reported that the initial combination of oral PAH-targeted medications consisting of ERA plus PDE5 inhibitors was beneficial in newly diagnosed patients with PAH, and that the combination with tadalafil produced a greater hemodynamic improvement than that with sildenafil irrespective of ERA brand, using real-world clinical data.[15] Determination of which combination is the best or least useful is highly warranted because we could not compare ERA in combination with PDE5 inhibitors in the present survey, because this retrospective survey was conducted as PMS only for ambrisentan under GPSP, and the dose of each PDE5 inhibitor was not sufficiently investigated. Additionally, the clinical classification of PAH in this survey was carried out according to an earlier classification method used in a Japanese phase 3 clinical trial.[9] This method is different from the current classification.

Conclusions

Ambrisentan combination therapy with tadalafil or sildenafil has been shown to be effective and safe. The safety profiles are consistent with that observed in previous clinical trials of combination therapies. Thus, ambrisentan combination therapy with tadalafil or sildenafil is a reasonable therapeutic option for Japanese patients.

Author Contributions

K.U., T.T. conceived and designed the study. M.K., T.S., H.M., K.Y., T.I., K.F. performed the study as investigators. K.U., T.T. managed and analyzed the data. M.K., T.S., H.M., K.Y., T.I., K.F., K.U., T.T., A.N. interpreted the data. M.K., T.S., H.M., K.Y., T.I., K.F., K.U., T.T., A.N. wrote the paper.

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Supplementary Files

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