Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
佐藤徹	静脈圧、循環血液量、循環時間．容積脈波、サーモグラフィ	小川総	内科学書 Vol. 3, 改訂第８版	中山書店	東京	2013	68-70
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Ⅳ. 研究成果の刊行物・別刷

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Letter to the Editor

Blood–injection-injury phobia: Profound sinus arrest

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A 26-year-old man was referred to our clinic for a medical check-up. During measurement of his blood pressure, the patient lost consciousness followed by persistent nausea and light-headedness. His condition deteriorated until no pulse was detected, upon which the doctors started cardiopulmonary resuscitation. Once a pulse returned, the patient was admitted to our hospital for investigation. Physical examination revealed no abnormal findings and his medical or family history was unremarkable, although he reported experiencing a similar attack of nausea in the past immediately following a venipuncture. ECG showed extreme bradycardia and a 10-second asystole, followed by junctional escape beats (Panel A). Subsequently, the patient again lost consciousness, requiring transcutaneous pacing and atropine sulfate injection for recovery. A thorough review of the patient's history revealed that he had collapsed during a vaccination as a 7-year-old, and thereafter was always on the verge of fainting during vaccination or venipuncture. Moreover, he felt nausea whenever hearing about blood, hospitals, or any medical procedures. Consequently, he had avoided medical examinations for a long time.

The current patient thus fitted a diagnosis of blood–injection-injury phobia according to the DSM-IV TR criteria. Suspecting the existence of vasovagal syncope with blood–injection-injury phobia, we also performed a tilt-table test. At 10 min of 60° tilt, he noted the onset of his usual prodromal symptoms followed by hypotension, bradycardia, and loss of consciousness. Our final diagnosis was vasovagal syncope with blood–injection-injury phobia.

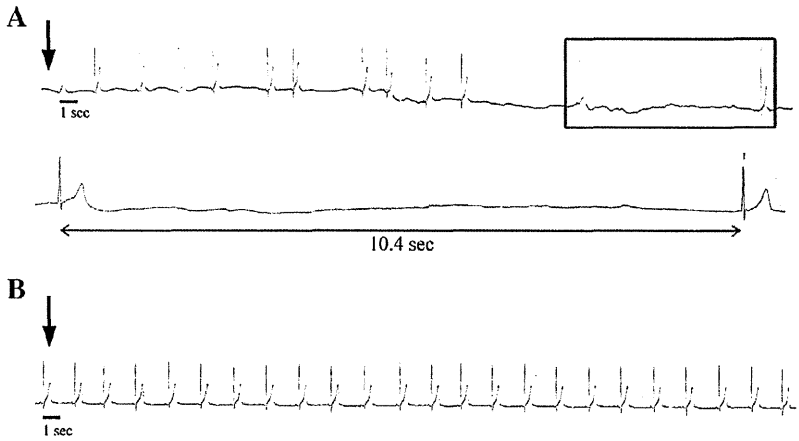

Fig. 1. Panel A: Upper ECG rhythm recorded during the asystole event. The ECG strip with a normal recording speed (25 mm/s). Panel B: ECG rhythm recorded after the cognitive behavioral therapy. The arrows indicate the time point of injection.

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Blood–injection-injury phobia is a common phobia with an estimated prevalence of 3–4% in the general population [1]. It can be triggered by seeing blood, sustaining an injury, receiving injections, or various other invasive medical procedures. It is noteworthy that blood–injection-injury phobia is the only phobia associated with syncope, and more than two thirds of patients with this condition have a history of syncope [2]. Although the etiology of syncope is poorly understood, a vasovagal mechanism has been implicated [3]. Blood–injection-injury phobia is often treated with exposure therapy, a component of cognitive behavioral therapy that involves repeated and systematic encounters with feared stimuli. A combination of applied tension and an isometric counter-pressure may significantly attenuate anxiety and avoidance behaviors [4].

Considering these facts, we instructed our patient to perform repeated physical counter-pressure maneuvers, such as leg crossing, during invasive medical procedures performed within our hospital over a few days. Subsequent tilt-table testing showed a negative result and the patient became free from any symptom or long pauses when receiving an injection (panel B). Uniquely, he remains free of further syncope after 5 years.

Despite syncope being common and severe, long-term treatments with medical insults are not established. The unique nature of the case presented herein could provide insights into the potentially permanent, positive effects of cognitive behavioral therapy in such cases (Fig. 1).

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ORIGINAL RESEARCH

Evaluation of a New Formulation of Epoprostenol Sodium in Japanese Patients with Pulmonary Arterial Hypertension (EPITOME4)

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ABSTRACT

Introduction: Pulmonary arterial hypertension (PAH) is associated with poor prognosis despite significant recent advances in its treatment. An intravenous formulation of epoprostenol sodium containing glycine and mannitol (epoprostenol GM; GlaxoSmithKline, London, UK) is widely used to treat PAH. A new formulation of epoprostenol sodium containing arginine and sucrose excipients (epoprostenol AS; Actelion Pharmaceuticals Japan Ltd., Tokyo, Japan) shows better stability at room temperature after preparing diluted solutions. The primary objective of this study was to evaluate the safety and tolerability of switching from epoprostenol GM to epoprostenol AS in Japanese patients with PAH. The authors also evaluated the efficacy and treatment satisfaction after switching formulations.

Methods: This was a two-site, open-label, single-arm, Phase 3b study. Eight adult Japanese PAH patients (seven females) treated with a stable dose of epoprostenol GM for ≥30 days were switched to epoprostenol AS and followed for 12 weeks. Outcomes included safety, changes from baseline to 12 weeks in pulmonary hemodynamic factors (pulmonary vascular resistance, mean pulmonary arterial pressure, and cardiac output), and treatment satisfaction, assessed using the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

Results: The mean (range) age and time since diagnosis of PAH were 48 (25–69) years and 6.2 (0.6–13.9) years, respectively. There were no

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unexpected safety or tolerability concerns after switching formulations. The epoprostenol dose was maintained after switching formulations. There were no significant changes in pulmonary hemodynamic factors from baseline to week 12. Regarding treatment satisfaction, there was a significant improvement in convenience, which is demonstrated in the score of the domain increased from 51.40 ± 10.19 at baseline to 58.33 ± 12.96 at week 12 ($P < 0.05$).

Conclusions: Switching from epoprostenol GM to the same dose of epoprostenol AS was well tolerated over 12 weeks of treatment, and pulmonary hemodynamics were maintained. Switching to epoprostenol AS was also associated with improvements in treatment satisfaction (convenience). Clinical Trials: JapicCTI-122017.

Keywords: Efficacy; Epoprostenol; Epoprostenol formulations; Japanese patients; Prostacyclin; Pulmonary arterial hypertension; Pulmonary hemodynamic factors; Safety; Treatment satisfaction

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease with poor prognosis. It is generally characterized by constriction of pulmonary arteries and vascular remodeling. Right ventricular afterload (right ventricular hypertrophy and enlargement) is increased because of elevated pulmonary arterial pressure and pulmonary vascular resistance, which ultimately leads to right cardiac failure and death [1]. Subjective symptoms of PAH include exertional dyspnea, fatigability, palpitations, chest pain, and syncope [2].

Although the underlying mechanisms of PAH are not fully understood, vascular endothelial abnormalities cause an imbalance between vasoconstricting and vasodilating factors. In this situation, vasoconstricting factors exert a greater influence and increase shear stress. It is generally thought that remodeling of the pulmonary arterial media and narrowing of the pulmonary intravascular lumens due to increased cell proliferation are responsible for this imbalance [3–5].

Prostacyclin (PGI_2) agents with various modes of action, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors are available for the treatment of PAH. Oral administration of any of these drugs is recommended for patients with PAH of World Health Organization (WHO) functional Class III or lower. For patients with Class IV PAH, continuous intravenous administration of PGI_2 is recommended. Concomitant treatment with several drugs having different modes of action is recommended if the clinical response to monotherapy is inadequate [6–8].

PGI_2 is a metabolite of arachidonic acid and plays an important role in maintaining pulmonary vascular homeostasis. It is produced by endocapillary cells, and acts as a potent vasodilator and inhibits platelet aggregation. Accordingly, the PGI_2 system plays an important role in the inhibition of vascular smooth muscle cell proliferation and helps to protect the vascular endothelium. A small decline in the function of the PGI_2 system leads to an imbalance between vasoconstrictors and vasodilators, and appears to contribute to the development of PAH [9–11].

Based on these findings, compounds that target prostacyclin receptors have been developed and are used clinically to treat PAH. One such example is intravenous epoprostenol sodium, a synthetic PGI_2 analog, which is prepared as a formulation containing glycine and mannitol as excipients (epoprostenol GM, GlaxoSmithKline, London, UK). Continuous

intravenous therapy with epoprostenol GM was reported to improve pulmonary hemodynamic factors, exercise tolerance, and the prognosis of PAH [12]. However, one limitation of this formulation is that the prepared solution is thermally unstable, and needs to be administered within 8 h at room temperature (1–30 °C) or within 24 h if cooled to 2–8 °C using frozen gel packs. Consequently, the medication cassette containing the solution has to be maintained at 2–8 °C using a frozen gel pack for the entire 24-h infusion period [13].

To overcome this limitation, another formulation of epoprostenol sodium, containing arginine and sucrose as excipients (Actelion Pharmaceuticals Japan Ltd., Tokyo, Japan; hereafter, epoprostenol AS), was developed to improve the convenience of using epoprostenol to treat PAH as the new formulation is stable for 24 h at room temperature [14].

To date, however, few studies have examined the safety, potential effects on hemodynamic factors, or treatment satisfaction associated with switching formulations of epoprostenol in patients with PAH [15]. Therefore, the authors performed a 12-week, open-label, Phase 3b study to examine the safety, efficacy, and treatment satisfaction of switching from epoprostenol GM to epoprostenol AS in Japanese patients with PAH. The authors hypothesized that switching from epoprostenol GM to epoprostenol AS would improve treatment satisfaction without increasing the incidence of adverse events or causing deteriorations in pulmonary hemodynamic factors.

METHODS

Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Subjects

Patients aged ≥20 years at the time of informed consent and who had pulmonary hypertension classified as Group 1 using the Dana Point classification [16,17] for pulmonary hypertension were eligible if they had any of the following: idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), PAH associated with drugs and toxins, or PAH associated with connective tissue disease. Only patients who had been treated with epoprostenol GM for ≥3 months before enrollment and at a stable dose for ≥30 days before the start of study treatment were included in the study. Females of childbearing potential had to have a negative serum pregnancy test at screening. They were also required to agree to take monthly urine/serum pregnancy tests and to use reliable contraceptives to avoid pregnancy from the time of the screening visit until 30 days after the end of the study.

Eligible patients were excluded if they met any of the exclusion criteria, such as diagnosis of respiratory or cardiovascular disorder requiring immediate surgery, presence of confirmed or suspected pulmonary vein occlusion, history of myocardial infarction, and resting pulse rate of ≥120 beats/min.

Trial Drug

Epoprostenol AS (Actelion Pharmaceuticals Japan Ltd.) was provided in 10-mL glass vials containing 0.5 mg or 1.5 mg epoprostenol

sodium. Epoprostenol AS was dissolved and diluted by adding isotonic sodium chloride solution. At the start of the 12-week treatment period, epoprostenol GM was switched to an equal dose of epoprostenol AS in the hospital. For home therapy, epoprostenol was administered via a central venous catheter by continuous drip infusion using a portable infusion pump.

Study Design

This was a two-site, open-label, single-arm, Phase 3b study. The study consisted of a 2-week pretreatment screening period, a 12-week open-label treatment period (visiting at baseline, week 1, 2, 4, 8, and 12), and a continuous treatment period until marketing of the study drug (visiting every 4 weeks). Pulmonary hemodynamic measurements and variables of clinical laboratory tests were collected at baseline and week 12. Medical interviews and checks for vital signs were performed at each visit. Females of childbearing potential received a pregnancy test every month.

Outcome Measures

Safety/Tolerability

The safety/tolerability endpoints were adverse events occurring during the 12-week treatment phase, together with changes from baseline to week 12 for vital signs (blood pressure and heart rate on the same arm in sitting or supine position), body weight, and abnormal changes from baseline to week 12 for clinical laboratory tests (general biochemistry tests, including thyroid function test and hematology test). Vital signs and body weight were assessed at each visit and clinical laboratory tests were performed at baseline and week 12 (only thyroid function was assessed every month). Adverse events reported during the 12-week evaluation period were coded according to system organ class and terms using the Medical Dictionary for Regulatory Activities/ Japanese version. The causality of adverse events in relation to the trial drug was judged by the investigators.

Efficacy Endpoints

The efficacy endpoints were changes in pulmonary hemodynamic factors, WHO functional class, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentrations from baseline (within 60 min before the first dose of epoprostenol AS) to immediately after switching (within 60 min after the first dose of epoprostenol AS) or week 12. Pulmonary hemodynamic factors included systolic pulmonary artery pressure, diastolic pulmonary artery pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac output, mean right atrial pressure, mixed venous oxygen saturation, cardiac index, pulmonary vascular resistance, and pulmonary vascular resistance index. Pulmonary hemodynamics were measured by right heart catheterization, which was performed according to standard local procedures through the internal jugular, subclavian, or femoral vein by a balloon catheter placed into either the right or left pulmonary artery in a sterilized cardiac catheterization laboratory. Cardiac Output (CO) was measured using Fick's method [18].

Treatment Satisfaction

The abbreviated nine-item Treatment Satisfaction Questionnaire for Medication (TSQM-9), employed for the quality of life assessment, is a validated questionnaire that permits comparisons of patients' treatment

satisfaction across medication types and patient conditions [19]. The changes from baseline to week 12 in treatment satisfaction were assessed using the TSQM-9. This questionnaire includes three items for each of three domains: effectiveness, convenience, and global satisfaction. The scores for each domain range from 0 to 100, where higher scores indicate higher satisfaction on that domain.

Statistical Analysis

This study was an exploratory study. No hypothesis was set and no power considerations were made for this study. Patients who received at least one dose of the study drug were included in the all-treated set for analyses. Patients who had assessable data at baseline and week 12 were included in the analysis of pulmonary hemodynamics. All statistical analyses were considered to be exploratory and the significance level was set at 5% (two-sided). The efficacy variables were summarized descriptively by calculating the mean, standard deviation, standard error, median, 25th and 75th percentiles, minimum and maximum. Changes from baseline were examined using the Wilcoxon signed rank sum test. All analyses were performed using SAS (Version 9.2; SAS Inc., Cary, North Carolina, USA).

RESULTS

Patients

The study was conducted at two Japanese study sites, and started in October 2011. Eight Japanese patients (one male, seven females) with PAH were treated with the study drug and completed the 12-week evaluation period by October 2012. The characteristics of the patients are summarized in Table 1 and Supplemental Table 1. The mean (range) age

Table 1 Patient characteristics

Background factors	$N = 8$
Sex, *n* (%)	
Male	1 (12.5)
Female	7 (87.5)
Age, years	
Mean ± SD	47.6 ± 12.5
Median	46.0
[Min, Max]	[25, 69]
Age in class	
20–64 years	7 (87.5)
≥65 years	1 (12.5)
Race, *n* (%)	
Asian	8 (100.0)
Body mass index, kg/m^2	
Mean ± SD	19.94 ± 2.21
Median	20.40
[Min, Max]	[15.4, 23.0]
Etiology of PAH, *n* (%)	
IPAH	7 (87.5)
HPAH	1 (12.5)
APAH-DT	0 (0.0)
APAH-CTD	0 (0.0)
Time since PAH diagnosis, years	
Mean ± SD	6.21 ± 5.24
Median	5.26
[Min, Max]	[0.6, 13.9]
WHO functional class, *n* (%)	
I	1 (12.5)
II	5 (62.5)
III	2 (25.0)
IV	0 (0.0)

APAH-CTD associated with pulmonary arterial hypertension-connective tissue disease, *APAH-DT* associated with pulmonary arterial hypertension-drugs and toxins induced, *HPAH* heritable pulmonary arterial hypertension, *IPAH* idiopathic pulmonary arterial hypertension, *PAH* pulmonary arterial hypertension, *SD* standard deviation

and time from PAH diagnosis were 47.6 (25–69) years and 6.21 (0.6–13.9) years, respectively. At baseline, seven patients had IPAH and one had HPAH. The WHO functional class was Class I for one patient, Class II for five patients, and Class III for two patients. Epoprostenol AS was started at the same dose of epoprostenol GM, with a mean (range) dose of 40.13 (17.0–61.0) ng/kg/min. The mean (range) duration of exposure to epoprostenol AS during the 12-week treatment period was 86.9 (78.4–91.6) days. There were no dose adjustments in any patient. All of the patients completed the study schedule during the evaluation period. The continuous treatment period was ongoing as of February 2013.

Safety

Adverse events reported during the 12-week evaluation period are summarized in Table 2 according to system organ class and preferred term using the Medical Dictionary for Regulatory Activities/Japanese version. Seven out of eight patients (87.5%) experienced a total of 18 adverse events. Three patients (37.5%) experienced a total of four adverse events that were considered related to the study drug. Two patients (25.0%) experienced serious adverse events: moderate pneumonia and mild device dislocation in one patient each, both of which were not considered related to the study drug. There were no deaths or adverse events leading to treatment discontinuation during the study. Seven out of eight patients (87.5%) experienced mild adverse events and three (37.5%) experienced moderate adverse events; there were no severe adverse events. The most frequent event was nausea, which was reported by two patients. The other adverse events occurred in one patient only. There were no clinically significant changes from baseline to week 12 in blood pressure, heart rate, body weight, or clinical laboratory tests.

Efficacy

Table 3 shows the hemodynamic factors measured within 60 min before (i.e., baseline) and 60 min after the first dose of epoprostenol, as well as the changes between these two times. As shown in Table 3, there were no marked changes in pulmonary hemodynamic parameters from 60 min before to 60 min after the first dose of epoprostenol AS. Wilcoxon signed rank sum tests revealed no significant differences at the 5% level for the changes from baseline. Table 4 presents the hemodynamic factors measured at baseline and at week 12, together with their changes between these times. As shown in Table 4, there were no remarkable changes in pulmonary hemodynamic factors from baseline to week 12. Additionally, Wilcoxon signed rank sum tests revealed no significant differences at the 5% level for the changes from baseline. The WHO functional class was unchanged from baseline to week 12, as one was categorized as Class I, five as Class II, and two as Class III (Table 5). The mean (range) NT-proBNP concentration was 139 (57–240) pg/mL at baseline and 106 (41–243) pg/mL at week 12. The mean (range) change from baseline to week 12 was −−43.3 (−196 to 43) pg/mL, which was not clinically significant (Wilcoxon signed rank sum test: $P = 0.5781$) (Fig. 1).

Treatment Satisfaction

Table 6 shows the scores for all three domains of the TSQM-9 recorded at baseline and week 12, together with the changes from baseline to week 12. As shown in this table, there were improvements in all three domains during the

Table 2 Summary of treatment-emergent adverse events by intensity and system organ class

	Asymptomatic	Mild	Moderate	Severe	Total (n = 8)
All system organ classes					
Total pts with at least one AE	0 (0.0%)	7 (87.5)	3 (37.5%)	0 (0.0%)	7 (87.5%)
Total number of AEs	0	11	7	0	18
Gastrointestinal disorders					
Total pts with at least one AE	0 (0.0%)	3 (37.5%)	3 (37.5%)	0 (0.0%)	5 (62.5%)
Total number of AEs	0	3	3	0	6
Nausea	0 (0.0%)	0 (0.0%)	2 (25.0%)	0 (0.0%)	2 (25.0%)
Diarrhea	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
Gastritis	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Vomiting	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Mikulicz's disease	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Infections and infestations					
Total pts with at least one AE	0 (0.0%)	1 (12.5%)	2 (25.0%)	0 (0.0%)	3 (37.5%)
Total number of AEs	0	1	2	0	3
Pharyngitis	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
Pneumonia	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
Cellulitis	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
General disorders and administrations site conditions					
Total pts with at least one AE	0 (0.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
Total number of AEs	0	2	0	0	2
Device dislocation	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Injury associated with device	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Skin and subcutaneous tissue disorders					
Total pts with at least one AE	0 (0.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
Total number of AEs	0	3	0	0	3
Dermatitis allergic	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Drug eruption	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Rash	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Ear and labyrinth disorders					
Total pts with at least one AE	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Total number of AEs	0	1	0	0	1
Vertigo	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)

Table 2 continued

	Asymptomatic	Mild	Moderate	Severe	Total ($n = 8$)
Musculoskeletal and connective tissue disorders					
Total pts with at least one AE	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Total number of AEs	0	1	0	0	1
Arthralgia	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Nervous system disorders					
Total pts with at least one AE	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
Total number of AEs	0	0	1	0	1
Hypoasthesia	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
Respiratory, thoracic and mediastinal disorders					
Total pts with at least one AE	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
Total number of AEs	0	0	1	0	1
Pleurisy	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)

AE adverse event, *pts* patients

12-week treatment period. The improvement in convenience was statistically significant (Wilcoxon signed rank sum test: $P = 0.0313$).

DISCUSSION

The results of this study demonstrate that patients with PAH can be switched from epoprostenol GM to a new formulation of epoprostenol sodium, epoprostenol AS, with no apparent safety concerns or deteriorations in pulmonary hemodynamic factors. Switching from epoprostenol GM to epoprostenol AS was also associated with an improvement in convenience across three treatment satisfaction domains.

The new formulation of epoprostenol is stable for 24 h at room temperature (1–30 °C) after preparation/dilution in saline, and the prepared solution does not require cooling with a frozen gel pack, which is expected to improve the quality of life of patients, particularly in terms of their daily activities. This expectation is supported by the results of the treatment satisfaction questionnaire, which showed an improvement in convenience. Therefore, patients with PAH treated with conventional formulations of epoprostenol sodium could be switched to epoprostenol AS, a stable formulation at room temperature, and may enhance their quality of life through improvements in treatment convenience.

The outdoor air temperature during the summer in many regions of Japan often exceeds 30 °C, and the temperature around the medication cassette of the diluted solution could be even higher [20]. As part of the risk-management strategy in this study, patients were instructed to use a frozen gel pack during the summer, especially when the environmental temperature exceeded room temperature. In this study, two out of eight patients used a frozen gel pack during the treatment period, but neither of these patients experienced any changes in their overall

Table 3 Changes in hemodynamic parameters from baseline to within 60 min after switching epoprostenol formulations

Hemodynamic parameter	Baseline (n = 8)			After 60 min (n = 8)						P value[a]
	Actual value			Actual value			Changes from baseline			
	Mean ± SD	Median	[Min, Max]	Mean ± SD	Median	[Min, Max]	Mean ± SD	Median	[Min, Max]	
Systolic pulmonary artery pressure, mmHg	50.6 ± 12.4	46.0	[34, 69]	50.5 ± 12.5	48.0	[33, 72]	−0.1 ± 4.2	−0.5	[−7, 6]	0.8438
Diastolic pulmonary artery pressure, mmHg	17.1 ± 2.2	17.0	[14, 22]	16.5 ± 2.2	16.0	[13, 20]	−0.6 ± 1.8	−0.5	[−4, 2]	0.5313
Mean pulmonary artery pressure, mmHg	31.1 ± 5.1	31.5	[22, 40]	30.4 ± 4.6	30.0	[22, 37]	−0.8 ± 2.2	−0.5	[−4, 2]	0.4375
Pulmonary capillary wedge pressure, mmHg	8.4 ± 1.8	8.0	[5, 11]	7.1 ± 1.7	6.5	[5, 10]	−1.3 ± 1.3	−1.5	[−3, 1]	0.0625
Cardiac output, L/min	4.829 ± 1.057	4.440	[2.72, 5.99]	4.834 ± 1.349	4.535	[3.45, 6.76]	0.545 ± 0.782	0.420	[−0.31, 1.84]	0.1094
Mean right arterial pressure, mmHg	4.8 ± 1.8	4.5	[3, 8]	3.6 ± 1.5	3.5	[1, 6]	−1.1 ± 2.0	−1.5	[−3, 3]	0.2031
Mixed venous oxygen saturation, %	73.43 ± 5.50	73.20	[63.4, 83.2]	73.86 ± 5.82	72.15	[66.0, 84.5]	0.44 ± 2.73	0.30	[−3.9, 3.7]	0.8438
Cardiac input, L/min/m^2	2.98 ± 0.86	2.80	[2.0, 4.3]	3.39 ± 1.20	2.95	[2.2, 5.4]	0.41 ± 0.60	0.20	[−0.2, 1.5]	0.1250
Pulmonary vascular resistance, dyn·s/cm^5	448.3 ± 158.1	429.5	[201, 676]	406.0 ± 143.6	380.0	[232, 680]	−42.3 ± 84.1	−14.0	[−166, 41]	0.4609
Pulmonary vascular resistance index, dyn·s/cm^5/m^2	646.5 ± 223.1	598.0	[338, 1,000]	594.8 ± 237.3	534.5	[384, 1,091]	−51.8 ± 124.3	−22.5	[−239, 91]	0.4609

SD standard deviation

[a] P value based upon Wilcoxon signed rank sum test

Table 4 Changes in hemodynamic parameters from baseline to 12 weeks after switching epoprostenol formulations

Hemodynamic parameter	Baseline (n = 8)			After 60 min (n = 8)						P value[a]
	Actual value			Actual value			Changes from baseline			
	Mean ± SD	Median	[Min, Max]	Mean ± SD	Median	[Min, Max]	Mean ± SD	Median	[Min, Max]	
Systolic pulmonary artery pressure, mmHg	50.6 ± 12.4	46.0	[34, 69]	49.8 ± 14.1	44.5	[29, 70]	−0.9 ± 3.5	−1.0	[−5, 4]	0.4375
Diastolic pulmonary artery pressure, mmHg	17.1 ± 2.2	17.0	[14, 22]	18.8 ± 4.6	19.0	[11, 24]	1.6 ± 3.7	2.0	[−3, 7]	0.4844
Mean pulmonary artery pressure, mmHg	31.1 ± 5.1	31.5	[22, 40]	31.4 ± 7.2	32.0	[18, 41]	0.3 ± 2.8	0.5	[−4, 4]	0.8906
Pulmonary capillary wedge pressure, mmHg	8.4 ± 1.8	8.0	[5, 11]	7.3 ± 1.2	7.5	[6, 9]	−1.1 ± 2.3	−2.0	[−4, 3]	0.2344
Cardiac output, L/min	4.829 ± 1.057	4.440	[2.72, 5.99]	4.499 ± 1.005	4.095	[3.25, 5.98]	0.210 ± 0.790	0.310	[−0.91, 1.35]	0.4609
Mean right arterial pressure, mmHg	4.8 ± 1.8	4.5	[3, 8]	4.8 ± 1.8	4.5	[3, 7]	0.0 ± 1.7	0.0	[−3, 3]	1.0000
Mixed venous oxygen saturation, %	73.43 ± 5.50	73.20	[63.4, 83.2]	72.10 ± 3.28	72.75	[67.1, 76.3]	−1.33 ± 4.64	−0.50	[−8.4, 4.7]	0.5469
Cardiac input, L/min/m^2	2.98 ± 0.86	2.80	[2.0, 4.3]	3.11 ± 0.72	3.00	[2.4, 4.3]	0.14 ± 0.52	−0.25	[−0.6, 0.9]	0.6563
Pulmonary vascular resistance, dyn·s/cm^5	448.3 ± 158.1	429.5	[201, 676]	453.6 ± 175.3	424.5	[154, 686]	5.4 ± 78.3	−25.0	[−61, 182]	0.5469
Pulmonary vascular resistance index, dyn·s/cm^5/m^2	646.5 ± 223.1	598.0	[338, 1,000]	648.5 ± 239.6	640.5	[251, 992]	2.4 ± 98.4	−15.5	[−87, 212]	0.7109

SD standard deviation

[a] P value based upon Wilcoxon signed rank sum test