Efficacy and Safety of a Novel Endothelin Receptor Antagonist, Macitentan, in Japanese Patients With Pulmonary Arterial Hypertension

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Background: Macitentan is a novel, dual endothelin receptor antagonist with sustained receptor binding, used for the long-term treatment of pulmonary arterial hypertension (PAH). In the present study, we assessed the efficacy and safety of macitentan in Japanese patients with PAH.

Methods and Results: Macitentan was administered at a once-daily dose of 10 mg in 30 patients. The primary endpoint was change in pulmonary vascular resistance (PVR) from baseline to week 24. Change to week 24 in the other hemodynamic parameters, 6-min walk distance (6MWD), World Health Organization (WHO) functional class, and plasma N-terminal pro-brain natriuretic peptide (NT-pro-BNP), as well as time to clinical deterioration up to week 52 were also assessed as secondary endpoints. In the 28 patients on per-protocol analysis, PVR decreased from 667 ± 293 to 417 ± 214 dyn·sec·cm⁻⁵ ($P < 0.0001$). 6MWD increased from 427 ± 128 to 494 ± 116 m ($P < 0.0001$). WHO functional class improved in 13 patients (46.4%) and was maintained in 15 patients (53.6%), and NT-pro-BNP was reduced by 18% ($P < 0.0001$). The favorable treatment effect on PVR was apparent regardless of concomitant therapy for PAH.

Conclusions: Macitentan was efficacious and well tolerated and improved the hemodynamic parameters, exercise capacity, symptoms, and clinical biomarkers in Japanese PAH patients. Macitentan can be a valuable therapeutic option for Japanese patients with PAH. (Trial registration: JAPIC Clinical Trials Information [JapicCTI-121986].) (*Circ J* 2016; **80**: 1478–1483)

Key Words: Endothelin receptor antagonist; Hemodynamics; Macitentan; Pulmonary arterial hypertension; Safety

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Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by vascular proliferation and remodeling of small pulmonary vessels leading to progressive increase in pulmonary vascular resistance (PVR) and, ultimately, to right heart failure and premature death.¹⁻³ In the past decade, remarkable advances have been made in the treatment of PAH. Currently, several drugs with different targets are available, including endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors, and prostacyclin and its analogues.⁴ Nevertheless, these treatments are still considered palliative and not curative.

Macitentan is an alkyl sulfamide-substituted pyrimidine resulting from modification of the structure of known ERA including bosentan.⁵ Characteristic features of this compound are sustained receptor binding and enhanced tissue penetration.^{6,7} Recently, a multi-national phase III trial (SERAPHIN) of this compound was carried out using a primary endpoint reflecting long-term disease progression, and the risk for morbidity and mortality was significantly reduced by 45% on 10 mg macitentan compared with placebo in symptomatic PAH patients.⁸ Japanese patients, however, were not enrolled in the multi-national study, and the Japanese regulatory authority proposed a clinical trial with only Japanese patients. In a previous study, the pharmacokinetics were shown to be similar in Japanese and Caucasian subjects.⁹ This met the requirement of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for extrapolation of the results of the SERAPHIN study to the Japanese population. The aim of the present study was to investigate the effect of macitentan on PVR at week 24 from baseline as a primary efficacy endpoint in Japanese patients with PAH. An open-label study design was chosen in order to facilitate extrapolation of the efficacy and safety of macitentan seen in the SERAPHIN trial to a Japanese PAH population.

Methods

Patient Selection

Japanese patients aged ≥ 16 years were eligible to participate in the study if they had idiopathic or heritable PAH, PAH associated with repaired congenital heart disease (≥ 1 year after repair) or connective tissue disease and were in World Health Organization (WHO) functional class I–IV. The diagnosis of PAH was confirmed on hemodynamic evaluation with right heart catheterization at rest, within 30 days before initiating macitentan treatment.

Inclusion criteria were mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, pulmonary artery wedge pressure (PAWP) or left ventricular end-diastolic pressure ≤ 15 mmHg, PVR at rest ≥ 320 dyn·sec·cm⁻⁵, and baseline 6-min walk distance (6MWD) ≥ 50 m. Patients were excluded from the study if they were pregnant, had total lung capacity $< 60\%$ of the normal predictive value, aminotransferase ≥ 1.5 -fold upper limit of normal (ULN), or severe hepatic impairment (Child-Pugh type C), hemoglobin $< 75\%$ of the lower limit of the normal range, hypotension with systolic blood pressure < 85 mmHg, and estimated glomerular filtration rate < 30 ml/min. Patients who had been receiving ERA, intravenous (i.v.) injection of diuretics, or i.v. or subcutaneous infusion of prostanoids within 30 days prior to right heart catheterization at baseline were also excluded.

Concomitant treatment with calcium channel blockers, phosphodiesterase type 5 inhibitors, and oral prostanoids for PAH was permitted if the patients had been receiving a stable dose for at least 90 days before right heart catheterization at baseline. Oral diuretics were permitted if they had been used

Table 1. Baseline Patient Characteristics

	n=30
Female	25 (83.3)
Age (years)	49 $\pm$ 16
PAH classification	
Idiopathic	11 (36.7)
Heritable	1 (3.3)
Associated with connective tissue disease	16 (53.3)
Associated with repaired congenital shunt	2 (6.7)
6-min walk distance (m)	418 $\pm$ 131, 439 (170–637)
WHO functional class	
I	1 (3.3)
II	16 (53.3)
III	13 (43.3)
Background treatment for PAH	
No	10 (33.3)
Yes	20 (66.7)
Phosphodiesterase type 5 inhibitor	16 (53.3)
Oral prostanoid	12 (40.0)

Data given as mean $\pm$ SD, n (%) or median (range). PAH, pulmonary arterial hypertension; WHO, World Health Organization.

for at least 7 days before catheterization at a stable dose.

The present study was conducted in accordance with ethics guidelines introduced by Ethics Committees that oversee studies in humans (conducted in participating facilities or regions) and the Declaration of Helsinki. The study design was approved by the local Institutional Review Boards. Informed consent was obtained from all patients enrolled.

Study Design

This study was a multicenter, open-label, non-comparative clinical study. Within 30 days after the baseline assessment, macitentan was administered at a once-daily dose of 10 mg. Hemodynamic measurements were performed with a Swan-Ganz catheter while patients were recumbent. Cardiac output (CO) was determined using the thermodilution or Fick's method. The same method was used for each patient throughout the study. Cardiac index (CI) was derived by normalization of CO with body surface area (BSA): CI=CO/BSA. PVR was calculated from the transpulmonary gradient and CO: PVR=80(mPAP–PAWP)/CO. Efficacy of treatment was also assessed up to week 24 on the basis of 6MWD and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). Patient symptoms were evaluated according to the Borg dyspnea index and WHO functional class. Follow-up hemodynamic measurements were performed after 24 weeks of treatment. PAH-related hospitalization or death were evaluated up to 52 weeks. Safety and tolerability were assessed on the basis of recorded adverse events, clinical laboratory parameters, vital signs, and electrocardiography at each visit up to 52 weeks from the baseline.

Statistical Analysis

Patients who had no valid PVR at week 24 were excluded and not imputed for analysis in the per-protocol set. PVR, as the primary efficacy parameter, and other hemodynamic values (CI, mPAP, mean right atrial pressure [mRAP], and mixed venous oxygen saturation), 6MWD, Borg dyspnea index and NT-pro-BNP at week 24 were compared with those at baseline on a per-protocol population basis using Wilcoxon signed-rank test as the primary analysis. Significant change was

	Baseline	Week 24	Week 24/Baseline % (95% CI)	Reduction/Increase from baseline (%)	P-value†
	Mean±SD (95% CI)	Mean±SD (95% CI)			
PVR (dyn·sec·cm ⁻⁵)	667±293 (554–781)	417±214 (335–500)	60.5 (52.4–69.9)	–39.5	<0.0001
mPAP (mmHg)	38±10 (35–42)	32±9 (28–35)	82.0 (75.4–89.2)	–18.0	<0.0001
Cardiac index (L·min ⁻¹ ·m ⁻²)	2.57±0.60 (2.34–2.80)	2.98±0.72 (2.70–3.26)	115.7 (108.8–123.2)	+15.7	<0.0001
mRAP (mmHg)	5±2 (4–6)	5±2 (4–6)	95.5 (74.1–123.1)	–4.5	0.883
SvO ₂ (%)	70.0±5.7 (67.8–72.2)	70.3±5.7 (68.1–72.5)	100.4 (98.1–102.8)	+0.4	0.673

†Wilcoxon signed-rank test. mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SvO₂, mixed venous oxygen saturation.

defined as $P < 0.05$ (2-tailed). All statistical analysis was performed using SAS (version 9.3; SAS, Cary, NC, USA).

Results

Patients

Thirty patients (5 male and 25 female), 11 with idiopathic PAH, 1 with heritable PAH, and 18 with PAH related to other diseases (16 associated with connective tissue disease and 2 associated with repaired congenital heart disease: 1 involving a ventricular septal defect and another involving an atrial septal defect) were enrolled at 20 centers from 2012. Patient demographics and baseline characteristics are listed in Table 1. Mean participant age was 49 ± 16 years (range, 20–74 years). WHO functional classification at baseline was predominantly class II (53.3%) and class III (43.3%). Twenty patients had been receiving oral prostanoids or phosphodiesterase type 5 inhibitors for PAH at baseline and their dose remained unchanged. The remaining 10 patients received macitentan monotherapy.

Two patients in WHO functional class III were excluded from efficacy analysis because hemodynamic data at week 24 were not available due to cardiac failure and suspected cardiac failure caused by interstitial lung disease and bacterial pneumonia that necessitated additional treatment (oral or i.v. diuretics). Both patients, however, continued to receive macitentan for an assessment of the safety profile.

Two patients discontinued study treatment permanently: one patient due to fatal pulmonary embolism (withdrawn on

day 339), and 1 because of initiation of forbidden medication on the basis of investigator decision (discontinued on day 229).

Efficacy

Cardiopulmonary hemodynamic parameters at baseline and week 24 are summarized in Table 2.

After 24 weeks of treatment with macitentan, PVR ($\pm$ SD) decreased from 667 ± 293 dyn·sec·cm⁻⁵ to 417 ± 214 dyn·sec·cm⁻⁵ ($P < 0.0001$). PVR at week 24 was decreased by 39.5% from that at baseline. Improvements in other hemodynamic parameters were also observed: mPAP decreased from 38 ± 10 mmHg to 32 ± 9 mmHg ($P < 0.0001$) and CI increased from 2.57 ± 0.60 L·min⁻¹·m⁻² to 2.98 ± 0.72 L·min⁻¹·m⁻² ($P < 0.0001$, Table 2). Ten of the 28 patients were evaluated using the thermodilution method, while the remaining 18 patients were evaluated using Fick’s method. No significant differences were observed in terms of mRAP and mixed venous oxygen saturation between that at baseline and week 24.

The reduction in PVR on macitentan treatment was independent of concomitant treatment (reduced by 40% in 18 patients with and by 39% in 10 patients without concomitant treatment). After 24 weeks of treatment, 6MWD ($\pm$ SD) increased from 427 ± 128 m to 494 ± 116 m ($P < 0.0001$; Figure 1). The slight increase in Borg dyspnea index (3.2 ± 2.2 to 3.5 ± 2.5) did not reach statistical significance ($P = 0.554$). Serum NT-pro-BNP decreased from 145 pg/ml (95% CI: 81–258) to 119 pg/ml (95% CI: 72–197), that is, by 18% from baseline ($P < 0.0001$).

At the beginning of the study, 1 patient had WHO functional class I, 16 had class II, and 11 had class III symptoms.

No patient had deterioration of condition during the study period. At the end of the 24-week macitentan treatment, the number of patients with class I symptoms increased to 5, and the number of patients with class III symptoms decreased to 2 (Figure 2). There were no PAH-related deaths up to 52 weeks after treatment initiation. Hospitalization for PAH was recorded for 1 patient on day 340.

Safety

Macitentan treatment at a once-daily dose of 10 mg was well tolerated. None of the patients discontinued study treatment due to safety reason, except for the 1 patient with fatal pulmonary embolism (died on day 340), which was considered to be unrelated to the study drug by the investigator. Adverse drug reactions (excluding unrelated events) were observed in 24 out of 30 patients (80.0%), including headache (33.3%), flushing (26.7%), and peripheral edema (6.7%). Increase in aspartate aminotransferase and alanine aminotransferase was noted in 1 patient but remained less than 3-fold of ULN. Throughout the study period of 52 weeks, anemia was observed in 8 of 30 patients (26.7%), but reduction in hemoglobin to ≤ 10 g/dl was noted only in 3 patients. No clinically significant change in blood pressure, pulse rate, or electrocardiographic findings was noted during the study.

Discussion

Before the development of recent therapeutic options, PAH was a rapidly progressive and lethal disease. In the 1980s, median survival in PAH was only 2.8 years after diagnosis.¹⁰ At the beginning of the 21st century, the oral non-selective dual ERA, bosentan, was first introduced for PAH treatment.^{11,12} In 2004, we assessed the effects of bosentan and showed that bosentan improved cardiopulmonary hemodynamics, 6MWD, Borg dyspnea index, functional capacity, and quality of life.¹³ On the basis of these results, bosentan received orphan drug status and marketing authorization in Japan. But, because bosentan was approved on the basis of a relatively small clinical trial, Japanese authorities required initiation of a post-marketing surveillance program to obtain further data on its efficacy and safety profiles. From June 2005 to May 2013, bosentan was used to treat 4,252 patients in 713 centers in Japan. In this program, clinical improvements were apparent in terms of parameters used the first Japanese clinical trial. Of these patients, however, 672 had elevated liver aminotransferase,¹⁴ corresponding to a crude incidence of 15.8%. Other side-effects included hematologic disturbance and peripheral edema. Aminotransferase returned to pretreatment levels without sequelae either spontaneously or after dose reduction or discontinuation. Nevertheless, this remains a challenge with bosentan treatment.

Under these circumstances, macitentan was developed using knowledge of the structure of bosentan. The efficacy of macitentan is related to its high affinity to both endothelin receptors, its favorable binding kinetics, enhanced tissue penetration, and to the formation of a long-lasting active metabolite: ACT-132577.¹⁵ The absorption of macitentan is slow, due to its low aqueous solubility. In phase I studies macitentan was well tolerated up to a single dose of 300 mg with a maximum plasma concentration of 8 h and with an elimination half-life of 17.5 h. The mean half-life of ACT-132577 ranged from 40 to 65 h. These properties have made a once-daily dose regimen possible.¹⁶ The International Conference on Harmonization guideline document "Ethnic Factors in the Acceptability of Foreign Data" recommends the measurement of pharmacoki-

netic/pharmacodynamic parameters to permit the clinical effects obtained in 1 population to be extrapolated to a different population.¹⁷ In an open-label, phase I study, 10 healthy Japanese and Caucasian subjects were treated with a single oral dose of macitentan at 10 mg. The plasma concentration-time profile of macitentan and its pharmacologically active metabolite ACT-132577 were similar between the ethnic groups.⁹

Macitentan is converted to the active metabolite ACT-132577 mainly by Cytochrome P450 3A4 (CYP3A4), and a strong CYP3A4 inhibitor doubles exposure to macitentan.¹⁸ Bosentan is also metabolized by CYP3A4 to 3 metabolites and excreted in bile.¹⁹ The adenine to guanine transition in the 5' promoter region of *CYP3A4* in a sequence motif, known as the nifedipine-specific element, indicated considerable ethnic differences in the frequency of this polymorphism between Caucasian and Japanese subjects. The rate of CYP3A4-dependent drug metabolism has been shown to be irrelevant to ethnic differences,²⁰ and differences in CYP3A activity between Caucasian and Japanese subjects were shown to be not statistically significant or clinically important.²¹ Therefore, we assumed that no dose adjustment was necessary when macitentan was used to treat Japanese patients.

In the present study, treatment with macitentan at a once-daily dose of 10 mg for 24 weeks resulted in a significant improvement of exercise capacity (6MWD), indicating that the patients were able to walk further without worsening of dyspnea, compared with baseline. Macitentan consistently improved pulmonary hemodynamic parameters, WHO functional class, and NT-pro-BNP level, although participant condition was stable, as indicated by the normal right atrial pressure and low NT-pro-BNP. 6MWD has been the most common primary end-

point in clinical trials, and many PAH-specific therapies have been approved on the basis of their ability to improve 6MWD. In the present study, a significant treatment effect in favor of macitentan was observed in terms of 6MWD, but, despite the advantages of simplicity and inexpensiveness, the difference observed in the change in 6MWD remains controversial. Improvement is smaller in patients without advanced disease (ceiling effect).²² In addition, on pooled analysis of data from the randomized placebo-controlled trials, 6MWD does not explain a large proportion of the prognostic treatment effects, but has only modest validity as a surrogate endpoint for clinical events, suggesting that this measure may not be a sufficient surrogate endpoint.²³ As a result, assessment of change in mortality and morbidity rates on long-term treatment is required.

A change in 6MWD from that at baseline does not indicate clinical worsening or mortality,^{24,25} but absolute 6MWD at baseline and during therapy correlates with long-term outcome.²⁶ Thus, the present results may support the findings of the recently published SERAPHIN trial wherein 10 mg macitentan significantly improved 6MWD. In the subset of patients who underwent hemodynamic assessment, decrease in PVR and increase in CI were apparent, along with the reduced risk of PAH-related events by 45% compared with those who received placebo.⁸ Given the aforementioned information from the SERAPHIN trial and the present results, we can extrapolate the efficacy of macitentan to reduce mortality and morbidity rates in Japanese patients with PAH.

Hepatocellular enzyme elevation is a well-known major side effect of bosentan. In the Japanese post-marketing surveillance of bosentan treatment, elevated aspartate aminotransferase and alanine aminotransferase was observed in 15.8% of patients, but in 64% of those the increase was <3-fold ULN. Even in this group of patients with mild elevation of transaminases, bosentan treatment was discontinued in 28% and the daily dose was reduced in 25%. Of particular interest, in the present study, the incidence of elevated transaminase was only 3.3% (1/30 patients), and no patient had >3-fold ULN. These findings are also consistent with the results of the SERAPHIN trial; the percentage of patients with aminotransferase elevation was not different in the active- and placebo-treated groups. Liver injury induced by bosentan and its metabolites is mediated through the inhibition of the canalicular bile salt export pump (BSEP) with a resultant intrahepatic accumulation of cytotoxic bile salts.²⁷ While passive diffusion is the driving force for macitentan uptake into the liver, low intrahepatic drug concentration limits BSEP transport proteins involved in hepatic bile salt homeostasis.²⁸ Therefore, in contrast to bosentan, macitentan does not interfere with BSEP.²⁸ The liver safety profile appears to give macitentan an additional advantage over bosentan in the treatment of PAH.

Of note, a decrease in hemoglobin, a known adverse effect with other ERA,¹⁶ occurred more frequently with macitentan than placebo in the SERAPHIN trial. In the present study, there was only one case of significant anemia (hemoglobin ≤ 8 g/dl) and no case leading to discontinuation of study drug due to anemia. These results, however, were based on limited use of macitentan, and further evaluation therefore needs to be carried out in future studies.

Study Limitations

This study had significant limitations. In particular, this was a non-randomized, open-label study in which both the participant and the investigator knew the drug and dose being used. Therefore, we cannot exclude the possibility that subjective

parameters such as WHO functional class and 6MWD might be affected by biases to a greater extent than NT-pro-BNP. In addition, the hemodynamic measurements may have been subject to some bias. The present study was short term with a small number of patients. Moreover, the ultimate safety and efficacy, compared with the placebo or an active control, was not investigated. Nevertheless, this study addressed the same directional changes in hemodynamics, exercise capacity, and symptoms recorded in the large-scale multi-national phase III trial and enabled comparison of outcome measures.

Conclusions

Macitentan was used for the first time to treat Japanese patients with PAH. In this study, macitentan significantly improved pulmonary hemodynamic parameters, exercise capacity, symptoms, and clinical biomarkers with a favorable tolerability and safety profile. Macitentan may be a valuable therapeutic option for Japanese PAH patients.

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Conflict of Interest

N. Tahara has received speaker fees from Actelion Pharmaceuticals Japan. H.D. has received travel fees from Actelion Pharmaceuticals Japan, Nippon Shinyaku, and Astellas Pharma. K.F. has received funding/grant support for research projects from Bayer Yakuhin, and Astellas Pharma. He belongs to the endowed chair by Actelion Pharmaceuticals Japan. M.F. has no conflict of interest. M.H. has received speaker fees from Actelion Pharmaceuticals Japan. S.I. has no conflict of interest. S.J. has no conflict of interest. Y.K. has no conflict of interest. T. Kimura has received funding/grant support for research projects from Toray Industries, and scholarship funds from Astellas Pharma. T. Kondo belongs to the endowed department by Actelion Pharmaceuticals Japan. M.M. has no conflict of interest. T.M. has received speaker fees from Actelion Pharmaceuticals Japan, Nippon Shinyaku, Pfizer Japan, Bayer Yakuhin, Mochida Pharmaceutical, Eli Lilly Japan and Astellas Pharma, and scholarship funds from Pfizer Japan, Bayer Yakuhin, Mochida Pharmaceutical and Astellas Pharma. N.N. belongs to the endowed chair by Actelion Pharmaceuticals Japan. Y.O. has no conflict of interest. T.S. has no conflict of interest. S. Sakai has no conflict of interest. N. Tanabe belongs to the endowed department by Actelion Pharmaceuticals Japan. H.W. has no conflict of interest. H.Y. has received speaker fees from Actelion Pharmaceuticals Japan. K.Y. has received speaker fees from Actelion Pharmaceuticals Japan. S. Sasayama has acted as a consultant for Actelion Pharmaceuticals Japan and Nippon Shinyaku.

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