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ORIGINAL RESEARCH ARTICLE

Real-World Safety and Clinical Outcomes of Macitentan in Asian Patients with Pulmonary Arterial Hypertension: A Prospective Multicenter Study

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Abstract

Background and Objective Macitentan is approved for treating pulmonary arterial hypertension. However, the real-world evidence of macitentan use is limited. Therefore, we evaluated the safety and clinical outcomes of macitentan use in clinical practice under a post-marketing surveillance.

Methods Patients with pulmonary arterial hypertension receiving macitentan treatment were prospectively and consecutively enrolled from 2014 to 2020 at 50 medical centers in Korea. Safety and clinical outcomes were monitored from baseline to the nearest timepoint of 24 weeks after macitentan initiation. The adverse events and adverse drug reactions were identified. Changes in the World Health Organization functional class were assessed as the primary clinical outcome, which was used to estimate the final effectiveness (both improved and maintained). Factors associated with safety and final effectiveness were identified.

Results Among 474 patients enrolled in the study, 467 and 440 were included in the safety and clinical outcome analyses, respectively. Dyspnea, nasopharyngitis, and worsening pulmonary arterial hypertension were the most frequent adverse events with incidences of 5%, 3%, and 3%, respectively. The final effectiveness rate was 93%. Older age (adjusted odds ratio [aOR] = 1.021, $p = 0.003$) and higher level (III vs II) of baseline World Health Organization functional class (aOR = 1.784; $p = 0.022$) were significantly associated with a higher adverse event occurrence. Younger age (aOR = 0.947; $p = 0.001$) and shorter disease duration (aOR = 0.991; $p = 0.010$) were significantly associated with positive final effectiveness.

Conclusions This real-world study demonstrated the safety and clinical outcomes of macitentan use in Korean patients with pulmonary arterial hypertension. Macitentan was well tolerated and significantly effective with no new safety concerns during the 24 weeks.

1 Introduction

Pulmonary arterial hypertension (PAH) is a challenging chronic progressive disease characterized by a narrowed or thickened pulmonary artery, abnormal elevation of pulmonary arterial pressure, and vascular resistance [1]. Pulmonary hypertension is classified into five groups by the World Health Organization (WHO) based on its causes using the WHO Group 1 referring to PAH [2]. The signs and symptoms of PAH include dyspnea, fatigue, dizziness, chest pressure/pain, peripheral swelling, and palpitations, which worsen with disease progression and can cause heart failure or death [3]. The severity of the symptoms can be assessed using the WHO functional classification (FC), with level I being the mildest and level IV the most severe [4]. Although management of PAH is challenging, the development of medical treatments has improved its prognosis in recent decades [5]. Currently, approved pharmacological options for the treatment of PAH in Korea include the following four classes based on the mechanisms of action: endothelin receptor antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase stimulators, and prostacyclin analogs or prostaglandin I_2 receptor agonists [6].

Macitentan, a new dual endothelin receptor antagonist, was approved for treating PAH in adults by the US Food and Drug Administration and the European Medicines Agency

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Key Points

The real-world safety and clinical outcomes of macitentan were investigated in a post-marketing study involving 474 Korean patients with pulmonary arterial hypertension enrolled from 50 medical centers.

The overall incidences of adverse events and adverse drug reactions were 39% and 8%, respectively, with no new safety concerns.

The final effectiveness rate, defined as the proportion of patients showing improvement or maintenance in the World Health Organization functional class from baseline to 24 weeks after macitentan treatment, was 93%.

in 2013. In 2014, it was approved in Korea with a recommended dosage of 10 mg/day for oral administration as monotherapy or in combination. Although evidence on the safety and efficacy of macitentan has been previously demonstrated in a global, randomized, controlled, phase III trial (SERAPHIN) in patients with PAH [7], the evidence under controlled conditions did not address its safety and effectiveness in real-world settings. Recently, real-world data from two studies (ClinicalTrials.gov Identifier: NCT02126943 and NCT03197688) on patients with PAH under macitentan treatment were reported in the USA [8, 9]. However, little information is available regarding macitentan use in Asian patients with PAH in similar settings. Of 242 patients administered 10 mg of macitentan in the phase III trial, the number of Asian patients was 65 (26.9%) [7]. As the number of Korean patients in that study was small, more data from Korean patients in actual clinical practice are valuable. Moreover, post-marketing surveillance is mandatory in Korea to collect and evaluate the safety and effectiveness data of drugs after product approval. The objectives of this study were to investigate the safety and clinical outcomes of macitentan in adult patients with PAH in a real-world setting and to identify potential patient-related factors or disease characteristics associated with the occurrence of adverse events (AEs) and clinical outcomes.

2 Methods

2.1 Study Design

This prospective, multicenter, real-world observational study was conducted from November 2014 to November 2020 as regulatory post-marketing surveillance of macitentan in Korea. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines [10] and was consistent with applicable local regulatory requirements. The institutional review board reviewed the study protocol. Written informed consent was obtained from all study participants.

Patients were eligible for inclusion if they were aged 18 years or older, diagnosed with PAH (WHO Group I) of WHO FC II–III, and recently started treatment with macitentan at any of the participating medical centers after the drug was launched. Patients were excluded based on the following exclusion criteria: pregnant women and those of childbearing potential using unreliable contraception methods; breastfeeding women; patients with severe hepatic impairment (with or without cirrhosis) or with baseline values of hepatic aminotransferases (aspartate aminotransferase and/or alanine aminotransferase more than three times the upper limit of normal); patients with rare hereditary disorders, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; patients with hypersensitivity to macitentan, any of the excipients, soybean oil, soy, or peanuts, or patients with an allergic history; or patients who were treated with macitentan before enrollment.

Patients were consecutively recruited and followed up by their physicians according to routine clinical practice. The observation period for each patient enrolled in this study started with the first prescription of macitentan (visit 1; baseline) to the most recent timepoint after 24 weeks of macitentan administration (visit 4). Visits 2 and 3 were defined as the most recent timepoints from 4 weeks to 12 weeks and from 12 weeks to 24 weeks of macitentan administration, respectively. All patients received macitentan 10-mg tablets once daily in accordance with the approved label.

2.2 Data Collection and Evaluation

Baseline demographics data and disease characteristics, including WHO PAH classification, disease duration, renal or hepatic impairment, and WHO FC, were collected from each patient. During the follow-up period, macitentan administration status, AEs, and clinical outcome data were collected at each visit.

Safety was evaluated in patients who received at least one dose of macitentan and for those with available safety data. Throughout the study, all reported AEs were identified using their names, date of onset, date of resolution, severity, and responsive change in macitentan administration. Moreover, the investigators assessed the causal relationship between macitentan and each AE based on the following six-grade system: certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable. The

AEs were judged as adverse drug reactions (ADRs) if the causality was decided as certain, probable/likely, possible, conditional/unclassified, or unassessable/unclassifiable. The AEs that were fatal, life-threatening, requiring hospitalization, prolongation of existing hospitalization, resulting in significant disability, congenital anomaly, or medically significant were considered serious AEs based on the International Conference on Harmonization guidelines on pharmacovigilance.

Clinical outcomes were evaluated in patients with primary clinical outcome data at visit one and at least one post-treatment visit. The primary clinical outcome was WHO FC. According to the WHO classification, FC I refers to patients with no symptoms during exercise or rest. FC II identifies patients with no symptoms at rest, however, feeling uncomfortable during ordinary activities. FC III includes patients with no symptoms at rest, however, experience limitations in carrying out normal activities. FC IV includes patients with symptoms during rest, which becomes severe with any activity. The secondary clinical outcomes include the 6-Minute Walk Distance (6MWD), Borg Dyspnea Index, and mean pulmonary arterial pressure. All clinical outcome variables were evaluated and collected at each visit as routine clinical practice. The final effectiveness evaluation was defined as the changes in WHO FC from visit 1 to visit 4 in accordance with the pre-specified criteria. The criteria consisted of two categories based on WHO FC: improvement/maintenance when symptoms were determined as clinically improved or unchanged (showing symptomatic change partially) and constant/exacerbation when symptoms were worse than before administration or were not determined as maintained without any symptomatic changes. Patients with improvement/maintenance were considered to have attained final effectiveness, and patients with constant/exacerbation were considered to have failed final effectiveness. The case was considered as maintained effect when symptoms might be exacerbated if administration was discontinued, or the equal effect continued after replacing the existing treatment. If a patient suspended visits before 24 weeks, the clinical outcome variables at the time of discontinuation were recorded, and the final clinical outcome was evaluated using data collected at the last visit. Patient background factors or disease characteristics associated with AE occurrence and final effectiveness at week 24 were investigated using the following variables: sex, age at enrollment, WHO PAH classification, duration of disease, renal (yes/no), and hepatic impairments (yes/no) at baseline, and baseline WHO functional class.

2.3 Statistical Analysis

Continuous variables are presented as descriptive statistics (mean and standard deviation) and categorical variables as frequencies and percentages. Safety profiles were reported based on the incidence of AEs or adverse drug reactions and the number of patients with AEs. A paired *t*-test was conducted to identify whether there were any significant changes in the secondary clinical outcomes. Multiple logistic regression was performed to identify factors associated with AE occurrence risk or final effectiveness based on the primary clinical outcomes. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). The last observation carried forward method was used for imputing the missing data at visit 4 for the final clinical outcome analysis. The distribution of WHO FC by visit was presented using graphs, and the final effectiveness was summarized as the overall effective rate. Statistical significance was defined as $p < 0.05$.

3 Results

3.1 Baseline Demographics and Disease Characteristics of Patients

In this study, 474 patients were enrolled from 50 medical centers in Korea. Among them, 467 were included in the safety analysis and seven were excluded because they did not meet the inclusion criteria, had exclusions, or were lost to follow-up. Of the 467 patients, 440 with baseline and post-baseline WHO FC data were included in the clinical outcomes analysis (Fig. 1).

The baseline demographics and disease characteristics of the 467 patients are presented in Table 1. The mean ± standard deviation age of the patients at enrollment was 48.5 ± 15.8 years, and 73.7% (344/467) of them were women. The mean ± standard deviation disease duration was 29.9 ± 48.2 months among the 350 patients with diagnosis date data. Four (0.9 %) patients had hereditary PAH, whereas 163 (34.9%) and 300 (64.2%) had idiopathic and associated PAH, respectively. Of the 467 patients, 24 (5.14%) and 28 (6.00%) had mild-to-moderate hepatic and renal impairment, respectively. The WHO FC at the initiation of macitentan treatment was 27.2% and 72.8% for Class II and Class III, respectively.

3.2 Macitentan Treatment Patterns

The median duration of macitentan administration was 27.1 weeks, with a range from 0.4 to 51.9 weeks. The number of patients receiving macitentan alone throughout the follow-up period was 306 (65.67%), and the remaining 160 (34.33%) received additional PAH-specific drugs as combination therapy (Table 2). The reported additive PAH-specific medications included phosphodiesterase 5 inhibitors or soluble guanylate cyclase stimulators (22.75%), prostacyclin analog or prostaglandin I_2 receptor agonists (6.22%), and

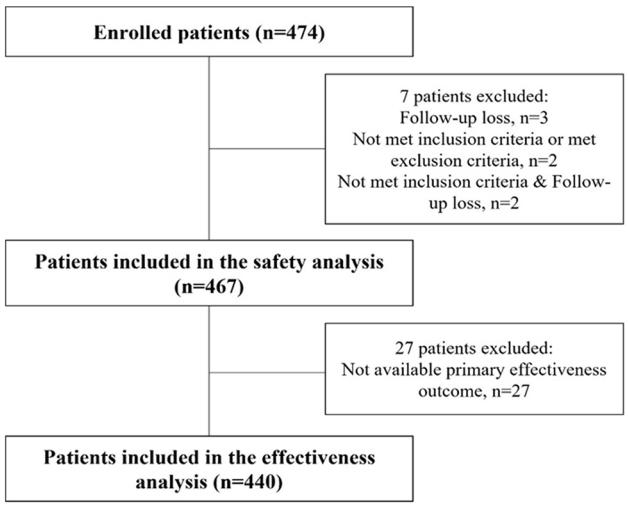

Fig. 1 Study flow chart

Table 1 Baseline demographics and disease characteristics of study population

Characteristics	*N* = 467
Female, *n* (%)	344 (73.7)
Age at study enrollment (year), mean ± SD	48.5 ± 15.8
Age at diagnosis with PAH (year)[a], mean ± SD	45.7 ± 16.7
Body weight (kg), mean ± SD	57.1 ± 11.2
Disease duration (months)[b], mean ± SD	29.9 ± 48.2
WHO PAH classification, *n* (%)	
Idiopathic	163 (34.9)
Heritable	4 (0.9)
Associated	300 (64.2)
Associated with congenital heart disease	202 (43.3)
Associated with connective tissue disease	98 (21.0)
Medical history (comorbidity)	
Hepatic impairment, *n* (%)	24 (5.14)
Renal impairment, *n* (%)	28 (6.00)
Neither hepatic nor renal impairment, *n* (%)	411 (88.0)
WHO functional class, *n* (%)	
II	127 (27.2)
III	340 (72.8)

IQR interquartile range, *n* number of patients, *PAH* pulmonary arterial hypertension, *SD* standard deviation, *WHO* World Health Organization

[a]Data collected from 424 patients

[b]From the date of first diagnosis to the date of first macitentan administration, data were collected from 350 patients with an unknown diagnosis date

phosphodiesterase 5 inhibitors or soluble guanylate cyclase and prostacyclin analog or prostaglandin I_2 receptor agonists (5.36%). Macitentan treatment was permanently discontinued in 56 (12.0%) patients because of AEs in 17, withdrawal (treatment refusal in four, economic burden in four, consent withdrawal in two, and pregnancy in two) in 13, death in seven, transfer to another hospital/department in six, drug ineffectiveness in five, no visits in four, lung transplantation in three, and symptom improvement in one patient.

Table 2 Medications used for treating PAH during the follow-up period

Medications for the treatment of PAH[a]	Patient number (%)
Macitentan monotherapy	306 (65.67)
Macitentan combination therapy	160 (34.33)
[Macitentan] + [PDE5 inhibitor *or* sGC stimulator]	106 (22.75)
[Macitentan] + [PCA *or* IP receptor agonist]	29 (6.22)
[Macitentan] + [PDE5 inhibitor *or* sGC stimulator] + [PCA *or* IP receptor agonist]	25 (5.36)

IP prostaglandin I_2, *PAH* pulmonary arterial hypertension, *PCA* prostacyclin analog, *PDE5* phosphodiesterase type 5, *sGC* soluble guanylate cyclase

[a]Data are available for 466 patients. The median administration period of macitentan was 27.1 weeks (range: 0.4–51.9 weeks)

3.3 Safety

Of the 467 patients included in the safety analysis, 15 (3.21%) deaths were reported. The most common AEs occurring in these patients were worsening PAH in five patients, followed by interstitial lung disease in three, cardiac failure in two, and pneumonia, subdural hematoma, aggravated condition, right-to-left cardiac shunt, and hepatic cirrhosis in one patient each. All AEs were judged as unlikely causality with macitentan except for three events assessed as assessable/unclassifiable (interstitial lung disease, worsening of PAH, and subdural hematoma).

The incidences of AEs and ADRs with an overall frequency of 1.5% or more in the safety analysis set are shown in Table 3. A total of 431 AEs occurred in 182 patients (39.0%) during the surveillance period, including dyspnea in 21 (4.50%), nasopharyngitis in 14 (3.00%), worsening of PAH in 14 (3.00%), headache in 13 (2.78%), pneumonia in 11 (2.36%), and other AEs in fewer than ten patients. Among the 51 ADRs, four serious ADRs were reported in four patients (0.84%), including dyspnea, interstitial lung disease, worsening of PAH, and pleural effusion in one patient each. Macitentan administration was maintained or temporarily discontinued despite serious ADRs in patients with worsening PAH, pleural effusion, and dyspnea; however, the treatment was permanently discontinued in one patient with interstitial lung disease.

Table 4 summarizes the incidences of AEs and ADRs of special interest. Anemia was the most common AE with an incidence of 1.28%, followed by increased alanine aminotransferase

Table 3 Incidences of adverse events and adverse drug reactions with an overall frequency of 1.5% or more

Term	Safety set ($N = 467$)	
	Adverse event	Adverse drug reaction
	n (%)	*n* (%)
Total	182 (39.0)	37 (7.92)
Dyspnea	21 (4.50)	4 (0.86)
Nasopharyngitis	14 (3.00)	0 (0)
Worsening of PAH	14 (3.00)	1 (0.21)
Headache	13 (2.78)	6 (1.28)
Pneumonia	11 (2.36)	0 (0)
Cough	9 (1.93)	1 (0.21)
Cardiac failure	9 (1.93)	0 (0)
Dizziness	9 (1.93)	3 (0.64)
Nausea	8 (1.71)	1 (0.21)
Palpitations	7 (1.50)	0 (0)
Constipation	7 (1.50)	0 (0)
Dyspepsia	7 (1.50)	4 (0.86)

PAH pulmonary arterial hypertension

(0.86%), increased aspartate aminotransferase (0.86%), peripheral edema (0.64%), decreased hemoglobin (0.64%), and increased bilirubin (0.21%). Among the ADRs of special interest, decreased hemoglobin levels and anemia were reported with an incidence of 0.43% and 0.21%, respectively.

3.4 Clinical Outcomes

Changes in the WHO FC of 440 patients at each visit are presented in Fig. 2. The proportion of patients with WHO FC III/IV at visit 4 was 59%, showing a considerable decrease compared with visit 1 (74%). The final effectiveness rate after macitentan treatment for approximately 24 weeks was 93.18% (410/440 patients). The secondary clinical outcomes at each visit and the change from visits 1 to 4 are shown in Table 5. A significant change was observed in the outcomes of the 6MWD (mean difference from visits 1 to 4, 58.5 ± 85.5; $p < 0.001$) and mean pulmonary arterial pressure (− 13.8 ± 17.7; $p = 0.007$); however, no significant change was identified in the Borg Dyspnea Index outcome (− 0.13 ± 1.44, $p = 0.644$).

3.5 Factors Associated with Safety and Effectiveness

Multiple logistic regression analysis for safety showed that initiation of macitentan at an older age (adjusted odds ratio [aOR] = 1.021, 95% confidence interval [CI] 1.007–1.035; $p = 0.003$) was significantly associated with a higher odds of AE occurrence. In addition, the odds of an AE was 1.78 times higher in patients with WHO FC III at baseline than patients with WHO FC II at baseline (aOR = 1.784, 95% CI 1.087–2.928; $p = 0.022$) (Table 6). Among the evaluated patient-specific factors, the other factors did not show a significant association with AE incidences. Multiple logistic regression analysis for final effectiveness revealed that initiation of macitentan at a younger age (aOR = 0.947, 95% CI 0.916–0.980; $p = 0.001$) and a shorter disease duration (aOR = 0.991, 95% CI 0.984–0.998; $p = 0.010$) were significantly associated with positive final effectiveness (Table 7). There was no significant association between the final effectiveness outcome and other assessed factors.

Table 4 Incidences of adverse events and adverse drug reactions of special interest

Term	Safety evaluation ($n = 467$)	
	Adverse event	Adverse drug reaction
	n (%)	*n* (%)
Anemia	6 (1.28)	1 (0.21)
ALT increased	4 (0.86)	0 (0)
AST increased	4 (0.86)	0 (0)
Edema peripheral	3 (0.64)	0 (0)
Hemoglobin decreased	3 (0.64)	2 (0.43)
Bilirubin increased	1 (0.21)	0 (0)

ALT alanine aminotransferase, *AST* aspartate aminotransferase

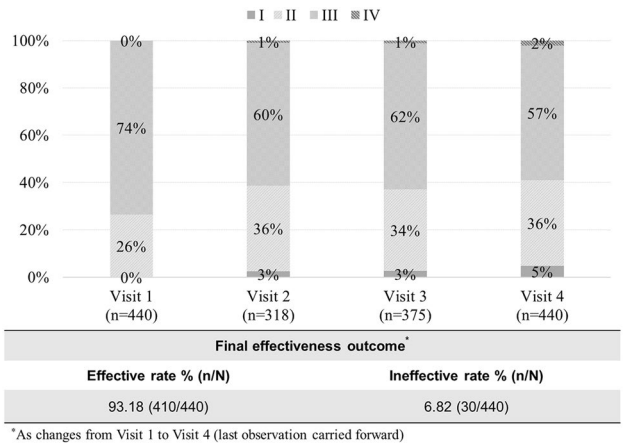

Fig. 2 Distribution of World Health Organization functional class by visits and final effectiveness outcome

4 Discussion

This prospective, observational, multicenter study provides real-world evidence of the safety and effectiveness of macitentan in Korean patients with PAH. Although the efficacy

Table 5 Secondary clinical outcomes by visits

Statistics	Variable (unit)		
	6MWD (m)	BDI (score)	mPAP (mmHg)
Visit 1			
N	67	45	73
Mean ± SD	348.7 ± 106.6	3.19 ± 2.42	44.9 ± 15.8
Visit 2			
N	26	16	7
Mean ± SD	410.0 ± 88.5	2.94 ± 1.65	36.7 ± 13.6
Visit 3			
N	52	29	16
Mean ± SD	411.9 ± 105.6	2.47 ± 1.64	38.4 ± 8.42
Visit 4[a]			
N	84	38	36
Mean ± SD	410.0 ± 109.9	2.59 ± 2.03	37.5 ± 13.6
Change (visit 4[a] to visit 1)			
N	41	27	16
Mean ± SD	58.5 ± 85.5	−0.13 ± 1.44	−13.8 ± 17.7
P value[b]	<0.001	0.644	0.007

6MWD 6-minute walk distance, *BDI* Borg Dyspnea Index, *mPAP* mean pulmonary arterial pressure, *SD* standard deviation

[a]Last observation carried forward

[b]Paired *t*-test

and safety outcomes of macitentan have been previously established in a pivotal, randomized, controlled SERAPHIN study [7], the study populations in those trials might not be representative of patients in a real-world setting. Therefore, it is essential to assess the safety and effectiveness of these drugs in routine clinical practice.

Regarding safety, the most commonly observed AEs, with an incidence of 2% or more, were dyspnea, nasopharyngitis, worsening of PAH, headache, pneumonia, and headache. The profile of the most frequent AEs reported in this study is consistent with the known safety profile of macitentan [7, 8, 11, 12]. All AEs of special interest associated with well-known side effects of approved endothelin receptor antagonists showed incidences of less than 2%, which were relatively lower than the corresponding incidences (range 3.4–18.2%) observed in the macitentan 10-mg treatment group in the SERAPHIN phase III study [7]. When listed in descending order, from most to least frequent, the AEs included anemia (1.28%), increased alanine aminotransferase/aspartate aminotransferase (0.86% each), peripheral edema (0.64%), decreased hemoglobin (0.64%), and increased bilirubin (0.21%). The order of AE frequency in this study was concordant with the results of a recent meta-analysis [13]. In that meta-analysis, the comprehensive risk ratio of drug to placebo was estimated by pooling data from all relevant clinical studies regarding each of the three representatives AEs of endothelin receptor antagonists, including anemia, increased hepatic transaminase, and peripheral edema. The pooled risk ratio of each AE associated with macitentan, in decreasing order, was 2.63 (95% CI 1.54–4.47), 1.17 (95% CI 0.42–3.31), and 1.08 (95% CI 0.81–1.48) for anemia, increased hepatic transaminase, and peripheral edema, respectively, suggesting that the difference between the macitentan treatment and placebo groups in hepatic transaminase elevation and peripheral edema was insignificant. Similarly, among these three AEs, anemia occurred frequently with macitentan compared with placebo (13.2% vs 3.2%) in the SERAPHIN phase III study [7]. The numerical incidence values could not be directly compared between different studies because of different study designs and the absence of a placebo group; however, it is apparent that the order of AE frequency reported in patients with PAH in this study corroborates these previous findings.

The final effectiveness rate was 93% based on the primary clinical outcome at approximately 24 weeks after treatment with macitentan, demonstrating its high effectiveness in improving WHO FC in real-world patients with PAH. In the SERAPHIN study, WHO FC improved in 22% of the patients in the macitentan 10-mg treatment group after 6 months of treatment [7]. Compared with the SERAPHIN study, the improvement rate of WHO FC after 24 weeks of treatment with macitentan was similar in our study (20.7%, data not shown). Similar effectiveness rates (65.2% and 28.7% of 230 patients were maintained and improved after 6 months of treatment, respectively) were also reported in a recent real-world study in the USA using a combined dataset of the OPUS registry (April 2014–August 2020: NCT02126943) and OrPHeUS cohort (October 2013–September 2018: NCT03197688) [8]. In this study, significant improvement was shown in other secondary effectiveness outcomes, such as 6MWD (from visits 1 to 4, 58.5 ± 85.5; $p < 0.001$) and mean pulmonary arterial pressure (− 13.8 ± 17.7; $p = 0.007$) compared with each corresponding baseline value after treatment with macitentan, although there were considerable missing data in those outcomes. This significant improvement in secondary outcomes corroborates the real-world effectiveness of macitentan in the 6MWD or cardiac index observed in several previous real-world studies [8, 14–17].

The demographics and disease characteristics of the study patients were similar to the SERAPHIN trial regarding female proportions, mean age, mean duration of PAH at macitentan initiation, and distribution pattern of WHO PAH classification [7]. Compared with patients receiving macitentan 10 mg in the SERAPHIN trial, all races were Asian (26.9% vs 100.0%), and the proportion of WHO FC III at baseline was higher (47.9% vs 72.8%) in our study population. When compared with recent US real-world studies, the OPUS registry, and OrPHeUS medical chart review, there were some differences in patient characteristics [8].

Table 6 Logistic multiple regression for adverse events

Variable	Odds ratio estimates			
	Point estimate	95% CI		*P* value
Sex, female vs male	0.980	0.595	1.613	0.936
Age at macitentan initiation (years)	1.021	1.007	1.035	0.003[a]
Disease duration (months)	0.999	0.994	1.003	0.579
PAH classification, HPAH vs IPAH	0.531	0.050	5.632	0.566
PAH classification, APAH vs IPAH	1.111	0.699	1.766	0.494
Hepatic impairment, yes vs no	1.816	0.722	4.564	0.204
Renal impairment, yes vs no	0.795	0.338	1.872	0.600
WHO FC at baseline, III vs II	1.784	1.087	2.928	0.022[a]

APAH associated PAH, *CI* confidence interval, *FC* functional class, *HPAH* heritable PAH, *IPAH* idiopathic PAH, *PAH* pulmonary arterial hypertension, *WHO* World Health Organization

[a]Statistically significant association

Table 7 Logistic multiple regression for final effectiveness

Variable[a]	Odds ratio estimates			*P* value
	Point estimate	95% CI		
Sex, female vs male	1.355	0.500	3.676	0.550
Age at macitentan initiation (years)	0.947	0.916	0.980	0.001[b]
Disease duration (months)	0.991	0.984	0.998	0.010[b]
Hepatic impairment, yes vs no	1.647	0.186	14.582	0.653
Renal impairment, yes vs no	0.905	0.180	4.565	0.904
WHO FC at baseline, III vs II	0.445	0.122	1.629	0.221

CI confidence interval, *FC* functional class, WHO World Health Organization

[a]Pulmonary arterial hypertension classification variables were not included in the multiple regression analysis because of sparse data and convergence problems

[b]Statistically significant association

Relatively younger adult patients were enrolled in our study (mean age, 48.5 years vs 61 years [OPUS] and 62 years [OrPHeUS]), and the proportion of WHO FC III/IV at baseline was higher in our study (72.8% vs 62.6% [combined population of OPUS and OrPHeUS]). Moreover, the proportion of patients receiving macitentan concurrently with other PAH-specific drugs as combination therapy during the median 27.1 weeks was lower compared with the combined data from OPUS and OrPHeUS (34.5% vs from 65 to 74% at 6 months after treatment by each year of enrollment between 2014 and 2018) [18]. Such differences in patient populations and treatment patterns of combination therapy might be attributed to the different clinical practices in real-world settings and insurance systems between countries, and the combination therapies should be used in high-risk patients with PAH in accordance with the reimbursement criteria in Korea.

The regression analysis regarding safety revealed that the AE occurrence risk was consistent across sex, disease duration, and absence or severity of hepatic or renal impairment. Age and baseline WHO FC levels were significant factors related to AE occurrence risk among the assessed patient-specific factors. The progression of PAH or aging is associated with cardiac decomposition [19–21]. This structural change in the cardiovascular system might affect the drug action at the targeted site, and the occurrence of unintended events to some extent. Moreover, given that older and severely ill patients might have a higher chance of receiving concomitant drugs for other underlying diseases, polypharmacy in those patients could increase the risk of adverse interactions with macitentan [22]. In patients with mild/moderate hepatic or renal impairment, the increase in AE risk was insignificant compared with patients without renal impairment in the real-world setting. In contrast, the final effectiveness was consistent across sex, absence or severity of hepatic or renal impairment, PAH classification, and baseline WHO FC in real-world clinical practice; however, a younger age at macitentan initiation and a shorter disease duration were significantly associated with positive final effectiveness. Similar to our results, relatively fewer improvements in the clinical outcome were reported in older patients [23, 24]. An explanation for this finding might be that older patients have poor adaptive mechanisms for elevated pressure load and resistance, associated comorbidity, or less intense initial treatment at diagnosis when there is little evidence on the importance of early intense/combination

therapy. Regarding the initiation of PAH treatments, current European Society of Cardiology/European Respiratory Society guidelines and previous pivotal studies recommend that early therapeutic intervention with an early diagnosis of PAH might improve long-term outcomes [6] [25, 26]. In agreement with growing evidence supporting early medication therapy, our results also suggest that early and timely initiation of macitentan treatment can improve outcomes.

Our study has some limitations because of the nature of the post-marketing surveillance design. Although all AEs were recorded during the study period, they stemmed from voluntary reporting by the participating investigators and patients. Regarding clinical outcomes, there were considerable missing data, particularly in the secondary outcomes, as the assessed data in routine practice were collected during the study period. Moreover, the absence of a control group hindered any treatment comparisons. Considering these limitations, caution is advised when interpreting the real-world results of this study and comparing them to other studies.

5 Conclusions

This study demonstrated the effectiveness and safety of macitentan in PAH treatment in real-world clinical practice in Korea. Macitentan was well tolerated and significantly effective without any new safety concerns during the 24-week follow-up period after macitentan initiation; however, long-term follow-up results are warranted to fully investigate the safety profile and effectiveness of macitentan in the real-world setting.

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Declarations

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Conflict of interest Hyung-Kwan Kim received research grants from Handok, GSK, Dae-Woong, Hanmi, Ildong, JW Pharmaceutical, Samjin, Daewon Pharm, and Boryoung. Su Young Jung, Minseok Park, and SuYoun Kim are full-time employees of Janssen Korea, Ltd. Hyuk-Jae Chang, Sung-A Chang, Jong-Min Song, Jae Young Choi, Jung Hyun Choi, Jung Yeon Chin have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This study was approved by the independent institutional review boards of all participating institutions. All procedures in this study were in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Consent to participate Written informed consent was obtained from all study participants.

Consent to publication Not applicable.

Availability of data and material Data supporting the findings of this study have been included in the published article. All data collected during this study are available from the corresponding authors upon reasonable request and with permission from Janssen Korea Ltd.

Code availability Not applicable.

Authors' contributions HJC and SYJ are the corresponding author and first author of this article, respectively. The authors contributed to the conceptualization of this study, interpretation of the data, and development of the manuscript. HJC, SAC, JMS, JYC, HKK, JHC, and JYC collected data and reviewed the manuscript. SYJ, MP, and SYK analyzed the data and generated tables and figures. All authors read and approved the final version. All authors attest that they meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

References

1. Vachiéry J-L, Gaine S. Challenges in the diagnosis and treatment of pulmonary arterial hypertension. Eur Respir Rev. 2012;21(126):313–20.
2. Sahay S. Evaluation and classification of pulmonary arterial hypertension. J Thor Dis. 2019:S1789–99.
3. Delcroix M, Howard L. Pulmonary arterial hypertension: the burden of disease and impact on quality of life. Eur Respir Rev. 2015;24(138):621–9.
4. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34(6):1219–63.
5. Maron BA, Abman SH, Elliott CG, Frantz RP, Hopper RK, Horn EM, et al. Pulmonary arterial hypertension: diagnosis, treatment, and novel advances. Am J Respir Crit Care Med. 2021;203(12):1472–87.
6. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119.
7. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809–18.
8. McLaughlin V, Channick R, Kim N, Flynn M, Leroy S, Wetherill G, et al. Combination therapy with macitentan and

phosphodiesterase type-5 inhibitor (PDE5i) in pulmonary arterial hypertension (PAH): real-world data from OPUS and OrPHeUS. Eur Heart J. 2020. https://doi.org/10.1093/ehjci/ehaa946.2297.
9. Kim N, Channick R, Chin K, Melendres-Groves L, Ravichandran A, Brand M, et al. Macitentan in pulmonary hypertension (PH): data from OPUS and OrPHeUS real-world data sets. Eur Respir J. 2019. https://doi.org/10.1183/13993003.congress-2019.PA5458.
10. Dixon JR Jr. The international conference on harmonization good clinical practice guideline. Qual Assur. 1998;6(2):65–74.
11. Wong AK, Channick RN. Safety and tolerability of macitentan in the management of pulmonary arterial hypertension: an update. Drug Healthc Patient Saf. 2019;11:71–85. https://doi.org/10.2147/DHPS.S173050.
12. Rahaghi F, Channick R, Kim N, McLaughlin V, Martinez E, Ong R, et al. Safety of macitentan in pulmonary hypertension patients with elevated pulmonary capillary wedge pressure: real-world evidence from OPUS/ORPHEUS. Chest. 2021;160(4):A2275–8.
13. Zhang Y-J, Wang N, Gu Z-C, Wei A-H, Cheng A-N, Fang S-S, et al. A network meta-analysis for safety of endothelin receptor antagonists in pulmonary arterial hypertension. Cardiovasc Diagn Ther. 2019;9(3):239.
14. Nashat H, Barbosa J, Harries C, Price L, McCabe C, Kempny A, et al. S121 efficacy of macitentan in a large, real life population of patients with pulmonary arterial hypertension. Thorax. 2018. https://doi.org/10.1136/thorax-2018-212555.127.
15. Belge C, Delcroix M. Treatment of pulmonary arterial hypertension with the dual endothelin receptor antagonist macitentan: clinical evidence and experience. Ther Adv Respir Dis. 2019;13:1753466618823440.
16. Cadenas-Menéndez S, Álvarez-Vega P, Martín-Moreiras J, Barreiro-Pérez M, Gómez-Sánchez M, Sánchez-Fernández P. Macitentan in daily clinical practice: a single centre, 1-year experience. Pulmonology. 2018;24(3):170–3.
17. Tahara N, Dobashi H, Fukuda K, Funauchi M, Hatano M, Ikeda S, et al. Long-term treatment of pulmonary arterial hypertension with macitentan in Japanese patients. Curr Med Res Opin. 2020;36(6):921–8.
18. Chin K, Channick R, McLaughlin V, Miller C, Flynn M, Ong R, et al. Treatment patterns in pulmonary arterial hypertension: changes in clinical practice over time using real-world evidence from the combined OPUS/ORPHEUS data sets. Chest. 2020;158(4):A2194–6.
19. Channick R, Cottreel E, Kiely D, Marcus J, Martin N, Moiseeva O, et al. The REPAIR study: effects of macitentan on RV structure and function in pulmonary arterial hypertension. JACC Cardiovasc Imaging. 2022;15(2):240–53. https://doi.org/10.1016/j.jcmg.2021.07.027.
20. Wei JY. Age and the cardiovascular system. N Engl J Med. 1992;327(24):1735–9.
21. Trifiro G, Spina E. Age-related changes in pharmacodynamics: focus on drugs acting on central nervous and cardiovascular systems. Curr Drug Metabol. 2011;12(7):611–20.
22. Rodrigues MCS, Oliveira CD. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. Rev Lat Am Enfermagem. 2016;24: e2800.
23. Trip P, Nossent EJ, Frances S, van den Berk IA, Boonstra A, Groepenhoff H, et al. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. Eur Respir J. 2013;42(6):1575–85.
24. Hjalmarsson C, Rådegran G, Kylhammar D, Rundqvist B, Multing J, Nisell MD, et al. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. Eur Respir J. 2018;51(5):1702310.
25. Humbert M, Sitbon O, Chaouat A, Bertocchi Ml, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010;122(2):156–63.
26. Humbert M, Coghlan JG, Khanna D. Early detection and management of pulmonary arterial hypertension. Eur Respir Rev. 2012;21(126):306–12.

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