Table 3. Univariate and Multivariate Cox Proportional Hazards Models for the Predictors of Survival

Factors	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
CI (L/min per m^2)	0.56 (0.423-0.747)	0.0001	0.60 (0.458-0.810)	0.0008
mPAP (mmHg)	1.03 (1.005-1.048)	0.0160	1.02 (0.992-1.038)	0.1875
ERA and/or PDE5 Inhibitors therapy (vs. PAH therapies without ERA and PDE5 inhibitor)	0.32 (0.137-0.636)	0.0008	0.39 (0.168-0.796)	0.0084

ERAs: endothelin receptor antagonists, PDE5: phosphodiesterase type 5 (PDE5)

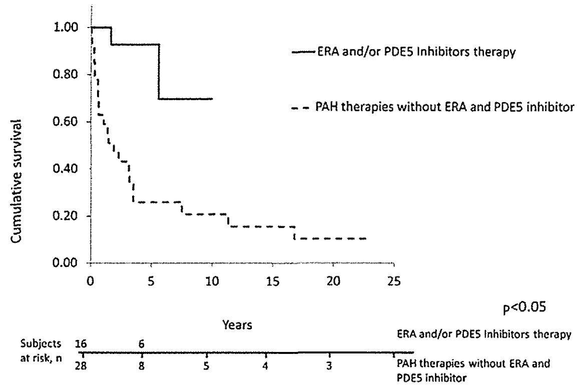

Figure 3. **The Kaplan-Meier survival estimates for the idiopathic and heritable PAH patients. The survival rates for patients treated with ERA and/or PDE5 inhibitor therapy (solid line) were 92.9% and 69.6% at five and eight years compared with 26.0% and 20.8% for patients treated with PAH therapies without ERA or PDE5 inhibitors (dashed line; p<0.05 by the Cox-Mantel log-rank test).**

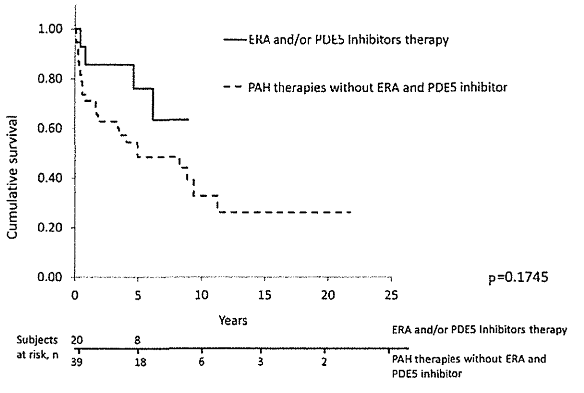

Figure 4. **The Kaplan-Meier survival estimates for the associated PAH patients. The survival rates for patients treated with ERA and/or PDE5 inhibitor therapy (solid line) were 76.2% and 63.5% at five and eight years compared with 48.5% and 32.6% for patients treated with PAH therapies without ERA or PDE5 inhibitors (dashed line; p=0.1745 by the Cox-Mantel log-rank test).**

tween 2005 and 2012 had a better survival rate (p<0.05) (Fig. 1); however, these patients had significantly less serious hemodynamic alterations (Table 1). The hemodynamic difference observed between the groups makes it difficult to attribute the superior outcome to the introduction of ERAs and PDE5 inhibitors (Fig. 1).

Although it is beyond the scope of this paper to argue delaying the diagnosis, the presence of less serious hemodynamic alterations in the patients diagnosed between 2005 and 2012 suggests that earlier detection of PAH in patients with mild/moderate hemodynamic changes was achieved more often in that group than in the group diagnosed between 1983 and 2004. Since signs and symptoms of PAH do not generally manifest until hemodynamic changes are advanced, there are significant delays in diagnosing this disease. Although primary pulmonary hypertension (PPH) registry data from 1987 show that, at that time, the time from symptom onset to diagnosis with catheterization was 2.3 years (12), there have not been any recent advances in the diagnostic processes. The registry to evaluate early and long-term PAH (REVEAL) study showed that the average time from onset to diagnosis is still more than two years (13). The advances observed in this study may be based on the development and approval of oral therapies and increased doctor recognition of PAH following the introduction of these drugs.

This single-center, uncontrolled study demonstrated that idiopathic and heritable PAH patients treated with ERAs and/or PDE5 inhibitors (n=13) have a higher survival rate than those treated with conventional therapy and/or oral beraprost (Fig. 3, Table 2). In line with previous reports (3), this result may support the concept that the use of these drugs provides benefits for the survival of Japanese patients with PAH. Nevertheless, the benefits of ERAs and/or PDE5 inhibitors on survival may be restricted to idiopathic and heritable PAH patients because no significant differences were observed between the groups in the associated PAH patients (Table 2, Fig. 4).

Because oral beraprost has a weak recommendation in the PAH evidence-based treatment algorithm (4) and has so far only been approved in Japan and Korea (10), this study was conducted without regard to oral beraprost therapy. However, this is a limitation of this study. It is impossible to deny that oral beraprost has a beneficial effect on the treatment of PAH. A randomized and properly controlled dose-response study of beraprost is currently underway (14).

There may be beneficial effects of high-dose oral beraprost on exercise capacity and hemodynamics in patients with PAH.

Epoprotenol was approved in Japan in 1999, and 23 patients treated after 1999 died in our center. In this study, only four patients (three between 1983 and 2004 and one between 2005 and 2012) were treated with epoprostenol and all survived. Although epoprotenol is strongly recommended by the WHO/NYHA class IV according to recent guidelines, we were unable to administer intravenous treatments in some of the 23 non-survivor cases because the patients were elderly (>70 years of age) (n=2), had comorbidities (n=5) or were unwilling (n=6) to undergo intravenous treatments. However, the early administration of epoprostenol therapy is suggested to improve survival in patients with a PVR >1,000 dynes.sec.cm^{-5}.

The data presented in this study were limited because this was an observational study from a single center and the PAH patients were not treated in a randomized manner according to hemodynamics and comorbidities, i.e., this study included patients treated with conventional therapy, which may have favorably biased the results. We realize the limitations of interpreting our results. We interpreted the results of this study as part of a hypothesis-generating analysis, which suggested that there are beneficial effects of treatment with ERAs and/or PDE5 inhibitors on overall survival in idiopathic and heritable PAH patients. This hypothesis will need to be further investigated in a large confirmatory long-term trial in the future.

This study has evolved over the 28-year time period of our practice. The results of six minute walk distance (6 MWD) tests and brain natriuretic peptide (BNP) tests were not obtained as consistently in the past as they have been in the most recent eight years. For this reason, in this observational study, we evaluated survival benefits only in PAH patients treated with PAH-specific therapy in comparison to patients treated with conventional therapy, instead of comparing the 6MWD and BNP results.

In conclusion, this study suggests that superior survival rates are observed in patients with idiopathic and heritable PAH after the introduction of ERAs and PDE5 inhibitors, and the use of these drugs provides a survival benefit in patients with idiopathic and heritable PAH.

Author's disclosure of potential Conflicts of Interest (COI).
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Original Article

Different sizes of centrilobular ground-glass opacities in chest high-resolution computed tomography of patients with pulmonary veno-occlusive disease and patients with pulmonary capillary hemangiomatosis

Aya Miura [a], Satoshi Akagi [a], Kazufumi Nakamura [a,*], Keiko Ohta-Ogo [b], Katsushi Hashimoto [a], Satoshi Nagase [a], Kunihisa Kohno [a], Kengo Kusano [a], Aiko Ogawa [c], Hiromi Matsubara [c], Shinichi Toyooka [d], Takahiro Oto [d], Aiji Ohtsuka [e], Tohru Ohe [a], Hiroshi Ito [a]

[a] *Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[b] *Department of Pathology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan*
[c] *Division of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan*
[d] *Department of Cancer and Thoracic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[e] *Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*

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ABSTRACT

Background: Centrilobular ground-glass opacity (GGO) is one of the characteristic findings in chest high-resolution computed tomography (HRCT) of patients with pulmonary veno-occlusive disease (PVOD) and patients with pulmonary capillary hemangiomatosis (PCH). However, clinical differential diagnosis of these two diseases is difficult and has not been established. In order to clarify their differences, we compared the sizes of GGOs in chest HRCT and the sizes of capillary assemblies in pulmonary vascular casts between patients diagnosed pathologically with PVOD and PCH.
Methods: We evaluated chest HRCT images for four patients with idiopathic pulmonary arterial hypertension (IPAH), three patients with PVOD and three patients with PCH, and we evaluated pulmonary vascular casts of lung tissues obtained from those patients at lung transplantation or autopsy.
Results: Centrilobular GGOs in chest HRCT were observed in patients with PVOD and patients with PCH but not in patients with IPAH. We measured the longest diameter of the GGOs. The size of centrilobular GGOs was significantly larger in patients with PCH than in patients with PVOD (5.60 ± 1.43 mm versus 2.51 ± 0.79 mm, $P<.01$). We succeeded in visualization of the 3-dimensional structures of pulmonary capillary vessels obtained from the same patients with PVOD and PCH undergoing lung transplantation or autopsy and measured the diameters of capillary assemblies. The longest diameter of capillary assemblies was also significantly larger in patients with PCH than in patients with PVOD (5.44 ± 1.71 mm versus 3.07 ± 1.07 mm, $P<.01$).
Conclusion: Measurement of the sizes of centrilobular GGOs in HRCT is a simple and useful method for clinical differential diagnosis of PVOD and PCH.

1. Introduction

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare diseases that are classified as a subgroup of pulmonary arterial hypertension (PAH) [1–3]. PVOD is histologically characterized by intimal fibrosis that narrows and occludes pulmonary veins and it accounts for 5–10% of cases initially thought to be idiopathic PAH (IPAH) [4]. PVOD occurs in a wide range of ages. Among adult patients, the incidence in men is about twice that in women. PCH is histologically characterized by localized capillary proliferation within the lung in which capillaries invade the pulmonary interstitium, vessels and, less commonly, airways [5]. PCH has been reported to be much less frequent than PVOD [6]. PCH and PVOD have similar clinical presentations with poor prognosis.

In recent years, PAH-targeted drugs including epoprostenol have improved the survival of patients with IPAH [3,7,8], but no medical treatment to improve the survival of patients with PVOD or PCH has been established. Several investigators have reported the possible efficacy of cautious application of epoprostenol [9,10], but incautious administration of vasodilators including epoprostenol sometimes causes massive pulmonary edema and can be fatal in these patients.

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* Corresponding author. Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikatacho, Kitaku, Okayama 700-8558, Japan. Tel.: +81 86 235 7351; fax: +81 86 235 7353.
E-mail address: chibun@cc.okayama-u.ac.jp (K. Nakamura).

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Therefore, the establishment of methods for medical treatment in these patients is required. To that end, accurate diagnosis of PVOD and PCH is also needed.

Histological proof is required for a definitive diagnosis of PVOD and PCH. Since surgical lung biopsy is too invasive and is a high risk for patients with PVOD or PCH, a noninvasive approach is preferable. High-resolution computed tomography (HRCT) of the chest is one of the diagnostic tools for PVOD and PCH. Centrilobular ground-glass opacities (GGOs), septal lines and mediastinal lymph node enlargement are characteristic findings in chest HRCT of patients with PVOD or PCH [6,11,12]. However, clinical differential diagnosis of these diseases has not been established.

We previously reported success in visualization of the 3-dimensional structures of pulmonary capillary vessels in patients with PAH, PVOD and PCH using scanning electron microscopy of blood vascular casts [13]. Study of blood vascular casts revealed differences in the three diseases. PAH was characterized by a deficient capillary network, PVOD was characterized by swollen capillary vessels and PCH was characterized by tumor-like outgrowth of capillaries. These differences in capillaries might reflect differences in the sizes of GGOs in chest HRCT since centrilobular GGOs reflect thickening of interstitial tissues, local fluid accumulation in airspaces, local alveoli collapse and increased capillary blood volume [14,15]. Thus, we compared the sizes of centrilobular GGO in chest HRCT and the sizes of capillary assemblies in pulmonary vascular casts in patients diagnosed pathologically with PVOD and patients diagnosed pathologically with PCH in order to clarify their differences.

2. Methods

2.1. Subjects

We obtained lung tissues from 27 patients clinically diagnosed with PAH by living-donor lobar lung transplantation (LDLLT), cadaveric lung transplantation (CLT) or autopsy between 1999 and 2011 in our institution. Twenty patients were diagnosed with pulmonary arteriopathy, four patients were diagnosed with PVOD and three patients were diagnosed with PCH by pathological examination. We could obtain findings of chest HRCT from four patients with idiopathic PAH (IPAH), three patients with PVOD and three patients with PCH before or just after the start of specific treatment for pulmonary hypertension. For non-pulmonary hypertension control experiments, samples of pulmonary arteries were also obtained at autopsy from a patient with cerebral infarction (male, 43 years old) who showed no evidence of PAH.

All human subject protocols were approved by the Human Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, and written informed consent was obtained from all patients before the procedure. The investigation also conforms to the principles outlined in the Declaration of Helsinki.

2.2. Histological analysis

Lung tissue was fixed in 10% formalin. Hematoxylin and eosin stain and elastica-van Gieson stain were used for all histological specimens to characterize pulmonary abnormalities. The pathologic hallmark of pulmonary arteriopathy was defined as medial hypertrophy, intimal thickening and plexiform lesions. The pathologic hallmark of PVOD was defined as an extensive and diffuse obstruction of pulmonary venules and veins of various sizes. The pathologic hallmark of PCH was defined as localized capillary proliferation within the lung in which capillaries have invaded the pulmonary interstitium, vessels and, less commonly, airways as previously described [5,16].

2.3. Pulmonary vascular casts

To visualize the 3-dimensional structures of pulmonary vessels, we made vascular casts as previously described [13,17]. In brief, lungs were isolated from patients undergoing lung transplantation or at autopsy, and their pulmonary arteries were cannulated. The pulmonary arteries were then perfused with saline and methacrylate resin (Mercox CL; Oken Shoji, Tokyo, Japan). These resin-injected lungs were placed in a hot water bath to completely polymerize the resin. The lungs with polymerized resin were immersed in a hot 10% NaOH solution and washed in water. This series of maceration and washing was repeated several times until tissue elements had been completely removed. The blood vascular casts of lungs were air-dried, coated with gold, and observed with a scanning electron microscope (S-2300, Hitachi) using an acceleration voltage of 5 kV. Digital images were also obtained with a digital camera (Canon IXY Digital 800IS), and the longest diameter of 14–16 capillary assemblies in the pulmonary vascular casts in each patient were measured.

2.4. Clinical and functional assessment

We obtained clinical data at HRCT of the chest including clinical diagnosis, World Health Organization functional class, pulmonary function test results and PAH-specific treatment from medical records as previously described [13,18–21]. Diffusion capacity of the lung for carbon monoxide (DLco) was measured by the single-breath method and expressed as %DLco (% predicted). We collected hemodynamic data from right heart catheterization performed within one month of HRCT of the chest examination. Event-free survival period was from

Table 1
Patients` characteristics

No.	Age (years old)	Sex	Histological diagnosis	WHO FC	mean PAP (mmHg)	%DLco (%)	Survival (years)	Outcome
1	10	F	IPAH	IV	84	59	0.8	LDLLT
2	27	M	IPAH	IV	50	58	4.0	Autopsy
3	16	M	IPAH	IV	106	79	11.7	CLT
4	20	F	IPAH	IV	58	81	3.7	LDLLT
5	41	M	PVOD	IV	39	24	2.0	Autopsy
6	32	F	PVOD	IV	57	23	1.2	LDLLT
7	26	M	PVOD	IV	57	31	0.4	Autopsy
8	11	M	PCH	IV	52	64	3.1	Autopsy
9	17	F	PCH	IV	NA	NA	0.1	Autopsy
10	25	F	PCH	IV	55	36	0.4	LDLLT

Age, age at chest CT examination; WHO FC, World Health Organization classification of functional status of patients with pulmonary hypertension; PAP, pulmonary artery pressure; %DLCO, diffusion capacity of the lung for carbon monoxide expressed as % predicted; survival, period between diagnosis and outcome; CLT, cadaveric lung transplantation; LDLLT, living-donor lobar lung transplantation; F, female; M, male; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; NA, not available.

diagnosis to an event (LDLLT, CLT or death). Chest radiography was performed at the same time as HRCT of the chest.

2.5. HRCT of the chest

HRCT of the chest was performed before or just after the start of PAH-specific treatment in all patients and at the time of the most recent follow-up from lung transplantation or death in three patients with IPAH (patient No. 1, 3 and 4), two patients with PVOD (patient No. 5 and 7) and patients with PCH. Follow-up HRCT of the chest was not performed in patient No. 2 and 6. CT scans were performed with a SOMATOM HiQ scanner (Siemens Healthcare, Germany), HiSpeed Advantage scanner (GE Medical Systems, Milwaukee, WI, USA) and Aquilion 16 scanner (Toshiba Medical Systems Corporation, Tokyo, Japan) from 1999 to 2009 and with an Aquilion 64 scanner (Toshiba Medical Systems Corporation, Tokyo, Japan) and SOMATOM Definition Flash scanner (Siemens Healthcare, Germany) from 2010 to 2012 at end inspiration with patients in the supine position. Thin-section CT was performed with 1-mm section thickness at 10-mm intervals. Scans were photographed with both soft-tissue (level, 30 H; width, 350 H) and lung (level, −600 H; width, 1600 H) window settings. Two radiologists reviewed the thin-section CT images and evaluated the CT findings of centrilobular GGOs, mosaic pattern, lymph node enlargement, septal lines, pleural effusion, pericardial effusion and pulmonary artery dilatation. GGO was defined as increased opacity of the lung parenchyma that was not sufficient to obscure pulmonary vessels, in contradistinction to true consolidation. Two cardiologists measured the longest diameter of 20 centrilobular GGOs in each right and left upper, middle and lower lobe per patient in patients with PVOD and PCH.

2.6. Statistical analysis

Statistical analysis was performed with SPSS software version 11.0 (SPSS, Chicago, IL, USA). Results are presented as means±standard deviation. Comparisons between patients with PVOD and patients with PCH were assessed by the Mann–Whitney *U* test. Values of $P<.05$ were considered to be statistically significant.

3. Results

3.1. Patient characteristics at chest CT examination

Patient characteristics at HRCT of the chest are shown in Table 1. Patients with IPAH included two males and two females with a mean age of 18.3±6.2 years at HRCT of the chest (No. 1–4). Three patients underwent LDLLT or CLT and one patient was an autopsy case (No. 2). Three patients were treated with a prostaglandin I_2 (PGI_2) analog or intravenous PGI_2 and the other patient was not treated with a PAH-specific drug (endothelin receptor antagonist or phosphodiesterase 5 inhibitor) at HRCT of the chest. Mean pulmonary artery pressure (PAP) was 74.5±25.5 mmHg and mean event-free survival period was 5.1±4.0 years.

Patients with PVOD included two males and one female with a mean age of 32.7±6.2 years at HRCT of the chest (No. 5–7). One patient underwent LDLLT and the other patients were autopsy cases. All patients were treated with a PGI_2 analog or intravenous PGI_2 at HRCT of the chest. Mean PAP was 51.0±10.4 mmHg and mean event-free survival period was 1.2±0.7 years.

Patients with PCH included one male and two females with a mean age of 17.7±5.7 years at HRCT of the chest (No. 8–10). One patient was diagnosed with PCH by open lung biopsy before autopsy (No. 9). The other patients were suspected to have PVOD or PCH clinically. One patient underwent LDLLT and the other patients were autopsy cases. One patient was treated with intravenous PGI_2 and the other patients were not treated with a PAH-specific drug at HRCT of the chest. Mean PAP was 53.5±2.1 mmHg and mean event-free survival period was 1.2±1.3 years.

3.2. Pulmonary function test

Patients with PVOD had a low %DLco (25.9±3.7%) compared with that in patients with IPAH (69.3±10.7%) ($P<.01$). However, there was no significant difference in %DLco between patients with PVOD and patients with PCH.

3.3. Pathological and electron microscopic findings

In a non-pulmonary hypertension control subject, normal small pulmonary arteries and capillary network were observed around the

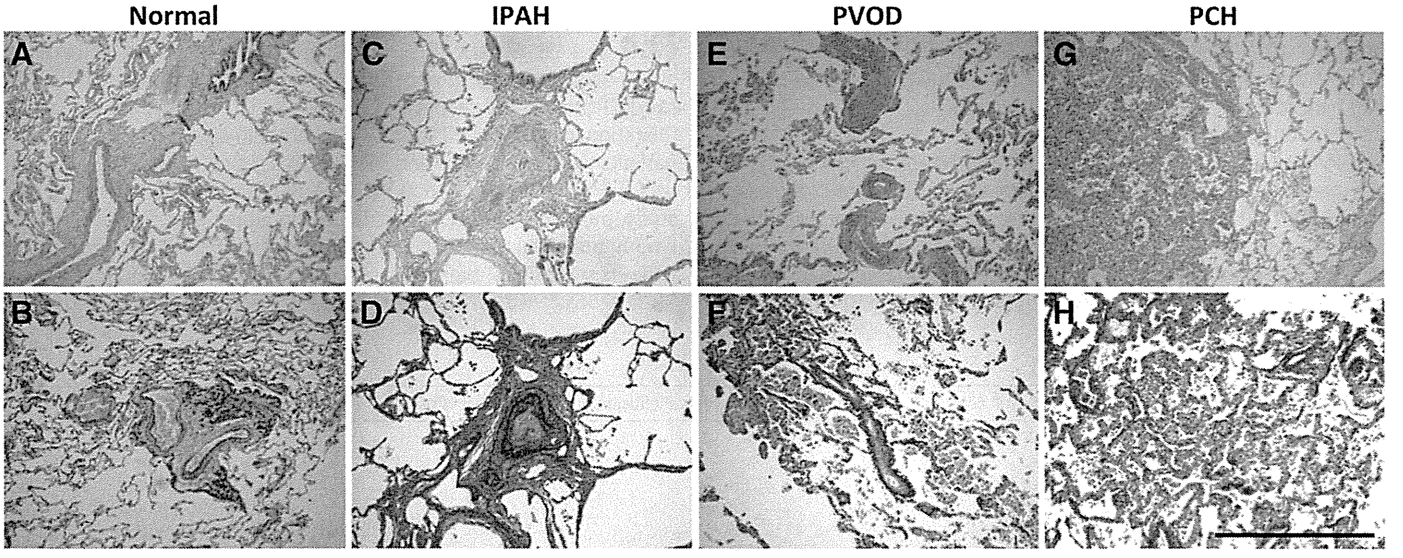

Fig. 1. Representative pathological findings of lung specimens. Upper panels are hematoxylin and eosin stain images (HE) and lower panels are elastica-van Gieson (EVG) stain images. (A and B) A non-pulmonary hypertension control subject. Normal pulmonary arteries are shown. (C and D) IPAH in a 10-year-old female (Patient No. 1). Intimal and medial hypertrophy was observed in small pulmonary arteries. Small peripheral pulmonary arteries were severely stenosed and occluded and capillaries were deficient. (E and F) PVOD in a 41-year-old man (Patient No. 5). Intimal fibrosis that narrowed the pulmonary veins and completely obliterated venous vessel walls is shown. (G and H) PCH in a 17-year-old female (Patient No.9). Proliferation of capillaries is shown. Bar=500 μm (HE stain and EVG stain).

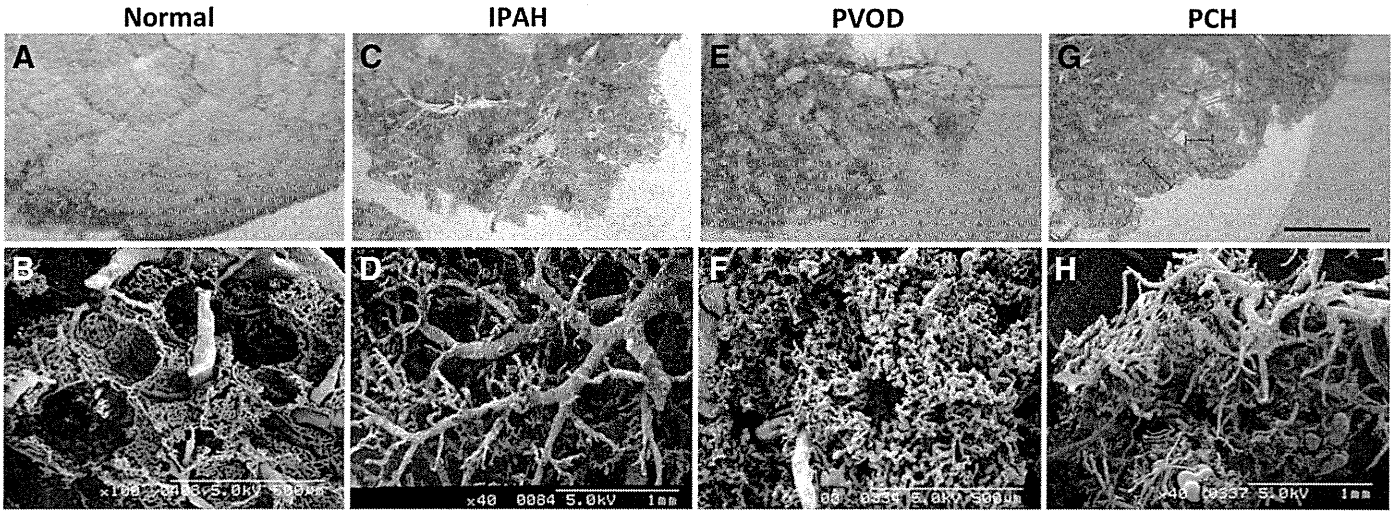

Fig. 2. Representative pulmonary vascular casts. Upper panels are digital images and lower panels are electron microscopic images. (A and B) A non-pulmonary hypertension subject. Normal capillary network casts are shown. (C and D) Patient with IPAH (Patient No. 5). Small peripheral pulmonary arteries were severely stenosed and occluded and capillaries were deficient. (E and F) Patient with PVOD (Patient No. 7). Some of the capillaries were deficient and others remained to form assemblies. In an electron microscopic image of pulmonary vascular casts, pulmonary capillaries were swollen compared with a normal pulmonary capillary. (G and H) Patient with PCH (Patient No.8). Some of the capillaries were deficient and others remained to form assemblies. In an electron microscopic image of pulmonary vascular casts, the capillary vessels resembled a tumorous cluster. Bar=2 cm (upper panels). Bar=500 μm (B and F). Bar=1 mm (D and H).

alveolus of the lung as previously described [13] (Figs. 1A, B and 2B). In patients with IPAH, intimal and medial hypertrophy was observed (Fig. 1C and D). In an electron microscopic image of pulmonary vascular casts, pulmonary arteries were severely stenosed and occluded and capillaries were deficient (Fig. 2D). In patients with PVOD, intimal fibrosis that narrowed the pulmonary veins and completely obliterated venous vessel walls was shown (Fig. 1E and F). In an electron microscopic image of pulmonary vascular casts, capillaries were swollen compared with a normal capillary (Fig. 2F). In patients with PCH, proliferation of capillaries was shown (Fig. 1G and H). In an electron microscopic image of pulmonary vascular casts, the capillary vessels resembled a tumorous cluster (Fig. 2H).

3.4. Size of centrilobular GGOs in chest HRCT

CT findings are summarized in Table 2. Septal lines and pericardial effusion were shown in all three groups at random. Lymph node enlargements were observed in patients with PCH. All patients had enlarged pulmonary artery diameter. Centrilobular GGOs were shown in all patients with PVOD and PCH (Table 2 and Fig. 3D and F). The size of centrilobular GGOs was larger in patients with PCH than in patients with PVOD (5.60±1.43 mm versus 2.51±0.79 mm, n=60 GGOs in each patient, P<.01) (Fig. 4A). At follow-up, a diffuse micronodular shadow and alveolar hemorrhage were observed in patients with IPAH but centrilobular GGOs were not observed. In patients with PVOD, the size of GGOs at follow-up tended to be larger than that at diagnosis, whereas the size of GGOs at follow-up tended not to be different than that at diagnosis in patients with PCH (Table 3).

3.5. Size of capillary assemblies in pulmonary vascular casts

The longest diameter of capillary assemblies in pulmonary vascular casts was also significantly larger in patients with PCH than in patients with PVOD (5.44±1.71 mm versus 3.07±1.07 mm, n=14 to 16 assemblies in each patient, P<.01) (Figs. 2E, G and 4B).

4. Discussion

PVOD and PCH have been diagnosed pathologically, making it difficult to examine the hemodynamics, reactivity to PAH-specific treatment and survival prospectively. Therefore, clinical diagnosis is important for clinicians to understand these diseases. Results of a pulmonary function test and HRCT findings can suggest a diagnosis of PVOD or PCH. Septal lines, lymph node enlargements, pulmonary artery dilatation, pericardial effusion and pleural effusion are observed in HRCT images of patients with PVOD and PCH [6]. Pulmonary artery dilatation, pericardial effusion and pleural effusion are observed in all patients with IPAH, PVOD and PCH, and these findings are therefore not useful for the differentiation of IPAH, PVOD and PCH. In the present study, pulmonary arteries were dilated in all patients. Septal lines and lymph node enlargement are the most common HRCT findings in patients with PVOD but not in patients with PCH [6,16,22]. However,

Table 2
CT findings

No.	GGOs	Mosaic pattern	Septal lines	LN enlargement	Pleural effusion	Pericardial effusion	ratio PA>1	Therapy at chest CT
1	-	+	+	-	-	-	+	None
2	-	+	-	-	-	+	+	PGI_2 5 ng kg^{-1} min^{-1}
3	-	-	-	-	-	-	+	PGI_2 analog
4	-	-	-	-	-	+	+	PGI_2 8 ng kg^{-1} min^{-1}
5	+	-	+	-	-	-	+	PGI_2 analog
6	+	-	-	-	-	+	+	PGI_2 19 ng kg^{-1} min^{-1}
7	+	-	-	-	-	-	+	PGI_2 9 ng kg^{-1} min^{-1}
8	+	-	-	+	-	-	+	none
9	+	-	+	-	-	+	+	none
10	+	-	+	+	-	+	+	PGI_2 2.5 ng kg^{-1} min^{-1}

GGOs, ground-glass opacities; LN, lymph node; ratio PA, ratio of diameter of the main pulmonary artery to that of the thoracic aorta.

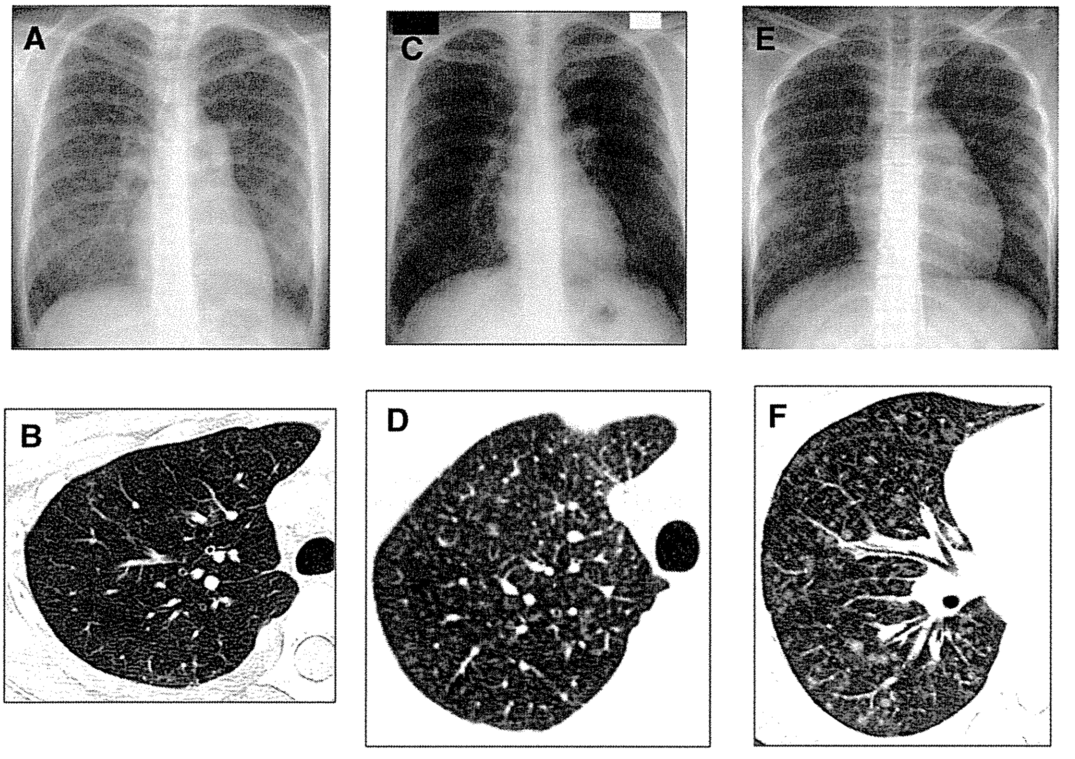

Fig. 3. Representative chest radiographic and HRCT findings. (A and B) IPAH in a 10-year-old female (Patient No. 1). A chest radiograph shows a prominent main pulmonary artery. HRCT shows a small reticulonodular shadow. (C and D) PVOD in a 41-year-old man (Patient No. 5). A chest radiograph demonstrates a prominent central pulmonary artery. HRCT demonstrates small GGOs and septal lines. (E and F) PCH in a 17-year-old female (Patient No.9). A chest radiograph shows a prominent central pulmonary artery. HRCT shows multiple large GGOs and septal lines.

these were observed in HRCT of the chest in both patients with PVOD and PCH in the present study. It has been reported that septal lines and lymph node enlargement were found in HRCT images of patients with PCH [23]. Thus, conventional HRCT findings are insufficient for distinguishing between PVOD and PCH, and clinical differential diagnosis of these diseases has not been established. We previously reported differences in the three-dimensional structures of pulmonary capillary vessels in patients with PAH, PVOD and PCH based on results of scanning electron microscopy of blood vascular casts [13]. PAH was characterized by a deficient capillary network, PVOD was characterized by swollen capillary vessels and PCH was characterized by tumor-like outgrowth of capillaries. These differences in capillaries might reflect differences in the sizes of GGOs in chest HRCT. Thus, we compared the sizes of GGOs in chest HRCT and the sizes of capillary assemblies in pulmonary vascular casts between patients diagnosed pathologically with PVOD and patients diagnosed pathologically with PCH in order to clarify their differences. The present study showed that the sizes of centrilobular GGOs and capillary assemblies were larger in patients with PCH than in patients with PVOD. Measurement of the sizes of centrilobular GGOs is very simple and might be informative for clinical diagnosis of PVOD or PCH.

Centrilobular GGOs are commonly observed in subacute hypersensitivity pneumonitis, bacterial pneumonitis, viral pneumonitis, atypical pneumonitis and interstitial pneumonitis[24]. These diseases are candidates as the first differential diagnosis when GGOs are observed even if PVOD and PCH are suspected clinically. In the present study, none of the patients with PVOD or PCH had fever or laboratory findings of pneumonitis such as elevation of white blood count or C-

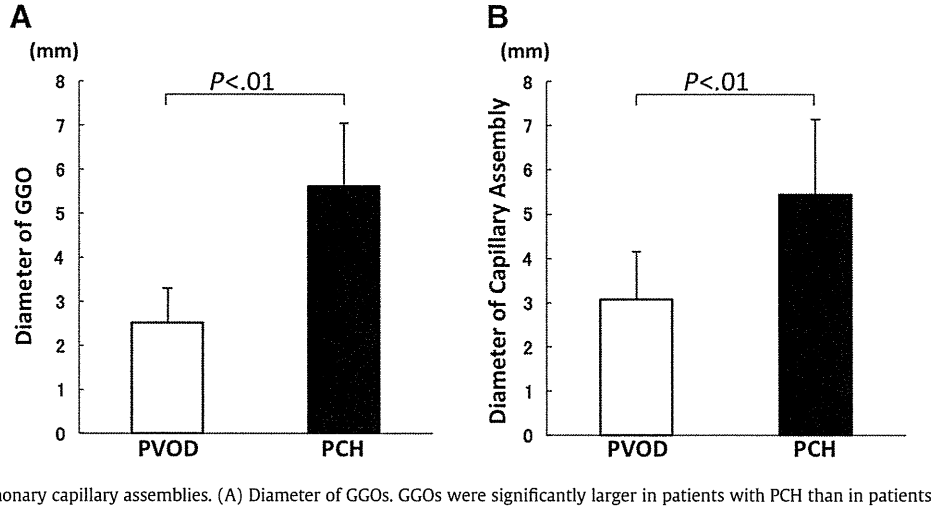

Fig. 4. Sizes of GGOs and pulmonary capillary assemblies. (A) Diameter of GGOs. GGOs were significantly larger in patients with PCH than in patients with PVOD. (B) Diameter of pulmonary capillary assemblies. Pulmonary capillary assemblies were significantly larger in patients with PCH than in patients with PVOD.

Table 3
The size of GGOs at diagnosis and follow-up

Patient No.	Diagnosis		At diagnosis	At follow-up	Period between diagnosis and follow-up (days)
5	PVOD	GGOs size (mm)	2.14	3.17	655
		PGI_2 dose (ng kg^{-1} min^{-1})	0	95	
6	PVOD	GGOs size (mm)	2.22	NA	NA
		PGI_2 dose (ng kg^{-1} min^{-1})	19	NA	
7	PVOD	GGOs size (mm)	3.07	3.97	46
		PGI_2 dose (ng kg^{-1} min^{-1})	9	30	
8	PCH	GGOs size (mm)	5.38	5.63	109
		PGI_2 dose (ng kg^{-1} min^{-1})	0	24	
9	PCH	GGOs size (mm)	6.52	6.55	50
		PGI_2 dose (ng kg^{-1} min^{-1})	0	0	
10	PCH	GGOs size (mm)	4.72	4.71	87
		PGI_2 dose (ng kg^{-1} min^{-1})	2.5	24	

Abbreviations as in Table 1 and 2.

reactive protein. Therefore, GGOs in HRCT of the chest in patients with PVOD or PCH were not involved in subacute hypersensitivity pneumonitis, bacterial pneumonitis, viral pneumonitis, atypical pneumonitis or interstitial pneumonitis. Centrilobular GGOs reflect thickening of interstitial tissues, local fluid accumulation in airspaces, local alveoli collapse and increased capillary blood volume [14,15]. In the present study, the size of capillary assemblies was significantly larger in patients with PCH than in patients with PVOD. Since PVOD is characterized by swollen capillary vessels and PCH is characterized by tumor-like outgrowth of capillaries [13], the sizes of capillary assemblies are different. These differences in capillaries might reflect differences in the sizes of centrilobular GGOs in chest HRCT.

The results suggested that measurement of the sizes of centrilobular GGOs in HRCT is a useful method for clinical differential diagnosis of PVOD and PCH compared with the pulmonary function test. However, it is difficult to accurately measure the sizes of centrilobular GGO since the size are affected by many factor. The size of centrilobular GGO can be affected by photographing conditions (slice thickness, kernel used for image reconstruction, caliper size), disease severity (pulmonary edema) and treatment (use of vasodilatation drugs). In the present study, visualization was better in the recent version of HRCT than that in the earlier version of HRCT. If the voxel size is between 0.2 and 0.4 mm, a 20-40% error in measurement is possible. The size of centrilobular GGOs also differs depending on the severity of pulmonary hypertension and PAH-specific drug therapy. Lung congestion sometimes occurs in patients with severe PVOD or PCH. Although intravenous PGI_2 is efficient in patients with IPAH [25], it sometimes causes the occurrence of life-threatening lung congestion in patients with PVOD or PCH [10,26]. In the present study, we excluded one patient with PVOD because that patient had severe pulmonary edema. Widespread pulmonary nodules with diffuse alveolar pulmonary edema were seen in the HRCT images as previously described [27]. We could not measure the size of GGOs in that patient. All patients with PVOD were treated with a PGI_2 analog or intravenous PGI_2, and one patient with PCH was treated with intravenous PGI_2 at HRCT of the chest. In patients with PVOD, the size of centrilobular GGOs at follow-up tended to be larger than that at diagnosis. Titration of PGI_2 dose has been involved in the increase size of centrilobular GGOs in patients with PVOD. On the other hand, the size of centrilobular GGOs at follow-up tended not to be different than that at diagnosis in patients with PCH. The period from HRCT at diagnosis to HRCT at follow-up was short, and this might be the reason for little change in centrilobular GGO size in patients with PCH. Photographing conditions, severity of PH and use of vasodilatation drugs such as PGI_2 might have affected the appearance of centrilobular GGOs.

This study has a limitation. The number of patients was very small. Accumulation of cases of PVOD and PCH is required.

In conclusion, the results of our study with a small sample size showed that the sizes of centrilobular GGOs and capillary assemblies were significantly larger in patients with PCH than in patients with PVOD. Measurement of the size of centrilobular GGOs in HRCT is a simple and useful method for clinical differential diagnosis of PVOD and PCH.

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Imatinib Mesylate as Add-on Therapy for Pulmonary Arterial Hypertension

Results of the Randomized IMPRES Study

Marius M. Hoeper, MD; Robyn J. Barst, MD; Robert C. Bourge, MD; Jeremy Feldman, MD; Adaani E. Frost, MD; Nazzareno Galié, MD; Miguel Angel Gómez-Sánchez, MD; Friedrich Grimminger, MD; Ekkehard Grünig, MD; Paul M. Hassoun, MD; Nicholas W. Morrell, MD; Andrew J. Peacock, MD; Toru Satoh, MD; Gérald Simonneau, MD; Victor F. Tapson, MD; Fernando Torres, MD; David Lawrence, PhD; Deborah A. Quinn, MD; Hossein-Ardeschir Ghofrani, MD

Background**—**By its inhibitory effect on platelet-derived growth factor signaling, imatinib could be efficacious in treating patients with pulmonary arterial hypertension (PAH).

Methods and Results**—**Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES), a randomized, double-blind, placebo-controlled 24-week trial, evaluated imatinib in patients with pulmonary vascular resistance ≥800 dyne·s·cm^{-5} symptomatic on ≥2 PAH therapies. The primary outcome was change in 6-minute walk distance. Secondary outcomes included changes in hemodynamics, functional class, serum levels of N-terminal brain natriuretic peptide, and time to clinical worsening. After completion of the core study, patients could enter an open-label long-term extension study. Of 202 patients enrolled, 41% patients received 3 PAH therapies, with the remainder on 2 therapies. After 24 weeks, the mean placebo-corrected treatment effect on 6-minute walk distance was 32 m (95% confidence interval, 12–52; *P*=0.002), an effect maintained in the extension study in patients remaining on imatinib. Pulmonary vascular resistance decreased by 379 dyne·s·cm^{-5} (95% confidence interval, –502 to – 255; *P*<0.001, between-group difference). Functional class, time to clinical worsening, and mortality did not differ between treatments. Serious adverse events and discontinuations were more frequent with imatinib than placebo (44% versus 30% and 33% versus 18%, respectively). Subdural hematoma occurred in 8 patients (2 in the core study, 6 in the extension) receiving imatinib and anticoagulation.

Conclusions**—**Imatinib improved exercise capacity and hemodynamics in patients with advanced PAH, but serious adverse events and study drug discontinuations were common. Further studies are needed to investigate the long-term safety and efficacy of imatinib in patients with PAH.

Clinical Trial Registration**—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00902174 (core study); NCT01392495 (extension). **(*Circulation*. 2013;127:1128-1138.)**

Key Words: drugs ■ exercise ■ hemodynamics ■ hypertension, pulmonary

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of the pulmonary vascular bed, eventually leading to right heart failure and death if not treated effectively.[1,2] Although some forms of PAH are heritable or associated with other conditions such as scleroderma, many cases are idiopathic in origin.[3]

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Clinical Perspective on p 1138

The median survival of patients with idiopathic or heritable PAH was >3 years before the availability of targeted PAH drugs.[4] Current treatment options consist of prostacyclin and

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From Medizinische Hochschule, Hannover, Germany (M.M.H.); Columbia University, New York, NY (R.J.B.); University of Alabama at Birmingham (R.C.B.); Arizona Pulmonary Specialists, Phoenix (J.F.); Baylor College of Medicine, Houston, TX (A.E.F.); Università di Bologna, Bologna, Italy (N.G.); Hospital Universitario Doce de Octubre, Madrid, Spain (M.A.G.-S.); University Hospital Giessen and Marburg GmbH, Giessen, Germany (F.G., H.G.); University Hospital Heidelberg, Heidelberg, Germany (E.G.); Johns Hopkins University, Baltimore, MD (P.M.H.); University of Cambridge School of Clinical Medicine, Addenbrooke's and Papworth Hospitals, Cambridge, United Kingdom (N.W.M.); Golden Jubilee National Hospital, Glasgow, United Kingdom (A.J.P.); Kyorin University School of Medicine, Tokyo, Japan (T.S.); Hôpital de Bicêtre, Le Kremlin-Bicêtre, Paris, France (G.S.); Duke University Medical Center, Durham, NC V.F.T.); University of Texas Southwestern Medical Center, Dallas (F.T.); Novartis Pharmaceuticals, East Hanover, NJ (D.L.); and Novartis Pharmaceuticals, Cambridge, MA (D.A.Q.).

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Correspondence to Marius M. Hoeper, MD, Department of Respiratory Medicine, Hannover Medical School, 30623 Hannover, Germany. E-mail hoeper.marius@mh-hannover.de

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its analogues, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors, all of which have been shown to improve exercise capacity, hemodynamic variables, and disease progression,[5–10] together with calcium channel blocker therapy in the rare patient responding to vasodilators and lung transplantation in the patients who are refractory to medical therapy. However, normalization of pulmonary vascular resistance (PVR) with long-term improvement is rarely achieved, even with combination treatment, and survival rates remain poor. Humbert and colleagues[11,12] recently reported a 3-year survival of <60% in patients with newly diagnosed PAH despite current therapy, highlighting the need for more treatment options.

Once considered a consequence of abnormal pulmonary vasoconstriction, PAH is now regarded as a disease caused mainly by pulmonary vascular remodeling. Proliferation of endothelial cells and vascular smooth muscle cells with narrowing or occlusion of the vessel lumina is a histopathological hallmark of the disease.[13] Evidence from animal models and human disease suggests that platelet-derived growth factor (PDGF) and c-KIT signaling are important in vascular smooth muscle cell proliferation and hyperplasia.[14–16]

Imatinib is an antiproliferative agent developed to target the BCR-ABL tyrosine kinase in patients with chronic myeloid leukemia. In addition, the inhibitory effects of imatinib on PDGF receptors α and β and c-KIT suggest that it may be efficacious in PAH.[15–17] Imatinib reversed experimentally induced pulmonary hypertension[17] and has pulmonary vasodilatory effects in animal models[18] and proapoptotic effects on pulmonary artery smooth muscle cells from patients with idiopathic PAH.[19] Case reports have suggested hemodynamic and clinical benefits in PAH patients.[20–22] A randomized, double-blind, placebo-controlled phase II study in 59 patients reported that imatinib significantly improved pulmonary hemodynamics.[23] In that study, a post hoc subgroup analysis suggested that patients with greater hemodynamic impairment might respond better to imatinib than patients with less advanced disease. The objective of the present study was to further evaluate the safety, tolerability, and efficacy of imatinib in patients with advanced PAH who were receiving at least 2 PAH therapies.

Methods

Patients

The study was conducted at 71 centers in 14 countries. Male and female subjects (aged ≥18 years) were enrolled if they had symptomatic PAH (World Health Organization functional class II through IV)[24] and met the criteria for one of the following categories of group 1 pulmonary hypertension: idiopathic or heritable PAH; PAH associated with connective tissue disease; PAH after ≥1 year repair of congenital systemic to pulmonary shunt; or PAH associated with anorexigens or other drugs.[25] Patients were required to be receiving at least 2 PAH therapies (endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, or prostacyclin analogues for ≥3 months) with a PVR ≥800 dyne·s·cm^{-5} at screening (see Appendix I in the online-only Data Supplement). Patients with World Health Organization functional class IV PAH were required to be receiving a prostacyclin analogue unless shown to be intolerant. Full details of enrollment criteria are in the protocol (Appendix II in the online-only Data Supplement).

Study Design and Treatments

Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES) was a 24-week, multicenter, double-blind, placebo-controlled, parallel-group study. Eligibility was determined in a 6-week screening period. Baseline 6-minute walk distance (6MWD) was derived from the mean of 2 consecutive tests with results that fell within 15% of each other.

Eligible patients were randomized in a 1:1 ratio to imatinib or placebo at an intended starting dose of 200 mg once daily (see Appendix I in the online-only Data Supplement). The dose was increased to 400 mg once daily after 2 weeks if the starting dose was tolerated; the dose could be reduced to 200 mg once daily if the 400 mg dose was not well tolerated. Patients were withdrawn from the trial after dose reduction if any of the following persisted for ≥2 weeks: liver function test ≥4 times the upper limit of normal; creatinine >1.5 times the upper limit of normal or >30% versus screening value; weight gain >2 kg when due to edema and decline in right heart function; or incapacitating peripheral edema or nausea/vomiting.

All patients gave written, informed consent to participate in the study. The study protocol was approved by ethics committees and/or institutional review boards at each study center.

Study Assessments

The primary efficacy end point was change in 6MWD from baseline to week 24. Six-minute walk tests were performed according to American Thoracic Society guidelines.[26] Secondary efficacy end points included changes in pulmonary hemodynamics and time to clinical worsening.

Hemodynamic variables were determined with the use of right heart catheter assessments at baseline and end of study. Time to clinical worsening was determined on the basis of time from baseline to the first occurrence of any of the following: death; overnight hospitalization for worsening of PAH (blind adjudication); worsening of World Health Organization functional class by at least 1 level; or ≥15% decrease from baseline in 6MWD (confirmed in 2 six-minute walk tests at 2 consecutive visits). Blood samples were collected for laboratory assessments, including measurement of N-terminal pro-B-type natriuretic peptide, at baseline and subsequent study visits. Safety assessments included echocardiographic assessment at baseline, week 12, and week 24 and monitoring and recording of all adverse events (AEs). All deaths and unplanned overnight hospitalizations were adjudicated by an independent committee to determine whether they were due to worsening PAH. Laboratory tests and ECGs were obtained at each visit. Patients in the core study were followed for 24 weeks after they received the first dose of study drug.

Long-term Extension Study

After completion of the 24-week core study, patients were eligible to enter a long-term open-label extension study (ongoing). Patients who were treated with 400 mg once daily of imatinib during the core study remained on 400 mg once daily, those who were treated with 200 mg once daily during the core study remained on 200 mg once daily, and those who were treated with placebo during the core study were started on 200 mg once daily and then uptitrated to 400 mg once daily after 2 weeks. Titration of dose between 200 and 400 mg was allowed on the basis of drug tolerability.

Statistical Analyses

Statistical power was estimated on the basis of 6MWD, drug tolerability (dropouts), and outcomes from prior studies. With assumption of a 30% dropout rate at 6 months, a sample size of 70 patients per group was calculated to detect a 50-m difference between imatinib and placebo with a SD of 75 m, an α of 5% (2-sided), and 90% power. Additional patients were included to enable analysis of time to clinical worsening.

Efficacy was assessed in all randomized patients who received at least 1 dose of study drug. Patients were analyzed according to randomized treatment. The assessment of 6MWD used a mixed-effects model for repeated measures, including treatment, week, and country as factors, and baseline 6MWD as a covariate as well as treatment-by-week and 6MWD baseline-by-week interactions. A random effect of center within country was also included. For the primary analysis, the null hypothesis (no change in 6MWD between imatinib and placebo at week 24) was rejected if the 2-sided *P* value was >5% and the confidence interval (CI) was entirely >0. Pulmonary hemodynamics were analyzed with a mixed-effects model including treatment and country as factors and baseline hemodynamic values as covariates. The random effect of center within country was also included in the model. Time to clinical worsening was analyzed with a Cox regression model, with terms for treatment and country and with baseline 6MWD as a covariate. Patients who discontinued the study were considered censored. Full details of the statistical approach, including sensitivity analyses and imputation rules for missing variables, are provided in the online-only Data Supplement.

Dr Hoeper, the Principal Investigator, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in the writing of the manuscript and saw and approved the final version.

Results

Patient Disposition, Characteristics, and Drug Exposure

A total of 103 patients were randomized to imatinib and 99 to placebo (Figure 1) between September 17, 2009, and May 12, 2011. One patient in the placebo group was randomized but did not receive study treatment. Baseline demographic and clinical characteristics were well balanced (Table 1). Long-term dose escalation (receipt of 400 mg once daily for ≥77 days) was successful in 48 imatinib-treated patients (47%) and 86 placebo recipients (88%).

Efficacy

Imatinib significantly improved 6MWD at week 24 compared with placebo, with a mean between-group difference of 32 m (95% CI, 12–52; *P*=0.002). Sensitivity analyses including multiple imputations for missing values retained statistical significance, although the treatment effects were slightly attenuated (Table 2). A post hoc sensitivity analysis using nonparametric statistical methods and imputation for missing values similar to other published trials[9] was performed (treatment effect, 29 m; 95% CI, 7–50; *P*=0.010) (Table 2 and Appendix I in the online-only Data Supplement).

Improvements in 6MWD from baseline with adjustment for covariates including baseline 6MWD were statistically significant from week 12 onward (Figure 2A). A responder analysis by thresholds of improvement in 6MWD is provided in Appendix III and Table I in the online-only Data Supplement. The change in 6MWD (with the use of last observation carried forward to week 24) remained significant in the subgroup of patients receiving triple combination therapy at baseline (between-group difference, 34 m; 95% CI, 5–62; *P*=0.021; Figure 2B).

In the patients who remained on imatinib in the extension (n=66), improvements in 6MWD at week 24 of the core study were maintained at week 24 of the extension (total of 48 weeks on imatinib; n=54). In these patients, 6MWD increased by 44.7±45.5 m (mean±SD) compared with core study baseline. In comparison, in patients treated with placebo in the core study and imatinib in the extension (total of 24 weeks on imatinib; n=53), the 6MWD increased by 19.3±71.6 m (mean±SD) compared with the core study baseline.

Patients receiving imatinib had greater improvements in hemodynamics. PVR decreased by 367 dyne·s·cm^{-5} in imatinib-treated patients (n=74) and increased by 12 dyne·s·cm^{-5} in placebo recipients (n=80), with a between-group difference of 379 dyne·s·cm^{-5} (95% CI, −502 to −255; *P*<0.001), equating to a change of −31.8% (95% CI, −42.2 to −21.4; *P*<0.001). In addition, mean pulmonary artery pressure

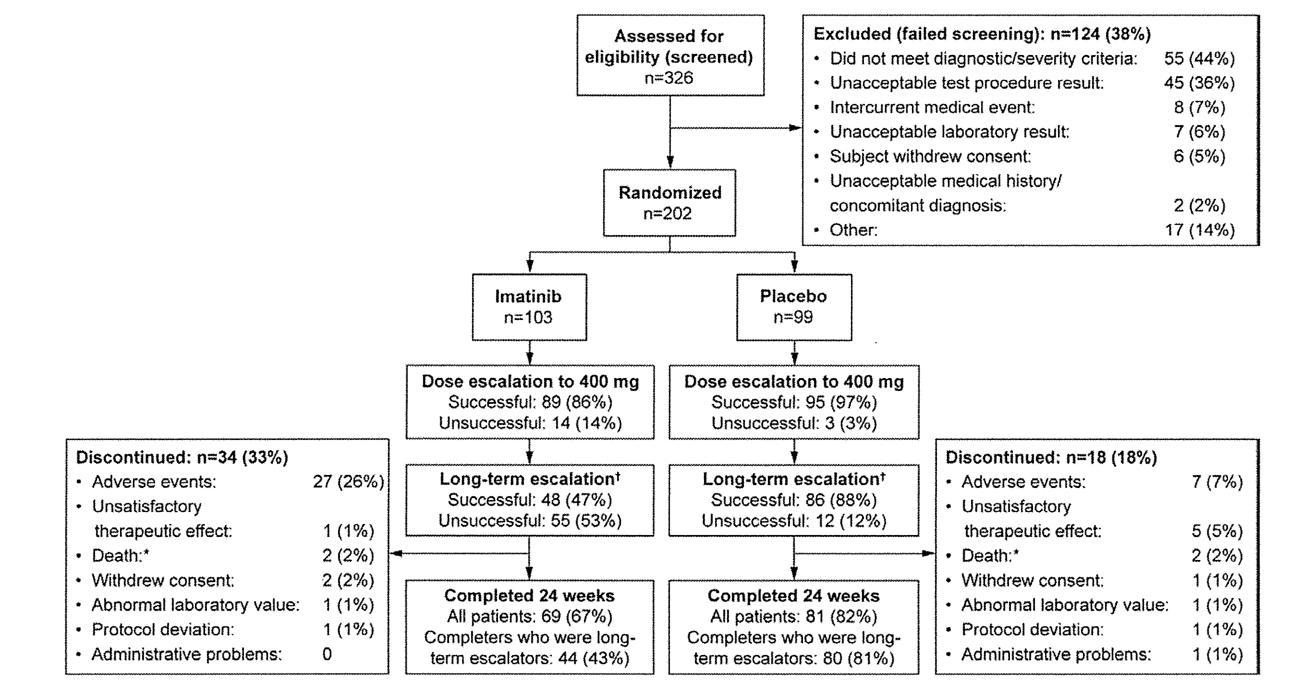


Figure 1. Patient disposition. *Two additional deaths occurred, 1 in each group, within 30 days of study drug discontinuation. †Long-term dose escalation was defined as ≥77 days (ie, ≥50% of the 22-week period during which patients could receive imatinib 400 mg).

Table 1. Baseline Demographic and Clinical Characteristics

	Imatinib (n=103)	Placebo (n=98)
Age, median (range), y	50 (18–77)	47 (18–77)
Age distribution, n (%)		
18–39 y	28 (27)	35 (36)
40–64 y	57 (55)	54 (55)
≥65 y	18 (18)	9 (9)
Male/female sex, n (%)	20 (19)/83 (81)	19 (19)/79 (81)
Race, n (%)		
White	77 (75)	72 (74)
Black	4 (4)	5 (5)
Asian	19 (18)	20 (20)
Other	3 (3)	1 (1)
PAH duration, median (range), y	3.7 (0–41)	5.1 (0–17)
Type of PAH, n (%)		
Idiopathic or heritable	77 (75)	74 (76)
Associated with other conditions	26 (25)	23 (24)
Other	0	1 (1)
WHO functional class, n (%)		
Class I	1 (1)	0
Class II	23 (22)	28 (29)
Class III	71 (69)	65 (66)
Class IV	8 (8)	5 (5)
PAH-specific background therapy, n (%)*		
ERA and PDE5	32 (31)	27 (28)
ERA and PG	15 (15)	10 (10)
PG and PDE5	14 (14)	20 (20)
ERA and PDE5 and PG	42 (41)	41 (42)
6MWD, median (range), m	355 (154–450)	366 (153–446)
Hemodynamics, mean (SD)		
Right atrial pressure, mm Hg	10 (6)	10 (7)
Mean pulmonary arterial pressure, mm Hg	59 (11)	60 (13)
Pulmonary capillary wedge pressure, mm Hg	9 (3)	9 (3)
Cardiac output, L/min	3.5 (0.9)	3.5 (0.7)
Cardiac index, L/min per m^2	2.1 (0.5)	2.1 (0.5)
Pulmonary vascular resistance, dyne·s·cm^{-5}	1202 (414)	1181 (360)

6MWD indicates 6-minute walk distance; ERA, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type-5 inhibitors; PG, prostacyclin analogues; and WHO, World Health Organization.

*In total, 69% of imatinib patients and 72% of placebo patients were treated with prostacyclin analogues. By formulation, 31% and 28% of patients received intravenous, 17% and 16% of patients received inhaled, 15% and 17% of patients received subcutaneous, and 7% and 11% of patients received oral prostacyclin analogues in the imatinib and placebo groups, respectively.

(imatinib/placebo, n=75/82), cardiac output (imatinib/placebo, n=75/81), and right atrial pressure (imatinib/placebo, n=73/81) improved compared with placebo (all $P \leq 0.03$; Figure 3; additional data are available in Appendix III and Table II in the online-only Data Supplement). The hemodynamic effects observed in patients with PAH associated with connective tissue disease or repaired congenital heart disease were similar to the hemodynamic changes seen in patients with idiopathic or heritable PAH, but the subgroups were too small to allow robust statistical analyses (Appendix III and Table III in the online-only Data Supplement). Similarly, improvements versus placebo were demonstrated with imatinib for 6MWD and PVR in patients in functional classes II and III (Appendix III and Table IV in the online-only Data Supplement).

At week 24, N-terminal pro-B-type natriuretic peptide levels (mean±SE) were lower in the imatinib group (n=68; 142±39 pmol/L) than in the placebo group (n=78; 188±40 pmol/L), with a mean difference of −45 pmol/L (95% CI, −88 to −2 pmol/L; $P=0.040$).

There was no significant difference in functional class at 24 weeks (imatinib, n=70; placebo, n=83). There was also no

Table 2. Sensitivity Analyses of the Primary End Point (6-Minute Walk Distance at Week 24) Including Imputation for Missing Data

	LS Mean Treatment Difference, Imatinib–Placebo at Week 24, m (95% CI)	*P*
Primary analysis (repeated-measures ANCOVA)	32 (12–52)	0.002
Univariate ANCOVA using LOCF	27 (7–47)	0.008
Univariate ANCOVA using BOCF	20 (5–35)	0.010
Modified multiple imputation using penalties* (repeated-measures ANCOVA)		
0% penalty	34 (14–54)	0.001
2% penalty	33 (13–53)	0.001
8% penalty	28 (8–48)	0.005
10% penalty	27 (7–47)	0.008
Multiple imputations using information from placebo patients (repeated-measures ANCOVA)†	27 (6–48)	0.013
Multiple imputations for specific reasons for discontinuation using information from placebo patients (repeated-measures ANCOVA)‡	28 (7–50)	0.009
Imputation based on published trials, CMH test		0.013
Imputation based on published trials, univariate ANCOVA	29 (7–50)	0.010

For full details of statistical methodology used to perform sensitivity analyses with adjustment for missing data, please refer to Appendix I in the online-only Data Supplement. BOCF indicates baseline observation carried forward; CI, confidence interval; CMH, Cochrane Mantel-Haenszel test; LOCF, last observation carried forward; and LS, least squares.

*Penalties were applied to patients in the imatinib arm, assuming a lower postwithdrawal 6-minute walk distance for patients who discontinued because of adverse events, unsatisfactory therapeutic effect, or death than for patients who remained in the study (allowing for the possibility of data being "missing not at random"). The scenarios investigated were 98%, 95%, 92%, and 90% lower 6-minute walk distance compared with imputations that assume that the data are missing at random.

†For patients in the active arm who discontinued for any reason, missing values were imputed on the basis of information of other patients who discontinued and placebo patients only.

‡For patients in the active arm who discontinued because of adverse events, unsatisfactory therapeutic effect, or death, missing values were imputed on the basis of information of other patients who discontinued for these reasons and placebo patients only.

significant difference in time to first clinical worsening event (hazard ratio, 1.16; 95% CI, 0.71–1.90; P=0.563) (Figure 4). During the study, 37 imatinib-treated patients (36%) had a clinical worsening event compared with 32 placebo recipients (33%) (Table 3). A detailed list of the timing of these events is shown in Appendix III and Table V in the online-only Data Supplement. Among the 37 clinical worsening events observed in the imatinib group, 24 occurred during the first 8 weeks. Of the 37 imatinib patients who experienced clinical worsening events, 15 continued on study drug and had a mean improvement in 6MWD of 15 m at the end of the study (Appendix III and Figure I in the online-only Data Supplement).

Safety

All patients including withdrawals were followed for survival data until 24 weeks after they received the first dose of study drug. Five patients in each group died during the core study (2 deaths in each group while on study drug and 3 deaths in each group after discontinuation of study drug [Appendix III and Table VI in the online-only Data Supplement]). One death in the imatinib group (renal failure) and 1 in the placebo group (clostridial infection) were considered by the respective investigators to be related to the study drug.

During the study, 28 patients (27%) discontinued because of AEs in the imatinib group compared with 9 (9%) in the placebo group, with the majority in both groups discontinuing in the first 8 weeks. The most frequent AEs were nausea, peripheral edema, diarrhea, vomiting, and periorbital edema, all known side effects of imatinib (Table 3; for additional data, see Appendix III and Tables VII through IX in the online-only Data Supplement). Anemia, leucopenia, and thrombocytopenia were observed in 14% (5% severe), 2% (0% severe), and 5% (1% severe) of imatinib patients, respectively. Serious AEs were also more frequent with imatinib than with placebo (Table 3).

Echocardiographic assessments did not show any evidence of cardiac dysfunction associated with imatinib therapy (Appendix III and Table X in the online-only Data Supplement). In addition, there was no indication of renal toxicity or hepatotoxicity due to imatinib therapy.

Long-Term Extension Study

Of the 150 patients completing the 24-week core study, 144 patients entered the extension study; 6 declined. As of March 16, 2012, of the 144 patients enrolled in the extension, 60 had withdrawn (32 of 60 because of AEs). As of October 31, 2012, a total of 18 patients had died in the extension, with 8 deaths in the core imatinib group (n=66) and 10 in the core placebo

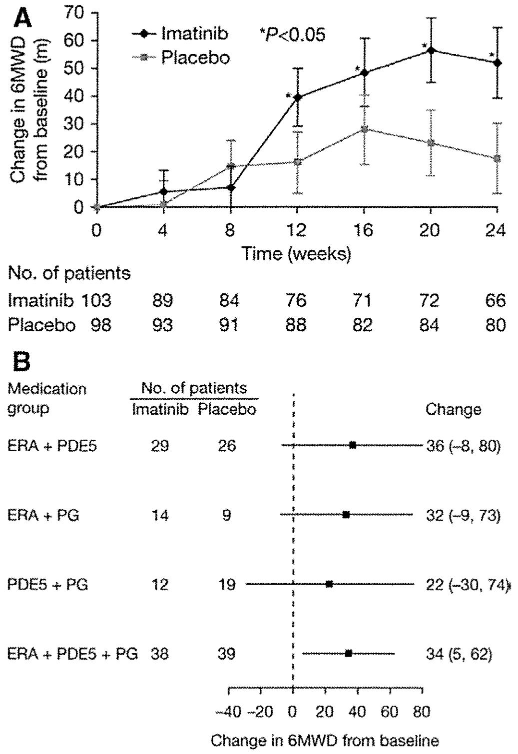


Figure 2. **A**, Change in 6-minute walk distance (6MWD) from baseline by treatment. Values are least squares means and SEs. *P* values are for between-group comparisons from ANCOVA of change from baseline in 6MWD (m) at each time. Sixty-nine patients receiving imatinib and 81 patients receiving placebo completed the study. Three patients receiving imatinib and 1 patient receiving placebo did not have a 6MWD test on completion. **B**, Subgroup analysis of changes from baseline in 6MWD (m) to end of study according to background therapy. Data are least squares mean change (m) with 95% confidence intervals. ERA indicates endothelin receptor antagonists; PDE5, phosphodiesterase type-5 inhibitors; and PG, prostacyclin analogues.

group (n=78). Fifteen of these deaths occurred while the subject was on imatinib or within 30 days of discontinuation (5 core imatinib and 10 core placebo patients), whereas 3 occurred >30 days after discontinuation (all from the core imatinib group). Sixteen deaths have been adjudicated, and 7 have been attributed to progression of PAH (3 core imatinib and 4 core placebo patients). None of these deaths were considered to be related to imatinib toxicity by the Adjudication Committee (Appendix III and Tables VI and XI in the online-only Data Supplement).

The most frequent AEs (>10%) during the extension were similar to those in the core study (Appendix III and Table XII in the online-only Data Supplement). Fifty-three percent of patients experienced serious AEs. Serious AEs that occurred in ≥3% of patients were cardiac failure (4.2%), subdural hematoma (4.2%), dyspnea (4.2%), worsening PAH (4.9%), syncope (4.9%), and device-related infection (3.5%).

Subdural hematomas occurred in 8 patients (2 of 103 imatinib patients in the core study [1.9%]; 6 of 144 patients in the extension [4.2%]) on imatinib and concomitant anticoagulation. Six patients recovered, 1 died of subdural hematoma, and 1 died of unrelated causes (Appendix III and Table XIII in the online-only Data Supplement).

In the IMPRES core study, there were no patients who received a lung transplantation on imatinib and 4 patients who received lung transplantation on placebo. Six extension study patients have undergone transplantation. Patients who underwent lung transplantation were withdrawn from the study, and imatinib treatment was stopped. No evidence of surgical complications attributable to imatinib has been identified. Although these discontinued patients are no longer in the study, reports of 2 extension study patients with serious AEs after the lung transplantation have been received. One patient had a cerebrovascular accident 2 days after transplantation, and 1 patient was reported to have died of complications related to the transplantation ≈4.5 months after the procedure.

Discussion

This multicenter, randomized, double-blind, placebo-controlled 24-week study demonstrates that imatinib improves exercise capacity and hemodynamics in patients with advanced PAH despite combination therapy with ≥2 PAH drugs. For all currently approved drugs, the 6-minute walk test was the primary end point or part of a primary composite end point. Studies of 3- to 4-month duration in patients who were treatment-naive to PAH therapies showed placebo-corrected changes in 6MWD of 31 to 50 m.[7–10] More recent trials in patients on a single background PAH therapy showed improvements in 6MWD of 20 to 26 m.[27,28] Unlike most previous phase III trials, the present study enrolled patients who were receiving a combination of at least 2 PAH therapies, with 41% on triple therapy including 29% on continuous parenteral prostanoid infusion. Against this background therapy, the 32-m improvement in 6MWD with imatinib after 6 months of treatment was not only statistically significant but also clinically meaningful,[29] especially in light of the currently available treatment options having been exhausted in many of these patients.

The present study also showed that imatinib resulted in significantly improved hemodynamic parameters. The mean placebo-adjusted improvements in cardiac output and PVR were 0.88 L/min and −379 dyne·s·cm^{-5}, respectively. The magnitude of hemodynamic improvement is remarkable given that all patients had severe PAH, with an average baseline PVR of ≈1200 dyne·s·cm^{-5} despite already being on multiple PAH treatments. Consistent with the changes in 6MWD, these hemodynamic differences were almost entirely due to improvements in patients randomized to imatinib rather than to deterioration in the placebo group. The improvements in cardiac output were accompanied by significant decreases in serum N-terminal pro-B-type natriuretic peptide.

Time to clinical worsening, a composite end point including all-cause mortality, hospitalization for worsening PAH, worsening of World Health Organization functional class, or a decrease in 6MWD of >15% from baseline, did not differ between the 2 treatment groups. Further analysis of these events suggests that the majority of the events in the imatinib group occurred during the first 8 weeks of the study in patients who did not tolerate the study medication and who had their dose reduced or who discontinued the study

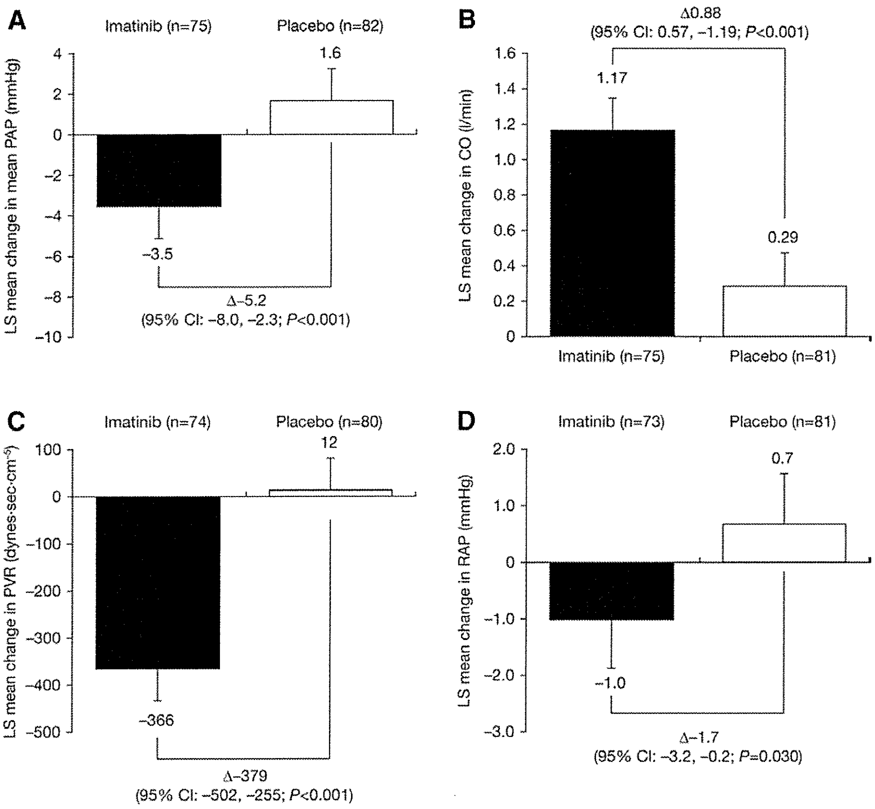
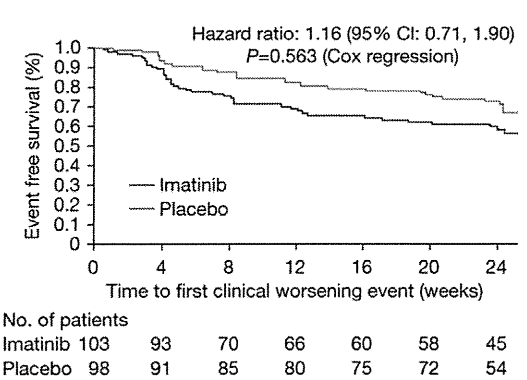


Figure 3. Least squares (LS) mean changes from baseline to end of study in mean pulmonary artery pressure (PAP; **A**), cardiac output (CO; **B**), pulmonary vascular resistance (PVR; **C**), and right atrial pressure (RAP; **D**). Δ indicates LS mean difference between groups; and CI, confidence interval. Patients included in analyses of hemodynamic parameters include those who completed the study plus those who discontinued early but had a right heart catheterization performed at discontinuation.

medication. A sizable proportion of the worsening events in the imatinib group were transient events associated with known imatinib side effects rather than events reflecting disease progression. Of those with clinical worsening events who continued on imatinib, improvements in 6MWD and PVR at 24 weeks were consistent with long-term improvement with imatinib therapy as opposed to PAH disease progression. The analysis method used for time to clinical worsening assumes a noninformative missing data mechanism (ie, that censoring is not related to the end point of interest). It is difficult to confirm this in the IMPRES trial because of the difficulty in distinguishing AEs from true clinical worsening events or signs of disease progression. Further investigations are needed to assess the effects of imatinib therapy on outcome in patients with PAH.



No. of patients							
Imatinib	103	93	70	66	60	58	45
Placebo	98	91	85	80	75	72	54

Figure 4. Time to clinical worsening. CI indicates confidence interval. Values below the graph are the number of patients remaining in the study at each time point.

Most of the AEs reported in the study were similar to those observed previously in association with the use of imatinib in patients with other approved indications. The most frequent AEs were nausea, peripheral edema, diarrhea, vomiting, and periorbital edema. There were no indications of liver toxicity or impaired renal function. However, particular note should be taken of the safety profile of imatinib in PAH because certain early AEs could be mistaken for progression of right heart failure, whereas progressive venous congestion in conjunction with worsening PAH could be interpreted erroneously as an imatinib side effect.

Study-drug discontinuations were comparatively high in the present study compared with previous studies with imatinib for malignant diseases (12% to 44% in studies up to 24 months in duration).[30,31] The exact reasons for this observation are unknown, but potential causes may include effects of the underlying disease and comedications as well as a lack of experience with the use of imatinib among PAH specialists.

Subdural hematomas occurred in 4.2% of the patients treated with imatinib in the extension study, all of them in patients receiving concomitant anticoagulation. The incidence of subdural hematomas in patients receiving imatinib for oncological indications is reported to vary between 0.2% and 5.8%.[32] A recent study by Henkens et al[33] showed a relatively high incidence of bleeding complications in patients receiving oral anticoagulants for PAH, but there was only 1 case of central nervous system bleeding in this series. A recent review of cases of subdural hematoma was reported from the 12-week Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)-1 (277 treatment-naive patients) and the 16-week Pulmonary arterial hypertension combination study of epoprostenol and

Table 3. Frequency of Adverse Events

	Imatinib (n=103)	Placebo (n=98)
Adverse event, n (%)*	100 (97)	94 (96)
Nausea	57 (55)	23 (24)
Peripheral edema	45 (44)	20 (20)
Diarrhea	36 (35)	19 (19)
Vomiting	31 (30)	10 (10)
Periorbital edema	30 (29)	7 (7)
Headache	25 (24)	22 (22)
Dyspnea	19 (18)	13 (13)
Nasopharyngitis	18 (18)	19 (19)
Hypokalemia	16 (16)	3 (3)
Anemia	14 (14)	3 (3)
Cough	11 (11)	15 (15)
Fatigue	11 (11)	7 (7)
Face edema	10 (10)	1 (1)
Muscle spasms	10 (10)	2 (2)
Serious adverse event, n (%)†	45 (44)	29 (30)
Worsening of pulmonary hypertension	6 (6)	8 (8)
Anemia	7 (7)	1 (1)
Dyspnea	6 (6)	2 (2)
Peripheral edema	6 (6)	0
Presyncope	5 (5)	0
Diarrhea	3 (3)	2 (2)
Device-related infection	3 (3)	0
Syncope	1 (1)	5 (5)
Subdural hematoma	2 (2)	0 (0)
Total patients with clinical worsening, n (%)	37 (36)	32 (33)
Death (all deaths)	3 (3)	3 (3)
Hospitalization for worsening of PAH (adjudicated events)	17 (17)	13 (13)
Worsening of WHO functional class by at least 1 level	15 (15)	11 (11)
15% reduction of 6MWD on 2 consecutive occasions compared with baseline	12 (12)	17 (17)
Worsening of WHO functional class by at least 1 level and 15% reduction in 6MWD on 2 consecutive occasions compared with baseline	2 (2)	3 (3)

6MWD indicates 6-minute walk distance; PAH, pulmonary arterial hypertension; and WHO, World Health Organization.
*Individual adverse events are shown if they occurred in >10% in the imatinib group (see online-only Data Supplement for full listing).
†Individual serious adverse events are shown if they occurred in ≥3 patients in either group.

sildenafil (PACES-1) (267 patients stable on intravenous epoprostenol) clinical trials, performed among patients with mean baseline PVR of 810.5 and 952.0 dyne·s·cm^{-5}, respectively.[34] Patients in both trials received open-label sildenafil for ≥3 years. The report identified only 2 cases of subdural hematoma (1 in each open-label extension), both in patients receiving oral anticoagulants. Thus, the incidence of subdural hematomas in the present study was unexpectedly high. However, the patient population was different from that of PACES-1 and SUPER-1 in terms of both hemodynamic severity and background treatment at baseline. The mechanism by which imatinib might cause subdural hematoma is unclear and requires further evaluation.

Limitations of this study include the short observation period, the relatively high dropout rates in both treatment arms, and the differential dropout rates on imatinib and placebo. However, the patient population was highly selected for disease severity, and the study duration was longer than in most previous trials in the field of pulmonary hypertension. Differential dropout was anticipated and was taken into account in the prespecified statistical analysis plan by the choice of primary analysis method and sensitivity analyses. Our statistical analyses also followed the principles identified by the National Research Council for drawing inferences from incomplete data,[35] but the possibility cannot be excluded that the higher discontinuation rate in the imatinib group may have led to an overestimation of the treatment effect. In addition, because 75% of the study population had idiopathic or heritable PAH, our findings are not necessarily applicable to all PAH subgroups.

The target dose of 400 mg once daily was selected because this dose is widely used in patients receiving imatinib for malignant disorders. The same target dose was also used in the phase II study of imatinib in PAH.[23] The present study protocol allowed dose reduction in patients not tolerating imatinib at 400 mg/d. Approximately half of the patients receiving imatinib were able to remain on the 400-mg dose. Although the number of patients was too small for a formal dose-effect analysis, the largest treatment effects were observed in patients who received a dose of 400 mg/d (Appendix III and Table XIV in the online-only Data Supplement), although this is a nonrandomized comparison. There was no difference in AEs between the patients who received 400 mg/d for ≥50% versus <50% of the study. However, the minimum efficacious dose of imatinib in PAH remains unknown and needs to be determined in future trials.

Finally, the present study did not further assess the mechanisms by which imatinib acts in PAH. Understanding these mechanisms is of key importance not only to predict the response to therapy but also to design more targeted tyrosine kinase inhibitors for this disease. These are crucial aspects for further research, particularly because broad-spectrum tyrosine kinase inhibition may have pleiotropic effects on the cardiopulmonary system. Sorafenib, for instance, had detrimental effects on cardiac output in patients with PAH,[36] and dasatinib has been identified as a potential cause of PAH.[37]

In conclusion, this study provides evidence that imatinib, as the first representative of a new class of drugs for the treatment of PAH, improves exercise capacity and hemodynamics in patients with advanced PAH who remain symptomatic on at least 2 drugs of the currently available 3 drug classes. Discontinuations of study medication and serious AEs, including subdural hematomas, were more common in the imatinib group, and further studies are required to assess the risk-benefit profile of imatinib in patients with advanced PAH. Until further data are available, the off-label use of imatinib for this indication is strongly discouraged.

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CLINICAL PERSPECTIVE

Pulmonary arterial hypertension (PAH) is a progressive and frequently fatal condition. Platelet-derived growth factor and c-KIT signaling are important in vascular smooth muscle cell proliferation and hyperplasia, which are cardinal features of the pathophysiology underlying the disease. Imatinib is an inhibitor of platelet-derived growth factor receptor α and β kinases and c-KIT and may have a role in the treatment of PAH. The Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES) was a double-blind, placebo-controlled, randomized, 24-week trial evaluating the efficacy and safety of imatinib in PAH patients with high pulmonary vascular resistance ($\geq$800 dyne·s·cm^{-5}) receiving $\geq$2 PAH therapies (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and/or prostacyclin analogues). Compared with placebo, imatinib significantly improved exercise capacity and hemodynamic parameters in patients with advanced PAH who remained symptomatic on at least 2 of the currently available drug classes. Discontinuations of study medication and serious adverse events, including subdural hematoma, were more common in the imatinib group. The results suggest that the efficacy profile of imatinib is promising for the treatment of PAH patients who are still symptomatic despite receiving $\geq$2 PAH therapies, although clinicians should take note of its safety profile, which continues to be assessed in ongoing studies.