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Effectiveness and Outcome of Pulmonary Arterial Hypertension-Specific Therapy in Japanese Patients With Pulmonary Arterial Hypertension

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on behalf of the Japan PH Registry (JAPHR) Network

Background: The trend of the initial treatment strategy for pulmonary arterial hypertension (PAH) has changed from monotherapies to upfront combination therapies. This study analyzed treatments and outcomes in Japanese patients with PAH, using data from the Japan PH Registry (JAPHR), which is the first organized multicenter registry for PAH in Japan.

Methods and Results: We studied 189 consecutive patients (108 treatment-naïve and 81 background therapy patients) with PAH in 8 pulmonary hypertension (PH) centers enrolled from April 2008 to March 2013. We performed retrospective survival analyses and analyzed the association between upfront combination and hemodynamic improvement, adjusting for baseline NYHA classification status. Among the 189 patients, 1-, 2-, and 3-year survival rates were 97.0% (95% CI: 92.1–98.4), 92.6% (95% CI: 87.0–95.9), and 88.2% (95% CI: 81.3–92.7), respectively. In the treatment-naïve cohort, 33% of the patients received upfront combination therapy. In this cohort, 1-, 2-, and 3-year survival rates were 97.6% (95% CI: 90.6–99.4), 97.6% (95% CI: 90.6–99.4), and 95.7% (95% CI: 86.9–98.6), respectively. Patients on upfront combination therapy were 5.27-fold more likely to show hemodynamic improvement at the first follow-up compared with monotherapy (95% CI: 2.68–10.36).

Conclusions: According to JAPHR data, initial upfront combination therapy is associated with improvement in hemodynamic status.

Key Words: Multicenter registry; Prognosis; Pulmonary arterial hypertension; Upfront combination therapy

Pulmonary arterial hypertension (PAH) is a progressive disorder. PAH is defined as an elevation in mean pulmonary artery pressure (mPAP) >25mmHg, as well as pulmonary vascular resistance (PVR) >3 Wood units associated with normal pulmonary artery wedge pressure (PAWP).[1] PAH is a complex and multifactorial disorder with a poor prognosis, and leads to right ventricular overload associated with severe right-sided heart failure.[2] According to recent reports from several countries, the prevalence of PAH is approximately 12–50 per million people.[3–5] The prognosis of PAH has improved since the approval of potent drugs, such as prostacyclin, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. The average survival time after diagnosis is now estimated

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to be 5–7 years.[6–8] Data from the US Registry to Evaluate Early and Long-Term PAH Disease Management show that the 1-year survival rate for PAH is approximately 91%.[9] Currently, combination therapies in PAH, especially upfront combination therapies, are becoming more important, especially for patients with severe PAH. Evidence for this increase in importance includes a report from a French group, who showed positive efficacy of triple combination therapy in patients with New York Heart Association (NYHA) classes 3–4.[10] Additionally, the AMBITION study showed a survival benefit of upfront combination therapies compared with single-sequential therapy.[11]

People in Japan have had universal health coverage since 1961, with coverage by employee-based and community-based insurance plans.[12] The medical services and fees set for physicians and hospitals are uniform across the nation. Moreover, especially for patients with rare diseases, such as PAH, almost 100% of medical fees are covered by insurance. Surprisingly, not only are almost all potent drugs for PAH approved, but also reimbursements to perform combination therapies are permitted. Accordingly, after 2008 when sildenafil was approved in Japan and 3 types of PAH drugs, including epoprostenol, sildenafil, and bosentan, started to be used, physicians treating patients with pulmonary hypertension (PH) in Japan actively performed combination therapies.

Given the progression of knowledge on upfront combination therapy and the absence of data on combination therapies from nationwide multicenter registries, we investigated PAH survival in the combination therapy era using registry data for PAH in Japan.

Methods

The Japan Pulmonary Hypertension Registry (JAPHR) network was established by government grant support in Japan. This network started to collect data from 8 PH centers in Japan. For the purpose of this study, we evaluated all patients with pre-capillary PH who were recruited between April 2008 and March 2013 at each center. The registry was approved by the Ethics Committees both at Keio University (approved No. 2010-227) and at International University of Health and Welfare (approved No. 5-16-23), followed by the Institutional Review Boards of all participating centers, and all participants provided written informed consent to participate in the study (UMIN000026680). All of the centers were monitored to verify the data and to avoid missing data. All of the institutions are members of a research group to establish a national registry for PH, which is supported by the Japanese government and funded by Health and Labor Sciences Research Grants in Japan (No. H24-nanchito-general-020).

Pre-capillary PH was defined as mPAP ≥25 mmHg at rest and PAWP ≤15 mmHg, as measured on right-heart catheterization. Among the patients diagnosed with pre-capillary PH, the participants were also categorized as follows: PAH (Dana Point classification group 1); chronic thromboembolic PH (Dana Point classification group 4); or PH due to lung disease and/or hypoxemia associated with significant reduction in forced expiratory volume in 1 s (FEV1) and total lung capacity (TLC) (Dana Point classification group 3). To avoid misclassification of patients into group 1, we excluded those with FEV1 <60% predicted or with significant parenchymal lung disease on HRCT regardless of spirometry from the PAH cohort. PAH was classified as idiopathic, heritable, or associated with anorexigen exposure, connective tissue disease, portal hypertension, congenital heart disease, and pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis.

For each case, we collected data on patient age, sex, Dana Point classification, date of diagnosis and of initial cardiac catheterization, NYHA functional class, 6-min walk distance, hemodynamics, laboratory data, and detailed information on medications for PH via a Web-based data registration system. Data for all patients visiting the participating centers were entered consecutively into the registry.

Data are collected at the time of the first right heart catheterization as a baseline measurement, and at least in 12-month intervals or whenever the patient had a serious clinical event, such as death or transplantation. Every change in PH drugs regarding whether they were scheduled was noted. For data quality management, out-of-range data or missing values were automatically queried in the system during data entry.

Inclusion criteria for the present analysis were diagnosis of PAH, age ≥18 years with availability of data from right heart catheterization at diagnosis, and mPAP ≥25 mmHg and mean PAWP ≤15 mmHg. The treatment-naïve group was defined as those with a diagnosis of PAH on right heart catheterization between April 2008 and March 2013. Treatment-naïve patients included those who were diagnosed and who started medication during the study period. The background therapy group was defined as those with a diagnosis made prior to starting the study. We divided the patients into 2 groups according to the performance of upfront combination therapy. Upfront combination therapy was defined as receiving multiple types of approved PH-specific drugs including bosentan, ambrisentan, sildenafil tadalafil and epoprostenol within <90 days without any additional evaluation, such as an echocardiogram or right heart catheterization, or with no tolerability issues.

Symptomatic and Hemodynamic Status Improvement

We examined the proportion of NYHA classifications at baseline and at the first follow-up visit according to treatment group (monotherapy vs. upfront combination therapy). We also measured mPAP, cardiac index, and PVR from baseline and at right heart catheterization on first follow-up in the treatment groups. For patients with information on right heart catheterization at follow-up, we assessed the proportion of those with improved hemodynamic status since baseline. We defined improvement using the following 3 criteria: (1) ≥20% reduction in mPAP; (2) ≥20% upregulation of cardiac index; and (3) ≥20% reduction in PVR. To exclude the possibility of confounding effects, we initially excluded the patients treated with only calcium channel blockers because such patients have extremely good response to each drug.

Statistical Analysis

We tabulated the characteristics of the 2 cohorts based on etiology of PAH, demographics, baseline cardiac conditions, and baseline hemodynamic status and laboratory data. We report the type(s) of starting drugs. We plotted the 3-year Kaplan-Meier survival curves for survival from all-cause death or lung transplant according to the 2 cohorts, as well as the subgroups defined by etiology type

Table 1. Subject Clinical Characteristics

	Treatment-naïve cohort (n=108)		Total cohort (n=189)	
	n	%	n	%
Etiology				
Idiopathic/heritable PAH	50	46.3	105	55.6
PAH associated with connective tissue disease	36	33.3	48	25.4
PAH associated with portal hypertension	10	9.3	13	6.9
PAH associated with CHD	6	5.6	16	8.5
Pulmonary veno-occlusive disease	3	2.8	4	2.1
Drug- and toxin-induced PAH	3	2.8	3	1.6
	n	%	n	%
Sex				
Female	86	79.6	144	76.2
	Mean	SD	Mean	SD
Age (years)				
At diagnosis	–	–	43.9	16.9
At treatment initiation	48.8	17.3	45.1	16.6
	n	%	n	%
NYHA class				
I	1	0.9	4	2.1
II	36	33.3	64	33.9
III	55	50.9	96	50.8
IV	16	14.8	25	13.2
Cardiac rhythm				
Sinus	105	97.2	183	96.8
Atrial fibrillation	2	1.9	4	2.1
Other	1	0.9	2	1.1
Use of anticoagulants				
Yes	46	42.6	78	41.3
No	62	57.4	111	58.7
	Mean	SD	Mean	SD
6-MWD (m)	281	145	306	146
Blood sample data				
Bilirubin (mg/dL)	1.1	0.9	1.0	0.7
Creatinine (mg/dL)	0.8	0.3	0.8	0.3
Uric acid (mg/dL)	6.5	2.3	6.5	2.4
BNP (pg/mL)	245	292	213	273

6-MWD, 6-min walk distance; BNP, B-type natriuretic peptide; CHD, congenital heart disease; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.

and baseline NYHA classification. We compared the proportion of patients with improvement in 3 indices (mPAP, cardiac index, and PVR) at the earliest follow-up of right heart catheterization between the groups (upfront combination and monotherapy) using Fisher's exact test. We created modified Poisson regression models[13] for the 3 outcomes to assess the association between the treatment group and the improvement in each of these criteria. We also created a fourth model for the outcome of improvement in all 3 indices to estimate the relative likelihood of the outcome for the upfront therapy group compared with those on regular treatment. In these models, we adjusted for baseline NYHA classification class, dividing them into binary groups of classes I–II vs. III–IV. $P<0.05$ was considered statistically significant. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Subjects

A total of 189 consecutive adult patients with PAH were enrolled in this study. In this total cohort, the number of patients with idiopathic, heritable, and drug-induced PAH was 108 (**Table 1**). With regard to the treatment-naïve group, this consisted of 108 patients who received initial treatment at the time of enrollment (**Table 1**). Hemodynamic parameters at baseline in both of the cohorts are given in **Table 2**.

Treatment-Naïve Cohort Analysis

Among the 108 patients in the treatment-naïve cohort, all patients received PAH-specific therapy of epoprostenol, bosentan, ambrisentan, sildenafil, and/or tadalafil (**Figure 1**). Patients receiving only calcium channel blockers or bera-

Table 2. Hemodynamics Parameters at Study Entry

	Treatment-naïve cohort (n=108)		Total cohort (n=189)	
	Mean	SD	Mean	SD
Mean PAP (mmHg)	46.9	14.4	48.2	13.8
PAWP (mmHg)	7.8	3.7	8.2	3.4
Mean right atrial pressure (mmHg)	6.5	4.0	6.6	4.1
PVR (dyn·s·cm^{-5})	1,106	733.0	1,036	653.0
Cardiac index (L/min/m^2)	2.2	0.7	2.4	0.8
Mixed venous oxygen saturation (%)	65.0	8.9	66.6	9.7

PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

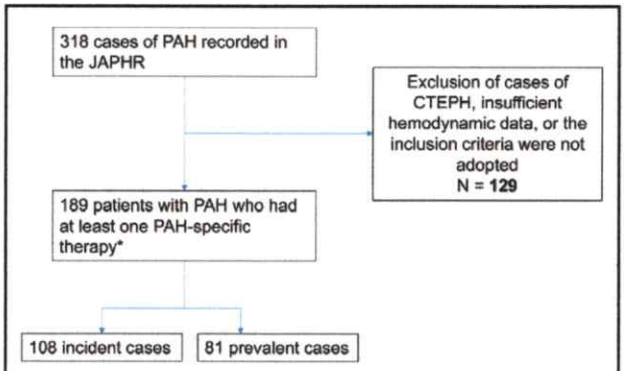

Figure 1. Subject selection. *Pulmonary arterial hypertension (PAH)-specific therapy: treatment with epoprostenol, bosentan, ambrisentan, sildenafil and/or tadalafil. CTEPH, chronic thromboembolic pulmonary hypertension; JAPHR, Japan Pulmonary Hypertension Registry.

Table 3. Characteristics of Initial Drug Use

Drug combination	n	%
Treatment-naïve cohort (n=108): drug use just after diagnosis		
Single		
Sildenafil	38	36.2
Tadalafil	16	14.8
Bosentan	14	13
Ambrisentan	4	3.7
Epoprostenol	2	1.9
Upfront double combination		
Bosentan and sildenafil	7	6.5
Ambrisentan and sildenafil	7	6.5
Bosentan and epoprostenol	5	4.6
Sildenafil and epoprostenol	5	4.6
Bosentan and tadalafil	4	3.7
Ambrisentan and tadalafil	2	1.9
Tadalafil and epoprostenol	1	0.9
Upfront triple combination		
Bosentan, sildenafil, and epoprostenol	2	1.9
Ambrisentan, tadalafil, and epoprostenol	1	0.9
Total cohort (n=189): drug use at study entry		
Single		
Sildenafil	46	24.3
Bosentan	46	24.3
Tadalafil	17	9
Ambrisentan	5	2.7
Epoprostenol	29	15.3
Double combination		
Bosentan and sildenafil	13	6.9
Ambrisentan and sildenafil	8	4.2
Bosentan and epoprostenol	6	3.2
Sildenafil and epoprostenol	6	3.2
Bosentan and tadalafil	5	2.7
Ambrisentan and tadalafil	3	1.6
Tadalafil and epoprostenol	1	0.5
Triple combination		
Bosentan, sildenafil, and epoprostenol	2	1.1
Ambrisentan, tadalafil, and epoprostenol	1	0.5
Bosentan, tadalafil, and epoprostenol	1	0.5

prost were excluded from this cohort. The characteristics of drug use just after diagnosis are given in **Table 3**. Surprisingly, 34 patients (31.5%) had already received upfront combination therapy at diagnosis, including 3 (2.8%) with triple combination therapy, including epoprostenol. A total of 65.7% of the patients had severe PAH symptoms and were categorized in NYHA classes 3–4. We analyzed the dosage of epoprostenol as an initial target. Sixteen patients received epoprostenol as the first-line therapy, including single and upfront combination therapies, and the mean (±SD) dosage was 40.4±19.4 ng/kg/min.

We performed 3-year survival analysis in the treatment-naïve cohort. Among the 108 patients in this cohort, 3 patients died or had lung transplantation performed during the follow-up period (**Figure 2A**). There was no loss to follow-up in each of the centers during the 3-year follow-up. Kaplan-Meier survival estimates for the 108 treatment-naïve PAH patients at 1, 2, and 3 years were 97.6% (95% CI: 90.6–99.4), 97.6% (95% CI: 90.6–99.4), and 95.7% (95% CI: 86.9–98.6), respectively. **Figure 2B** shows the Kaplan-Meier survival estimates for patients with idiopathic, heritable, and drug-induced PAH (n=50), and for patients with other types of PAH (n=58). The estimated 3-year survival rates were 100% and 91.7% (95% CI: 75.4–97.4), respectively, with no significant difference between the 2 subgroups. In the subgroups of PAH associated with other diseases, the estimated 3-year survival rate for patients with autoimmune disease, congenital heart disease, and portal hypertension was 93.0%, 80.0%, and 100%, respectively (**Figure S1**).

Combined Cohort Analysis

Among the 189 patients in the combined cohort, all patients

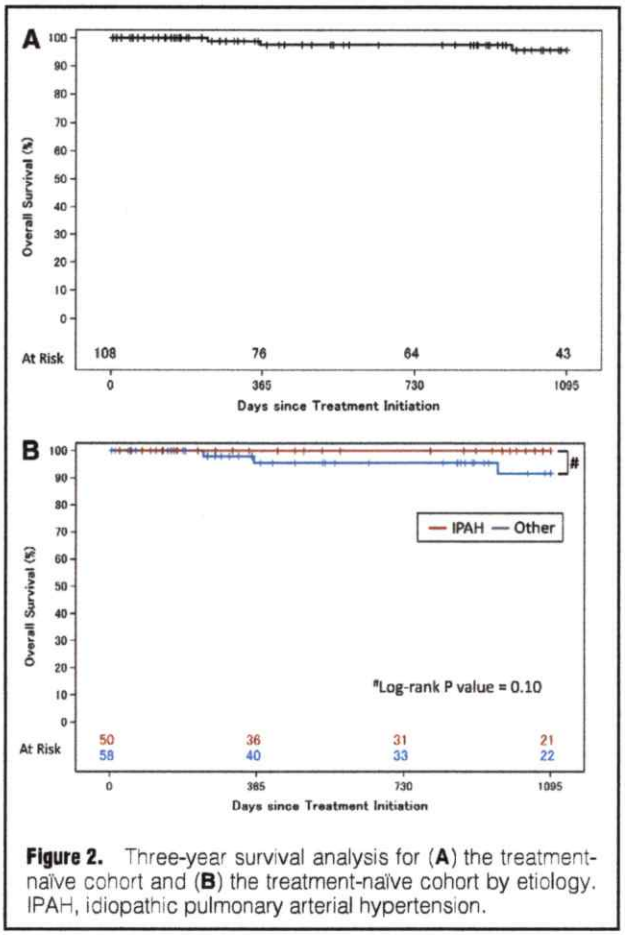

Figure 2. Three-year survival analysis for (**A**) the treatment-naïve cohort and (**B**) the treatment-naïve cohort by etiology. IPAH, idiopathic pulmonary arterial hypertension.

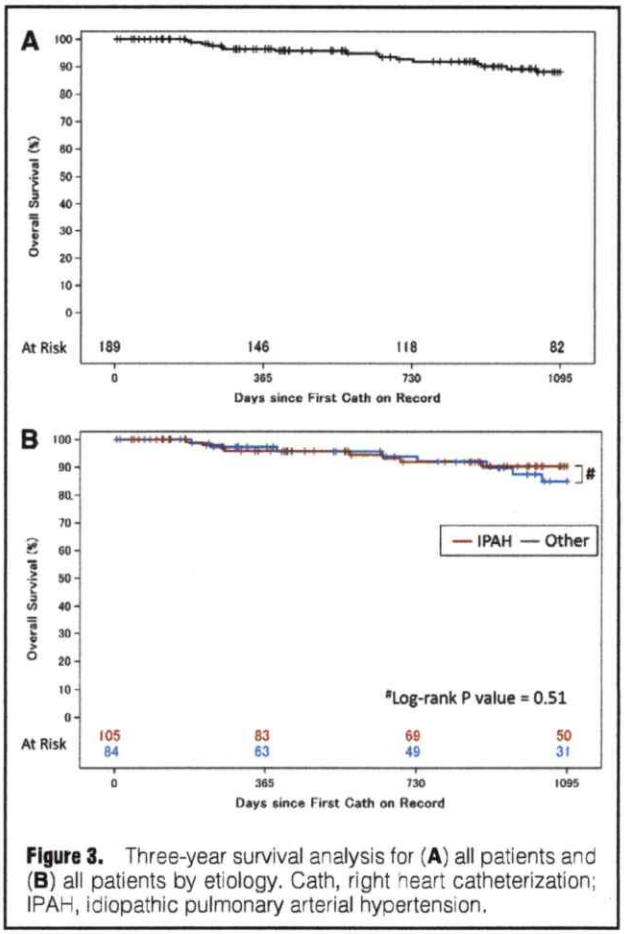

Figure 3. Three-year survival analysis for (**A**) all patients and (**B**) all patients by etiology. Cath, right heart catheterization; IPAH, idiopathic pulmonary arterial hypertension.

also received PAH-specific therapy. Patients receiving only calcium channel blockers or beraprost were excluded from this cohort. The mean (±SD) age at diagnosis was 43.9±16.9 years. Therefore, the mean time from diagnosis to study enrollment was 1.2 years. The characteristics of drug use at study entry are listed in **Table 3**. A total of 143 patients (75.6%) received monotherapy, including 29 (15.3%) with epoprostenol monotherapy. The number of patients who had double and triple combination therapies, including sequential and upfront combination therapy, was 42 (22.3%) and 4 (2.1%), respectively. On 3-year survival analysis of the 189 patients in this cohort, 16 patients died or had lung transplantation during the follow-up period (**Figure 3A**). There was no loss to follow-up in each center during the 3-year follow-up. Kaplan-Meier survival estimates for the 189 patients with treatment-naïve PAH at 1, 2, and 3 years were 97.0% (95% CI: 92.1–98.4), 92.6% (95% CI: 87.0–95.9), and 88.2% (95% CI: 81.3–92.7), respectively. **Figure 3B** shows the Kaplan-Meier survival estimates for idiopathic, heritable, and drug-induced PAH (n=105) and for patients with other types of PAH (n=84). The estimated 3-year survival rate was 90.4% (95% CI: 81.6–95.1) and 84.9% (95% CI: 71.5–92.3), respectively, with no significant difference between the 2 subgroups.

Hemodynamic Status Improvement and Upfront Combination Therapy

Among the 108 patients in the treatment-naïve cohort, we obtained follow-up information on NYHA classification and right heart catheterization measures for 92 patients. Baseline and first follow-up NYHA classification, hemodynamic status and other clinical characteristics are listed in **Tables 4,S1**. The median time to first follow-up from baseline was 292.5 days. Among the 66 patients on monotherapy, 36 (54.6%) had NYHA class III or IV, while 23 of 29 (88.4%) had NYHA class III or IV in the upfront combination therapy group. At first follow-up, 34.8% and 53.8% of patients were in NYHA classes III and IV, respectively. And hemodynamic improvements for each treatment strategy were associated with the improvements in exercise function (**Tables 4,S2**). Among 26 patients on upfront combination therapy, 84.6% had a ≥20% reduction in mPAP at the first right heart catheterization. Improvement in the cardiac index and pulmonary ventricular resistance was observed in 84.0% and 88.5% of the patients, respectively. In contrast, 42.4%, 43.1%, and 64.1% of patients had improvement in mPAP, cardiac index, and PVR in the monotherapy group, respectively. After adjustment for baseline NYHA classification status, those on upfront combination therapy were 1.98-fold more likely to have an improvement in PAP at their first follow-up right heart catheterization (95% CI: 1.37–2.84) compared with those on regular treatment (**Table 5**). The relative risks for improvement of the cardiac index and PVR were 1.90 (95% CI: 1.32–2.73) and 1.39 (1.06–1.81), respectively. Taken together, patients on upfront combination therapy were 5.27-fold more likely to show improvement in all 3 of these indices (95% CI: 2.68–10.36) compared with those on

Table 4. Improvement vs. Therapy Type in the Treatment-Naïve Cohort

	Monotherapy (n=66)				Upfront combination therapy (n=26)				P-value
	Baseline		First follow-up		Baseline		First follow-up		
	n	%	n	%	n	%	n	%	
NYHA class									
I	1	1.5	1	1.5	0	0	1	3.8	
II	29	43.9	42	63.6	3	11.5	11	42.3	
III	31	47.0	23	34.8	14	53.8	11	42.3	
IV	5	7.6	0	0.0	9	34.6	3	11.5	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Hemodynamic changes									
Mean PAP (mmHg)	44.4	13.8	38.6	13.4	55.9	14.5	37.6	16.7	
Cardiac index (L/min/m^2)	2.21	0.68	2.76	1.01	1.94	0.68	2.96	1.02	
PVR (dyn·s·cm^{-5})	1,023.2	697.4	664.8	424.6	1,405.7	852.1	564.1	430.6	
			n	%			n	%	
Improved hemodynamic status									
Mean PAP (≥20% reduction)			28/66	42.4			22/26	84.6	<0.001
Cardiac index (≥20% upregulation)			28/65	43.1			21/25	84.0	<0.001
PVR (≥20% reduction)			41/64	64.1			23/26	88.5	0.02
All 3 indices			10/64	15.6			19/25	76.0	<0.001

Abbreviations as in Tables 1,2.

Table 5. Estimated Relative Risk of Improvement at First Follow-up RHC†

Improvement index	Relative risk	P-value
Mean PAP	1.98 (1.37–2.84)	<0.001
Cardiac index	1.90 (1.32–2.73)	<0.001
PVR	1.39 (1.06–1.81)	<0.02
All 3 indices	5.27 (2.68–10.36)	<0.001

†In the upfront combination therapy group vs. the regular treatment group. RHC, right heart catheterization. Other abbreviations as in Table 2.

regular treatment, and the results were not different after adjustment for age and gender (**Table S3**). Finally, the Kaplan-Meier survival estimates for monotherapy and for upfront combination therapy are given in **Figure S2**. Interestingly, there was no significant difference between the 2 subgroups, nevertheless the monotherapy group had less severe PAH at baseline. This result was in line with the hemodynamics results.

Discussion

This is the first report of a multicenter registry on PAH from Japan, and it strongly supports the benefit of upfront combination therapy. Even in patients with NYHA functional class III or IV, upfront combination therapy resulted in improvement in hemodynamics, as well as exercise capacity. Such improvement might result in a better prognosis of PAH. Despite most patients having NYHA functional class III or IV, 26 patients who received initial upfront combination therapy had remarkable improvement in PVR, cardiac index, and PAP.

The combination therapy paradigm has advanced over the span of several years. Initially, a French network of PAH investigators reported their initial experience with upfront triple combination therapy, including epoprostenol.[10] Despite the fact that the investigators retrospectively reviewed only 19 patients with severe PAH who were treated with bosentan, sildenafil, and i.v. epoprostenol simultaneously as initial treatment, there was significant improvement in the hemodynamics of 18 of 19 patients (cardiac index, 3.5±0.7 vs. 1.7±0.4 L/min/m^2; PVR, 7.1±3.3 vs. 21.5±7.8 Wood units). They also showed improvement in the 6-min walk distance (463±94 vs. 227±171 m) at the initial follow-up evaluation compared with baseline. These beneficial effects were sustained to the final follow-up evaluation at 32±10 months. Additionally, the AMBITION study compared dual upfront combination therapy with ambrisentan and tadalafil with monotherapy, with the 2 agents as a pooled group in treatment-naïve PAH patients.[11] This previous study demonstrated that upfront combination therapy was superior to monotherapy with either single agent and it had long-term benefits.[11] The advantage of combination therapy is suggested to be ubiquitous because the French network of PAH investigators also reported their retrospective data of initial dual oral combination therapy.[14] All regimens of a combination of sildenafil or tadalafil plus bosentan or ambrisentan showed significant improvement with a better prognosis than the expected survival rates from the French equation. The 2015 European Society of Cardiology/European Respiratory Society PH guidelines recommend performing initial combination therapy, especially in critically ill patients with PAH.[1] Data from only a few studies, however, were used to support these guidelines. The present data strongly support the advanced recommendation because improvement in hemodynamics and prognosis were hopeful in severe patients.

Another unique point of the treatment method in Japan

is that the use of high-dose epoprostenol is eligible for insurance reimbursement. In the present study, the initial mean target dosage of epoprostenol was 40.4 ng/kg/min, which is similar to previous reports.[15,16] We cannot conclude yet that "more is better" for use of epoprostenol because side-effects of long-term epoprostenol use have been reported, such as IgG4-related disease,[17] and we also should consider the cost-effectiveness of high-dose epoprostenol. We should reconsider, however, the optimal dosage of epoprostenol, because in the French double combination study, patients who received tadalafil appeared to have greater hemodynamic improvement than those who received sildenafil.[14] This could be explained by the fact that the approved dose of sildenafil was 20 mg 3 times daily. Additionally, the change in PVR from baseline was dose dependent from 20 mg 3 times daily to 80 mg 3 times daily in an initial randomized, controlled trial of sildenafil vs. placebo (SUPER-1).[18] Such findings suggest that the method "more is better" could have considerable advantages if compliance and side-effects are acceptable.

The present study has a few limitations with regard to the interpretation of findings. This study was retrospectively designed and the initial follow-up period was not uniform between each center. The data, however, were well monitored and validated to exclude inclusion bias. Additionally, because of the limited number of patients, extracting and adjusting all of the conceivable factors to decide whether each patient should be enrolled in upfront combination therapy was difficult. Therefore, residual confounding may exist in the assessment of the association between hemodynamic improvement and treatment choice. Given that patients with severe PAH were treated with combination therapy, the baseline difference was by nature associated with better improvement. Second, the data were not useful with regard to health economics. The higher the number of drugs, the higher the cost of treatment, therefore we should analyze this aspect at the next step. Additionally, we defined "upfront combination therapy" as receiving multiple types of approved PH-specific drugs within <90 days without any additional evaluation. The consensus of the term has not been established as yet, and although we adopted a definition similar to previous reports,[10,14] the present findings may not be generalizable to upfront combination therapies based on other definitions. Finally, the centers that were enrolled in this registry were experienced in the treatment of PAH. Therefore, the present data may not reflect the practices and observations at other locations across Japan. This is because there is an imbalance in treatment strategies owing to the difference in relative experience with patient care and drug use.

Conclusions

Initial upfront combination therapy, which is a standard treatment strategy in Japan, appears to have an advantage in the treatment of PAH. This therapy was associated with improvement in hemodynamic status at first follow-up, similar to the AMBITION trial. Because the prognosis of PAH is poor on classical treatment regimens, the present results suggest the use of combination therapies for these patients.

Disclosures

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Author Contributions

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Appendix

List of JAPTR Investigators

The JAPHR study included the following principal investigators: Takahiro Sato, Hiroshi Ohira, Taku Watanabe and Masaharu Nishimura (Hokkaido University, Tokyo, Japan), Yuichiro Shirai (Nippon Medical School, Tokyo, Japan), Hisataka Maki, Toshiro Inaba, Minatsuki Shun and Hironori Muraoka (The University of Tokyo Hospital, Tokyo, Japan), Mai Kimura, Makoto Takei, and Tomohiko Ono (Keio University, Tokyo, Japan), Seiichiro Sakao and Yasunori Kasahara (Chiba University, Chiba, Japan), Hiroki Uyama, Atsuhiro Nakamura and Takefumi Itoh (Nara Medical University, Nara, Japan), and Akiko Ohina (National Hospital Organization Okayama Medical Center, Okayama, Japan).

Supplementary Files

Supplementary File 1

Figure S1. Three-year survival analysis for patients with (**A**) autoimmune diseases; (**B**) congenital heart disease; and (**C**) portal hypertension.

Figure S2. Three-year survival analysis for the treatment-naïve cohort by treatment strategy.

Table S1. Baseline clinical characteristics vs. therapy type in the treatment-naïve cohort

Table S2. Hemodynamic improvement vs. therapy type in the treatment-naïve cohort

Table S3. Relative risk for improvement at first follow-up RHC

Please find supplementary file(s);
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●原 著

肺高血圧症疾患特異的PRO指標emPHasis-10日本語版の開発と言語的妥当性

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要旨：emPHasis-10は，肺高血圧症患者のQOL評価のための疾患特異的PRO指標である．今回，本指標をわが国に導入するため，言語的妥当性を担保した日本語翻訳版を作成した．まず順翻訳では，2人の翻訳者が原作版の概念を踏まえてそれぞれ英語から日本語に翻訳し，第3の翻訳者がそれを1つの翻訳案にまとめた．次に，英語を母語とする翻訳者がそれを英語に逆翻訳した．その後，肺高血圧症患者10人に調査を行い，文章表現の適切さなどを確認した．上記の過程を経て，言語的に妥当な日本語版emPHasis-10を確定した．

キーワード：肺高血圧症，emPHasis-10，PRO指標，言語的妥当性
Pulmonary hypertension, emPHasis-10, Patient-reported outcome measure, Linguistic validity

緒 言

肺高血圧症とは，さまざまな原因により肺動脈圧が正常より高くなった病態であり，進行すると右心不全をきたし，その結果死に至ることもある重篤な疾患である[1]．主な症状としては息切れや呼吸困難が挙げられるが，肺高血圧症の症状は身体面のみならず患者の精神面にも影響を与えるため，生活の質（quality of life：QOL）が著しく障害されることが報告されている[2)~4)]．近年，肺動脈性肺高血圧症（pulmonary arterial hypertension：PAH）に対する有効な治療法の開発などにより，肺高血圧症の長期予後は著明に改善してきており[1,5)]，現在の肺高血圧症の治療においては，適切なマネジメントによるQOLの向上が重要な治療目標になっている．

emPHasis-10は，肺高血圧症患者のQOLを評価するための疾患特異的patient-reported outcome（PRO）指標で，Manchester大学と肺高血圧症患者を中心に組織された英国肺高血圧症協会（Pulmonary Hypertension Association UK：PHA UK）との共同研究により2014年に開発された[6)]．質問数は10問で，息切れ，疲労等の症状や，自信，周囲への負担感などの精神面の項目について，それぞれ0から5の6段階で評価する．得点化も容易で，10問の各スコアの合計（0～50点）が総スコアとなる．肺高血圧症が患者の生活に与える影響を総合的に，かつ短時間に評価できるという点で，臨床現場での使用に適したツールであると言える．その妥当性については，慢性血栓塞栓性肺高血圧症患者における使用についても検討した開発者らによる後続試験でも確認されている[7)]．

emPHasis-10は比較的新しい指標であるが，すでに他言語への翻訳版も開発されており，我々の知る範囲では，現在までにオランダ語，スペイン語，フランス語，ドイツ語，イタリア語に翻訳されている[8)]．その簡便さおよび，現時点では非営利目的の研究・診療目的であれば申請のみで使用料がかからない点からも，今後ますますその使用は広がるものと思われる．そこでわが国でもemPHasis-10の利用を可能にするため，英語の原作版を日本語に翻訳し，言語的妥当性を担保した日本語版emPHasis-10を作成したので報告する．

対象および方法

日本語版の開発に先立ち，まず原作者のDr. Janelle Yorkeから許可を得た．その後，原作者より受領した翻訳版開発のプロセスを規定したプロトコールに従い，順翻訳→逆翻訳→パイロットテストの流れで開発を進めた．これは，言語的に妥当な翻訳版を作成するのに標準的に用いられる手順[9)~11)]である．

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1. 順翻訳および逆翻訳

まず，日本語を母語とする2人（翻訳者1人，研究者1人）が，あらかじめ原作者から受領していた用語の概念の説明内容を踏まえて，原作版をそれぞれ日本語に翻訳した．その後，翻訳した2人とは別の第3者が2つの翻訳案を検討し，1つの日本語翻訳案にまとめた（順翻訳）．次に，その日本語翻訳案を，英語を母語とし，医学英語教育および他のPRO指標翻訳の実績がある翻訳者1人が英語に翻訳した（逆翻訳）．研究者および原作者が逆翻訳の結果を確認し，必要な検討を加えた後，日本語暫定版とした.

2. パイロットテスト

日本語暫定版の言語表現が妥当であるかどうかを検討するため，国際医療福祉大学三田病院に通院中の肺高血圧症患者を対象に，個別面談方式によるパイロットテスト（調査）を実施した．実施に際しては，個人情報は一切収集せず，患者のプライバシーには十分に配慮した.

まず，調査参加者が自己記入でemPHasis-10に回答した．その後，面談のトレーニングを受けた担当者（臨床研究コーディネーター）が，質問票全体の印象（質問票の長さや回答に要する時間は適当か，重複するような項目はないか，読みづらい箇所はないか）や，各項目の内容（理解しやすいか，回答したくない項目はないか）などについて，参加者に意見を求めた.

パイロットテストの結果を踏まえて日本語暫定版に必要な修正を加え，日本語確定版とした.

成　績

英語の原作版と日本語暫定版および日本語確定版の比較を表1に示した.

1. 順翻訳および逆翻訳（日本語暫定版の作成）

設問6の“walk up one flight of stairs”は，慣用的な英語表現で「一続きの階段を上まで登る」という意味であり，一般的には1階分登る場合の半階分の階段を示すことが多いが，「一続きの階段」という表現は直訳的でわかりにくいため，概念を踏まえたうえでより自然な表現とするため，「階段の踊り場まで登る」と訳した.

設問9の“dependent”については，原作者より受領していた概念の説明文書で，“reliant on other people, not able to do things on one's own”と言い換えがなされていた．日本語に訳す際には，この概念をより正確に表現するため，言葉を補って「誰かに頼って生活している」と表現した.

設問10の“feel like a burden”の訳に関しては，「他者に対して自分がどれだけ負担となっているか」を測るものであるというこの項目の概念を踏まえ，誰にとっての負担を問うているのかがわかるように，「周囲への」という言葉を補って訳した.

次に，順翻訳により得た日本語翻訳案を逆翻訳し，原作版との概念の同等性を原作者に確認した．その結果，原作者より特筆すべき問題はないとの回答を得た．上述した日本語訳についても，原作者が逆翻訳結果を確認し，問題はないとの回答を得たため，そのまま日本語暫定版の訳として採用した.

1点，設問3では，“rest”の訳語である「安静にする」という内容が，逆翻訳では“lie quietly in bed”と訳されていたため，原作者より“in bed”である必要はないとの指摘を受けた．しかし，これは逆翻訳時に補足表現として追加されたものであり，日本語訳のなかには“in bed”にあたる表現はなく，日本語の文章を適切に表現すれば“lie quietly”で間違いないとの確認がとれたため，日本語訳自体は修正不要と判断した.

上記の検討を経て，日本語暫定版を得た（表1）.

2. パイロットテスト

肺高血圧症の患者10人を対象に調査を実施した．対象患者の平均年齢は48.6歳（26～67歳）で，男性3人，女性7人であった．いずれも肺動脈性肺高血圧症の患者（9人が特発性/遺伝性肺動脈性肺高血圧症，1人が先天性心疾患に伴う肺動脈性肺高血圧症）であり，その他合併症はなかった.

設問6の「踊り場まで」という表現については，何かわからない，わかりづらいという意見があったほか，「10段くらい」，「14～15段で2階までくらい」，「20段程度」，「3階くらい」等，参加者間でイメージするものに差があった．また，この“one flight of stairs”の概念については，原作者より受領した概念の説明文書のなかで，“walking up 8 stairs”と言い換え可能であると説明されており，被験者が「踊り場まで」という言葉に対して抱くイメージは概してそれよりも多い負荷量のものであったため，表現の変更が必要であると判断した．これらの認識の相違を生み出した文化的背景として，日本の家屋では1階から2階まで直線的に一気に続く階段の方が多く，欧米の建物で一般的な，途中に踊り場があり折り返す形の階段にはあまり馴染みがないため，10段以上という比較的長い距離をイメージした参加者が多かったと推察される．以上の経過から，概念の説明文書にある“walking up 8 stairs”を参照し，具体的に「階段を8段登っても息切れしない」という表現に変更した.

設問10については，「周囲への負担」を，「周囲の自分に対する気遣いが，自分自身の負担であると感じること」だと捉えた参加者が1人いた．しかし，他の参加者は設問の内容を正しく理解していたため，この日本語表現自

表1　原作版emPHasis-10（英語版）と日本語暫定版および日本語確定版の比較

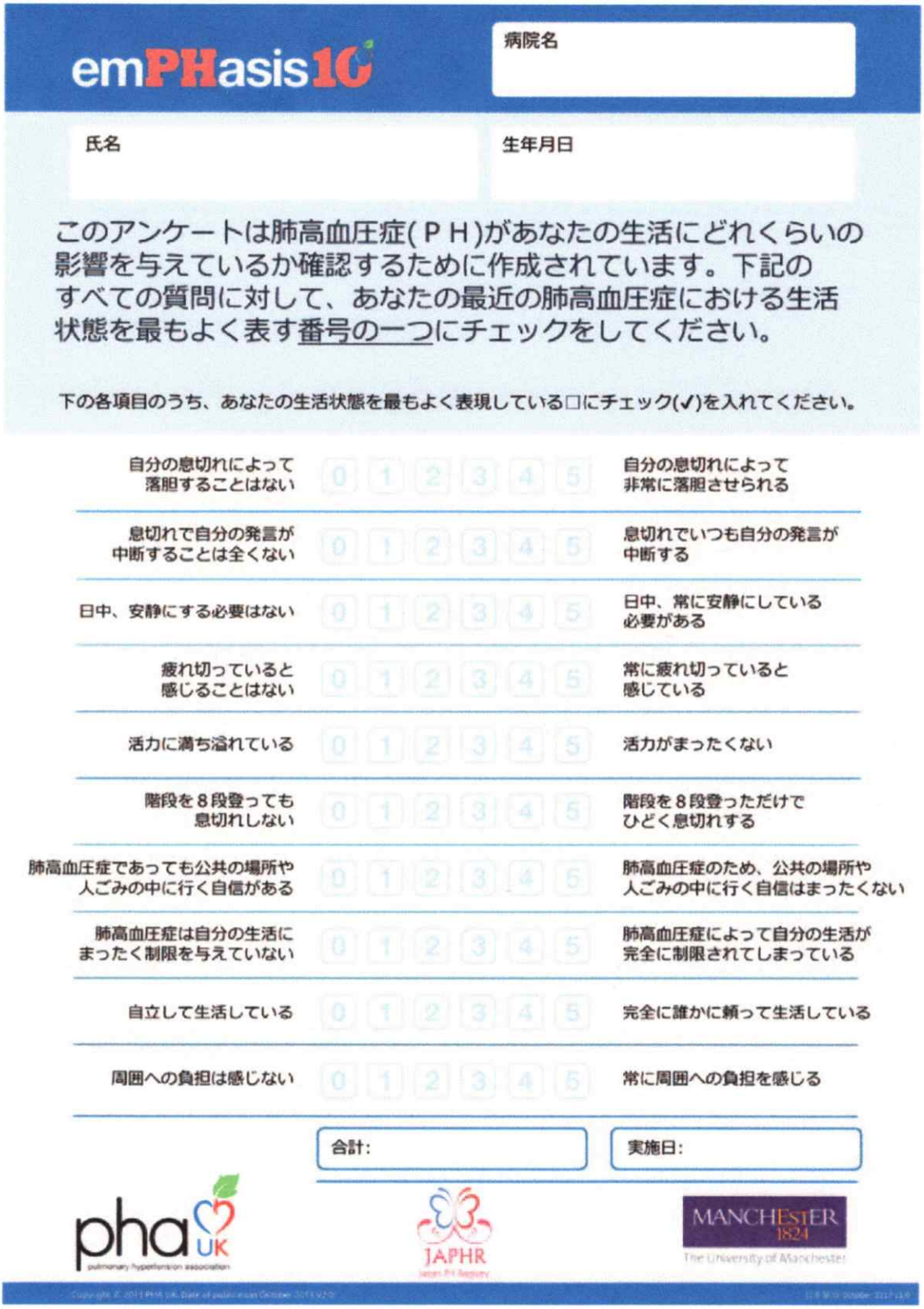
	原作版（英語）	日本語暫定版	日本語確定版
	NHS/Hospital number, Name, Date of birth	病院名，氏名，生年月日	病院名，氏名，生年月日
説明文	This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH. For each item below, place a tick (✓) in the box that best describes your experience.	このアンケートは肺高血圧症（PH）があなたの生活にどれくらいの影響を与えているか確認するために作成されています．下記のすべての質問に対して，あなたの最近の肺高血圧症における生活状態を最もよく表す番号の一つにチェックをしてください． 下の各項目のうち，あなたの生活状態を最もよく表現している□にチェック(✓)を入れてください．	このアンケートは肺高血圧症（PH）があなたの生活にどれくらいの影響を与えているか確認するために作成されています．下記のすべての質問に対して，あなたの最近の肺高血圧症における生活状態を最もよく表す番号の一つにチェックをしてください． 下の各項目のうち，あなたの生活状態を最もよく表現している□にチェック(✓)を入れてください．
1	I am not frustrated by my breathlessness	自分の息切れによって落胆することはない	自分の息切れによって落胆することはない
	I am very frustrated by my breathlessness	自分の息切れによって非常に落胆させられる	自分の息切れによって非常に落胆させられる
2	Being breathless never interrupts my conversations	息切れで自分の発言が中断することは全くない	息切れで自分の発言が中断することは全くない
	Being breathless always interrupts my conversations	息切れでいつも自分の発言が中断する	息切れでいつも自分の発言が中断する
3	I do not need to rest during the day	日中，安静にする必要はない	日中，安静にする必要はない
	I always need to rest during the day	日中，常に安静にしている必要がある	日中，常に安静にしている必要がある
4	I do not feel exhausted	疲れ切っていると感じることはない	疲れ切っていると感じることはない
	I always feel exhausted	常に疲れ切っていると感じている	常に疲れ切っていると感じている
5	I have lots of energy	活力に満ち溢れている	活力に満ち溢れている
	I have no energy at all	活力がまったくない	活力がまったくない
6	When I walk up one flight of stairs I am not breathless	階段の踊り場まで登っても息切れしない	階段を8段登っても息切れしない
	When I walk up one flight of stairs I am very breathless	階段の踊り場まで登っただけでひどく息切れする	階段を8段登っただけでひどく息切れする
7	I am confident out in public places/crowds despite my PH	肺高血圧症であっても公共の場所や人ごみの中に行く自信がある	肺高血圧症であっても公共の場所や人ごみの中に行く自信がある
	I am not confident at all in public places/crowds because of my PH	肺高血圧症のため，公共の場所や人ごみの中に行く自信はまったくない	肺高血圧症のため，公共の場所や人ごみの中に行く自信はまったくない
8	PH does not control my life	肺高血圧症は自分の生活にまったく制限を与えていない	肺高血圧症は自分の生活にまったく制限を与えていない
	PH completely controls my life	肺高血圧症によって自分の生活が完全に制限されてしまっている	肺高血圧症によって自分の生活が完全に制限されてしまっている
9	I am independent	自立して生活している	自立して生活している
	I am completely dependent	完全に誰かに頼って生活している	完全に誰かに頼って生活している
10	I never feel like a burden	周囲への負担は感じない	周囲への負担は感じない
	I always feel like a burden	常に周囲への負担を感じる	常に周囲への負担を感じる
	Total, Date	合計，実施日	合計，実施日

体に問題はないと判断した．

その他，設問3の「安静」の度合い，設問4の「疲れ切っている」の意味，設問5の「活力」の意味，設問9の「自立」の意味（経済的自立なのか，日常生活動作の自立なのか），設問10の「負担」の意味（精神的負担なのか，肉体的負担なのか）について，それぞれ1人からわかりにくいという意見があったが，どの参加者も問題なく回答できていたため，日本語の変更は不要と判断した．

また，質問票全体の印象について，複数の参加者から，老眼のため字が小さくて見づらい．文字は青色より黒色の方が見やすい，番号が薄くて見えない等，見づらさを訴える意見があった．説明文は，原作版の文字色に合わせて青色にしていたが，これらの意見を受け，読みやすくするため黒色に変更した．また，各項目のフォントサイズも大きくした．

パイロットテストの結果およびそれを踏まえた上記検



emPHasis10

病院名

氏名

生年月日

このアンケートは肺高血圧症(ＰＨ)があなたの生活にどれくらいの影響を与えているか確認するために作成されています。下記のすべての質問に対して、あなたの最近の肺高血圧症における生活状態を最もよく表す番号の一つにチェックをしてください。

下の各項目のうち、あなたの生活状態を最もよく表現している□にチェック(✓)を入れてください。

自分の息切れによって落胆することはない	0 1 2 3 4 5	自分の息切れによって非常に落胆させられる
息切れで自分の発言が中断することは全くない	0 1 2 3 4 5	息切れでいつも自分の発言が中断する
日中、安静にする必要はない	0 1 2 3 4 5	日中、常に安静にしている必要がある
疲れ切っていると感じることはない	0 1 2 3 4 5	常に疲れ切っていると感じている
活力に満ち溢れている	0 1 2 3 4 5	活力がまったくない
階段を８段登っても息切れしない	0 1 2 3 4 5	階段を８段登っただけでひどく息切れする
肺高血圧症であっても公共の場所や人ごみの中に行く自信がある	0 1 2 3 4 5	肺高血圧症のため、公共の場所や人ごみの中に行く自信はまったくない
肺高血圧症は自分の生活にまったく制限を与えていない	0 1 2 3 4 5	肺高血圧症によって自分の生活が完全に制限されてしまっている
自立して生活している	0 1 2 3 4 5	完全に誰かに頼って生活している
周囲への負担は感じない	0 1 2 3 4 5	常に周囲への負担を感じる

合計: 実施日:

pha UK pulmonary hypertension association

JAPHR Japan PH Registry

MANCHESTER 1824 The University of Manchester

図1 日本語版emPHasis-10．本指標は，原作者かつ共著者であるDr. Janelle Yorkeを介して著作権者より許可を得て掲載．

討内容については原作者に報告し，変更内容についても了承を得た．こうして，言語的妥当性を担保した「日本語版emPHasis-10」を確定した（図1）．なお，日本語版emPHasis-10の著作権は原作者のPHA UKに帰属する．研究目的であれば無償で使用できるが，非営利目的で使用する場合でも，原作者より使用許諾を得る必要がある．

考　察

今回我々は，肺高血圧症患者のQOLを評価するためのemPHasis-10をわが国でも利用可能にするため，言語的妥当性を担保した日本語翻訳版を作成した．他言語で作成された質問票の翻訳版を作成する際には，原作版の内容との整合性を保ちながら，文化的背景や言語の違いを考慮し，日本語としても違和感のない表現を目指す必要がある．そのため，日本語暫定版を作成する過程では，原作版で用いられている用語の概念を都度確認し，その概念を適切に表現できるような日本語訳を検討した．そのうえで，パイロットテストを実施し，実際にこのツールを使用することになるであろう日本人患者にとっても，理解しやすい，あるいは受け入れやすいものであるかを確認し，最終的な日本語版を確定した．

肺高血圧症患者のQOL評価指標・PRO指標には，emPHasis-10のほかにもCambridge Pulmonary Hypertension Outcome Review (CAMPHOR)[12]やPAH-SYMPACT®[13]などがあるが，emPHasis-10は臨床現場での使用も意図して開発された経緯があるように，短く，回答や評価も容易であるため，治療の経時的評価のためにも利用しやすく，その使用は今後ますます広がっていくものと思われる．また，日本語以外の他言語にもすでに翻訳されていることから，国際的な指標とも言えるemPHasis-10を用いて今後評価を行っていけば，英語圏のみならずその他の地域との国際比較も可能となる．また疾患特異的なPRO指標は臨床研究や患者レジストリーにおいても今後ますます重要なアウトカムや測定項目になることが期待されるため，その意味でも本研究により国際的に使用されている疾患特異的なPRO指標が日本語圏において使用できることになったことは意義深い．

今回，一連の検討を経て，言語的に妥当な翻訳がなされた日本語版emPHasis-10が完成し，わが国での使用も可能にはなったが，このツールを実際に臨床現場で使用していくには，質問票としての性能評価（計量心理学的妥当性の検討）も実施することが望ましいため，引き続き日本語版emPHasis-10の信頼性および妥当性の検討を予定している．

謝辞：本研究は，厚生労働科学研究費補助金　難治性疾患政策研究事業：疾患予後と医療の質の改善を目的とした多領域横断的な難治性肺高血圧症症例登録研究班および難治性呼吸器疾患・肺高血圧症に関する調査研究班の助成を受けたものである．翻訳版作成にあたりPRO指標の一般的な表現方法や，言語性妥当性の高い翻訳版作成に関して助言をいただいたMelinda Hull氏にお礼を申し上げます．

著者のCOI（conflicts of interest）開示：田村　雄一；報酬（アクテリオン ファーマシューティカルズ ジャパン），講演料（アクテリオン ファーマシューティカルズ ジャパン，日本新薬），研究費・助成金（アクテリオン ファーマシューティカルズ ジャパン），古川　明日香；寄付講座（日本新薬）．他は本論文発表内容に関して特に申告なし．

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Abstract

Development of a linguistically validated Japanese version of emPHasis-10, a patient-reported outcome measure for pulmonary hypertension

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The emPHasis-10 is a patient-reported outcome measure used to assess health-related quality of life in patients with pulmonary hypertension. The emPHasis-10 was originally developed in English and has been translated into various languages. This project aimed to develop a linguistically validated Japanese version of the emPHasis-10 to make the tool available in Japan. The process used to develop the Japanese version included forward translation, back translation, and cognitive debriefing. Initially, two translators independently translated the original tool into Japanese, taking into consideration the concepts described in the concept elaboration report provided by the original developer. A third translator then reconciled the two translations. Next, the reconciled version was translated back into English by a native English translator. The results were reviewed by the original developer to check concept equivalence. Finally, cognitive debriefing was conducted among 10 patients with pulmonary hypertension. The wording of one item was amended to clarify the meaning, and minor changes were made to improve readability. This translation and adaptation process resulted in a linguistically validated Japanese version of the emPHasis-10.