Efficacy and safety of oral pulmonary vasodilators in pulmonary veno-occlusive disease

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Abstract
Pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH) is a rare subtype of pulmonary hypertension with dismal prognosis. Limited data are available on the efficacy and safety of orally administered pulmonary vasodilators for PVOD/PCH. Whether and how systemic sclerosis (SSc) affects the clinical outcomes of PVOD/PCH is also unknown. This study aimed to determine the clinical and hemodynamic efficacy and safety of oral pulmonary vasodilators for PVOD/PCH and clarify the possible effects of SSc on the clinical presentation of PVOD/PCH. We retrospectively analyzed the clinical data of 15 patients with PVOD/PCH treated with oral pulmonary vasodilators in our department since 2001. Six of them had SSc. Oral pulmonary vasodilators were administered either as single agents (n = 10) or in combination (n = 5). Treatment improved the functional class of five patients, and pulmonary arterial pressure and pulmonary vascular resistance decreased by 10 ± 12 mmHg and 36 ± 19%, respectively (p < 0.05 for both, n = 13), whereas pulmonary edema developed in three patients. The mean survival was 3.9 years, and the 1- and 3-year survival rates were 93% and 65%, respectively. The clinical presentation, including survival, was similar between patients with and without SSc. In our PVOD/PCH cohort, oral pulmonary vasodilators caused pulmonary edema in 20% of patients, but more than 80% of patients experienced significant pulmonary vasodilatory effects, and the overall prognosis was better than that previously reported. SSc does not adversely affect the clinical outcomes of PVOD/PCH.

KEYWORDS
capillaries, pulmonary hypertension, treatment, vasodilation, veins

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Pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH) is a rare disorder of the pulmonary vasculature characterized by obstructive changes in the veins/venules and alveolar capillary proliferation. The prevalence of PVOD/PCH is extremely low and its outcomes remain dismal in contrast with other types of pulmonary hypertension (PH). Lung transplantation is the only definitive treatment for PVOD/PCH, and although PVOD/PCH is classified as a form of pulmonary arterial hypertension, the use of pulmonary vasodilators for pulmonary arterial hypertension has not been proven to be effective and causes pulmonary edema in some cases. However, oral drugs for pulmonary arterial hypertension have made significant progress in recent years, and there have been some reports of their efficacy in PVOD/PCH. In contrast to studies of early-phase drugs such as intravenous prostaglandin I2 and calcium channel blockers, these reports have been limited to a small number of cases, and detailed data on their efficacy and safety are lacking.

Recent reports have documented pulmonary vascular lesions corresponding to PVOD/PCH in systemic sclerosis (SSc). Connective tissue diseases, including SSc, are considered one of the underlying conditions of PVOD/PCH. However, it is not known whether and how SSc affects the clinical presentation and outcomes of patients with PVOD/PCH.

This study aimed to determine the efficacy and safety of oral pulmonary vasodilators and the possible impact of SSc on the clinical presentation and outcomes in patients with PVOD/PCH.

**METHODS**

**Study participants**

We retrospectively reviewed a database of patients diagnosed with PH confirmed by right heart catheterization at our department between January 2001 and July 2022, and extracted data of patients diagnosed with group 1 PH (pulmonary arterial hypertension) based on the current classification. Next, we selected patients with PVOD/PCH who fulfilled all of the following three criteria: (1) hemodynamically determined precapillary PH (mean pulmonary arterial pressure \(\geq 25\) mmHg, pulmonary artery wedge pressure \(\leq 15\) mmHg, and pulmonary vascular resistance \(\geq 3\) Wood units); (2) at least two of the following high-resolution computed tomography (CT) findings: (i) thickening of the interlobular septa, (ii) centrilobular ground-glass opacities, and (iii) mediastinal lymph node enlargement; and (3) diffusion capacity of the lung for carbon monoxide of \(<60\%\). Here, chest CT evaluations were performed by a certified radiologist who was blinded to the clinical data. Patients with findings indicative of interstitial lung disease on CT were excluded.

In the present study, we included patients with SSc when they met the above-mentioned criteria for PVOD/PCH. SSc was diagnosed by rheumatologists based on the 2013 American College of Rheumatology classification criteria of SSc. Patients with CT findings indicative of interstitial lung disease were also excluded as in patients without SSc.

Then, among the selected patients with and without SSc, those who were treated with oral pulmonary vasodilators and whose response to treatment could be evaluated based on pre- and posttreatment assessments were selected. Oral pulmonary vasodilators included phosphodiesterase-5 inhibitors (sildenafil and tadalafil), soluble guanylate cyclase stimulator (riociguat), endothelin receptor antagonist (bosentan, ambrisentan, and macitentan), and prostacyclin receptor stimulant (selexipag).

**Data collection**

The medical records of the study population were reviewed, and the following data were collected: baseline clinical data at the time of PVOD/PCH diagnosis, physical examination findings, World Health Organization functional class (WHO-FC), treatment details, and laboratory findings (blood tests, pulmonary function tests, echocardiography, high-resolution chest CT, 6-min walk distance, and right heart catheterization data). We also collected data on the pulmonary vasodilators and the patients’ response to treatment, including the oxygenation status, imaging data, follow-up right heart catheterization data, and survival.

Regarding the decision-making on the use of oral vasodilator, it was left to the discretion of the physician in charge. Basically, an oral vasodilator was started as a single agent and, if it was well tolerated without any signs/symptoms of pulmonary edema, an addition of another vasodilator was carefully considered.

The present study was approved by the review board of the institution. Owing to the retrospective nature of this study, informed consent was obtained using the opt-out method. The study was performed in accordance with the 1964 Declaration of Helsinki and its later amendment.

**Analysis**

Categorical variables are presented as numbers and percentages; continuous variables are presented as the
median (25%–75%). Continuous and categorical variables were compared between or among groups using Wilcoxon’s rank sum test or the χ² test. Changes in the clinical parameters before and after the introduction of oral pulmonary vasodilators were evaluated using the Wilcoxon signed-rank test for continuous variables and χ² test for categorical variables, and comparisons of changes between groups were made by an analysis of variance.

Five different analyses were performed. First, the basic statistics of the overall population and comparison of data between patients with and without SSc were calculated. Second, changes in clinical parameters before and after the introduction of oral pulmonary vasodilators were analyzed (if patients received more than one regimen, data obtained before and after the first regimen were analyzed). Third, to identify potential factors by which the response to PAH drugs could be predicted in advance to treatment, baseline data were compared between groups with or without improvement according to WHO-FC and satisfactory clinical responses, defined by the following criteria: WHO-FC I or II, a 6-min walk distance of at least 440 m, and a cardiac index of 2.5 L/min/m² at the follow-up assessment. We also evaluated the hemodynamic response by the %change in PVR ([PVR at follow-up] − [baseline PVR])/[baseline PVR]), and analyzed the relationship of %change in PVR with the baseline CT findings suggestive of PVOD/PCH. To further examine the relationship between the baseline characteristics and hemodynamic response, patients were equally divided into three groups—good, moderate, and poor hemodynamic responders—and baseline parameters were compared between these three groups. Fourth, baseline clinical parameters were compared between patients who developed pulmonary edema after the oral pulmonary vasodilator treatment and those who did not. Pulmonary edema was diagnosed when both congestion on imaging (chest radiography or chest CT) and worsening hypoxemia were present. Finally, survival was analyzed using Kaplan–Meier curves, log rank tests, and Cox proportional hazard models. Survival was compared between the three groups according to hemodynamic response to pulmonary vasodilators and to presence or absence of SSc.

RESULTS

The selection process of cases for analysis is shown in Figure 1. There were 352 patients with PH in our database, and 15 of them met the inclusion criteria for this study. Of the 15 cases, 6 were diagnosed with SSc as well as PVOD/PCH.

Baseline data at the time of PVOD/PCH diagnosis are shown in Table 1. Of the 15 patients, 11 (73%) were women, and the median age was 68 years. The median

FIGURE 1 Flow of patient selection. CCB, calcium channel blocker; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVOD/PCH, pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis; SSc, systemic sclerosis.
|                              | Total | Without SSc | With SSc | p-value (without vs. with SSc) |
|------------------------------|-------|-------------|----------|--------------------------------|
| **N**                        | 15    | 9           | 6        |                                |
| **Age (year)**               | 68 (61–75) | 68 (64–72) | 73 (49–81) | 0.814                         |
| **Male, n (%)**              | 4 (27%) | 4 (44%)     | 0 (0%)   | 0.103                          |
| **Body mass index (kg/m²)**  | 22.9 (20.0–26.3) | 22.9 (18.7–28.3) | 22.6 (20.4–26.1) | 1                               |
| **Smoking history (never/past/current)** | 9/6/0 | 4/5/0       | 5/1/0    | 0.287                          |
| **Smoking history (pack years)** | 0 (0–51) | 12 (0–59.3) | 0 (0–7.5) | 0.111                          |
| **Cardiovascular comorbidities** |        |             |          |                                |
| Body mass index ≥30 kg/m², n (%) | 2 (13%) | 2 (22%)     | 0 (0%)   | 0.486                          |
| Arterial hypertension, n (%) | 7 (47%) | 4 (44%)     | 3 (50%)  | 1                               |
| Diabetes mellitus, n (%)     | 3 (20%) | 1 (11%)     | 2 (33%)  | 0.525                          |
| Coronary heart disease, n (%) | 1 (7%)  | 1 (11%)     | 0 (0%)   | 1                               |
| Atrial fibrillation, n (%)   | 0 (0%)  | 0 (0%)      | 0 (0%)   | 1                               |
| **Duration from the onset of PH (months)** | 14 (6–31) | 14 (10–46) | 10 (5–26) | 0.289                          |
| **Duration from the diagnosis of SSc (months)** | NA     | NA          | 1 (0–64) | NA                             |
| **WHO-FC (I/II/III/IV)**     | 0/1/12/2 | 0/1/8/0     | 0/0/4/2  | 0.143                          |
| **6MWD (m)**                 | 210 (155–326) | 322 (206–430) | 150 (130–180) | 0.053                          |
| **Blood test**               |        |             |          |                                |
| BNP (pg/ml)                  | 344 (47–723) | 344 (134–605) | 378 (31–1507) | 1                               |
| Scl70 antibody (+), n (%) (n = 14) | 0 (0%) | 0 (0%) (n = 8) | 0 (0%)   | 1                               |
| Centromere antibody (+), n (%) (n = 12) | 7 (58%) | 2 (33%) (n = 6) | 5 (83%) | 0.242                          |
| RNP antibody (+), n (%) (n = 14) | 0 (0%) | 0 (0%) (n = 8) | 0 (0%)   | 1                               |
| RNA polymerase III Ab (+), n (%) (n = 5) | NA | NA | 5 (100%) (n = 5) | NA                             |
| **Arterial blood gas analysis** |        |             |          |                                |
| PO₂ (torr)                   | 62 (57–69) | 64 (51–69) | 60 (58–70) | 0.724                          |
| PCO₂ (torr)                  | 33 (25–36) | 33 (25–34) | 34 (28–40) | 0.289                          |
| **Pulmonary function test**  |        |             |          |                                |
| %FVC (%) (n = 14)            | 104 (90–112) | 103 (90–112) | 104 (90–119) (n = 5) | 0.842                          |
| %FEV₁ (%) (n = 14)           | 102 (85–104) | 102 (90–105) | 89 (79–115) (n = 5) | 0.386                          |
| FEV₁/FVC (%) (n = 14)        | 75 (68–81) | 77 (68–80) | 74 (62–91) (n = 5) | 0.842                          |
| %DLCO (%)                    | 26 (22–34) | 26 (21–32) | 27 (24–37) | 0.556                          |
| %Kco (%)                     | 32 (22–37) | 32 (20–39) | 33 (26–40) | 0.768                          |
| **Chest CT findings suggestive of PVOD/PCH** |        |             |          |                                |
| Interlobular septal thickening, n (%) | 13 (87%) | 9 (100%) | 4 (67%) | 0.143                          |
| Centrilobular ground-glass opacities, n (%) | 13 (87%) | 8 (89%) | 5 (83%) | 1                              |
| Mediastinal lymph node enlargement, n (%) | 13 (87%) | 8 (89%) | 5 (83%) | 1                              |
| Number of findings suggestive of PVOD/PCH (1/2/3) | 0/6/9 | 0/2/7 | 0/4/2 | 0.096                          |
diffusion capacity of the lung for carbon monoxide (%DLco) was reduced to 26%, and the transfer factor (%Kco) was also low, at 32%. The chest CT showed thickening of the interlobular septa, centrilobular opacities/nodules, and enlarged mediastinal lymph nodes in 13 (87%) patients and, by definition, at least two of these findings were present in each patient. Representative CT images are shown in Figure 2. MPAP was 42 (39–48) mmHg and PVR was 10.0 (9.3–13.4) Wood units. Of the 15 patients, 4 (3 without and 1 with SSc) had pathologically confirmed PVOD/PCH diagnosis at autopsy. None of the patients had a family history of PVOD/PCH. One patient without SSc had exposure to medications/toxins that may induce PVOD/PCH, i.e., cyclophosphamide, before the diagnosis. Lung transplantation was not indicated for any of the 15 patients because of age or comorbidities. Genetic analysis of seven PH-related genes including eukaryotic translation initiation factor 2 alpha kinase 4 was

**TABLE 1 (Continued)**

| Pulmonary hemodynamics                        | Total       | Without SSc | With SSc    | p-value (without vs. with SSc) |
|-----------------------------------------------|-------------|-------------|-------------|-------------------------------|
| PAWP (mmHg)                                   | 7 (3–9)     | 7 (3–11)    | 6 (3–8)     | 0.551                         |
| MPAP (mmHg)                                   | 42 (39–48)  | 42 (40–49)  | 40 (27–50)  | 0.408                         |
| RAP (mmHg)                                    | 5 (2–8)     | 5 (2–8)     | 7 (2–11)    | 0.374                         |
| CO (L/min)                                    | 3.1 (2.9–3.5) | 3.3 (3.0–3.4) | 2.9 (2.5–4.4) | 0.443                         |
| CI (L/min/m²)                                 | 2.0 (1.8–2.3) | 2.0 (1.8–2.3) | 1.9 (1.6–3.3) | 0.556                         |
| PVR (WU)                                      | 10.9 (9.3–13.4) | 10.9 (9.5–13.1) | 11.1 (6.9–16.9) | 0.953                         |
| Pulmonary arterial compliance                 | 1.1 (0.8–1.5) | 1.1 (0.8–1.4) | 0.9 (0.7–2.9) | 0.724                         |

Abbreviations: BNP, brain-type natriuretic peptide; CI, cardiac index; CO, cardiac output; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, functional vital capacity; KCO, transfer factor; MPAP, mean pulmonary arterial pressure; 6MWD, 6-min walk distance; PAWP, pulmonary artery wedge pressure; PCH, pulmonary capillary hemangiomatosis; PCO₂, partial pressure of carbon dioxide; PH, pulmonary hypertension; PO₂, partial pressure of oxygen; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; RNA, ribonucleic acid; RNP, anti-ribonucleoprotein; Scl70, anti-scleroderma antibody; SSc, systemic sclerosis; WHO–FC, World Health Organization–functional class; WU, Wood unit.

*aExamined under room-air conditions except for one patient who was examined under 3 L/min of nasal oxygen.

*bCalculated by [stroke volume (=RHC-derived cardiac output divided by heart rate)]/[systolic pulmonary arterial pressure – diastolic pulmonary arterial pressure].

**FIGURE 2** Representative computed tomography images of the chest. (a) Thickening of the interlobular septa (arrow heads), (b) centrilobular ground-glass opacities, and (c) mediastinal lymph node enlargement (arrow heads) can be seen.
performed in five patients using next generation sequencing (Kazusa DNA Research Institute, Chiba, Japan); none of the patients exhibited biallelic eukaryotic translation initiation factor 2 alpha kinase 4 mutations.

The therapeutic effects of oral pulmonary vasodilators are summarized in Table 2. Ten patients received one drug, while five received two or more drugs. The most commonly used drug was a phosphodiesterase-5 inhibitor (n = 10, 67%), followed by endothelin receptor antagonist (n = 9, 60%), riociguat (n = 1, 7%), and selexipag (n = 1, 7%). Three (20%) of the patients developed pulmonary edema 3, 7, and 20 days after starting the causative drug (sildenafil, tadalafil, and macitentan). In all three patients, the pulmonary edema resolved with the discontinuation of the causative drug and use of diuretics. Notably, in one of the three patients, pulmonary edema developed after adding macitentan to the preceding tadalafil. However, she subsequently fully recovered from the event after the cessation of macitentan and was able to undergo a follow-up assessment while taking tadalafil. Thirteen patients underwent follow-up right heart catheterization 4 (3–7) months after initiation of pulmonary vasodilators. As presented in Table 2, MPAP and PVR significantly decreased (MPAP, −10 ± 12 mmHg; PVR, −36 ± 19%), and the pulmonary arterial compliance increased from 1.1 to 1.9 ml/mmHg (p < 0.01). The parameters listed in this table did not differ in those with and without SSc.

Changes in the WHO-FC, partial pressure of arterial oxygen, MPAP, and PVR after the introduction of oral vasodilators in each patient are shown in Figure 3. WHO-FC improved in five of the patients (Figure 3a). Post-treatment partial pressure of arterial oxygen was obtained in nine patients (Figure 3b), and only one patient who developed pulmonary edema exhibited a notable worsening in partial pressure of arterial oxygen (case with an asterisk). As shown in Figure 3c,d, MPAP decreased in 9 of 13 patients (p = 0.012 by paired t-test), and PVR also decreased in all 13 patients (p < 0.001 by paired t-test).

Comparing patients whose WHO-FC improved (n = 5) with patients whose WHO-FC did not improve (n = 10) showed no significant differences in any of the baseline parameters listed in Table 1. The criteria for a “satisfactory clinical response” were not met in any of the 15 patients after treatment and thus, comparative analysis of the baseline parameters between those with and without the satisfactory clinical response was not conducted.

Regarding the relationship between the number of CT findings suggestive of PVOD/PCH at baseline and the %change in PVR, the %change in PVR of patients with two CT findings was 43 [26–57] which was slightly higher than that of those with three findings with 37 [7–48], although the difference was not significant (p = 0.391).

Table 3 shows the clinical parameters of the three groups with poor, moderate, and good hemodynamic responses. There were five patients in each group. The % change in PVR was −10 ± 6% in the poor response group (cut-off range: −7 to −16); −35 ± 10% in the moderate response group (cut-off range: −22 to −43%); and −54 ± 8% in the good response group (cut-off range: −48 to −67). Two of the patients did not undergo follow-up right heart catheterization because of pulmonary edema. In these two cases, during the episodes of pulmonary edema, brain-type natriuretic peptide BNP levels increased, and imaging studies (chest X-ray, CT, and echocardiography) indicated deteriorated pulmonary hemodynamics after the pulmonary vasodilating treatment. Thus, these two cases were classified into the poor hemodynamic response group. Comparing the three groups, the number of chest CT findings suggestive of PVOD/PCH (p = 0.045) was associated with the %change in PVR. Also, although the relationship did not reach statistical significance, the %transfer factor (%Kco) tended to be higher in those with better hemodynamic response (p = 0.064). Other parameters did not differ between the three groups. Also, comparison of survival indicated no significant differences between the three groups (log rank test: p = 0.318; Cox proportional Hazard Model: p = 0.294).

Table 4 shows the results of the comparison between the groups with (n = 3) and without treatment-induced pulmonary edema (n = 12). The pulmonary arterial compliance was lower for patients with pulmonary edema, although the difference did not reach statistical significance (p = 0.08). There was no significant difference in other indices between the groups. The prevalence of pulmonary edema was also compared between those with two CT findings suggestive of PVOD/PCH (n = 6) and those with three such CT findings (n = 9); prevalence between the two groups did not differ significantly (1/6 and 2/9, respectively; p = 0.79).

Figure 4 shows the survival curves for the 15 patients, with a mean survival of 3.9 years, and 1- and 3-year survival rates of 93% and 65%, respectively (Figure 4a). There were no statistical differences between patients with and without SSc (Figure 4b).

DISCUSSION

In the present retrospective study of 15 patients with PVOD/PCH, we examined the efficacy and safety of oral pulmonary vasodilators. We also analyzed the possible impact of SSc on the presentation and outcomes of PVOD/PCH. The main findings of this study were as follows: (1) after the use of oral pulmonary vasodilators,
### TABLE 2  Therapeutic effect of oral pulmonary vasodilators

| Administered oral pulmonary vasodilators | Pretreatment | Posttreatment | *p*-values (pre vs. post) |
|-----------------------------------------|--------------|--------------|--------------------------|
| Monotherapy, n (%)                      | –            | 10 (67%)     |                          |
| Sildenafil, n (%)                        | –            | 2 (20%)      |                          |
| Tadalafil, n (%)                        | –            | 4 (40%)      |                          |
| Bosentan, n (%)                         | –            | 3 (30%)      |                          |
| Macitentan, n (%)                       | –            | 1 (10%)      |                          |
| Dual combination therapy, n (%)         | –            | 4 (27%)      |                          |
| Sildenafil + bosentan, n (%)             | –            | 1 (25%)      |                          |
| Sildenafil + ambrisentan, n (%)          | –            | 2 (50%)      |                          |
| Riociguat + macitentan, n (%)           | –            | 1 (25%)      |                          |
| Triple combination therapy, n (%)       | –            | 1 (7%)       |                          |
| Tadalafil + macitentan + selexipag, n (%)| –            | 1 (100%)     |                          |
| Duration between the pre- and posttreatment assessment (months) | – | 4 (3–7) | |
| Development of pulmonary edema, n (%)   | –            | 3 (20%)      |                          |
| WHO-FC (I/II/III/IV) 0/1/11/3           |              | 0/4/8/3      | 0.563                    |
| Oxygen supplementation (L/min) (n = 13, those with pulmonary edema excluded) | 0 (0–2.5) | 2 (0–3) | 0.175 |
| Number of patients who had “satisfactory clinical response” | NA | 0 | |
| BNP (pg/ml)                             | 260 (47–723) | 47 (11–395) | 0.277                    |
| %DLCO (n = 11)                          | 27 (22–31)  | 34 (27–35)  | 0.067                    |
| %KCO (n = 11)                           | 32 (23–37)  | 32 (25–42)  | 0.506                    |
| Pulmonary hemodynamics (n = 13)         |              |              |                          |
| PAWP (mmHg)                             | 7 (3–9)      | 5 (4–9)      | 0.782                    |
| MPAP (mmHg)                             | 42 (38–48)   | 32 (26–38)   | 0.012                    |
| RAP (mmHg)                              | 5 (2–8)      | 4 (1–6)      | 0.422                    |
| CO (L/min)                              | 3.0 (2.9–3.3)| 3.6 (3.3–4.2)| 0.022                    |
| CI (L/min/m²)                           | 2.0 (1.7–2.2)| 2.4 (2.1–2.6)| 0.052                    |
| PVR (WU)                                | 11.9 (9.5–13.2)| 6.6 (5.6–9.5)| <0.001                   |
| Pulmonary arterial compliance (ml/mmHg) b| 1.1 (0.8–1.6)| 1.9 (1.1–2.3)| 0.005                    |

Abbreviations: BNP, brain-type natriuretic peptide; CI, cardiac index; CO, cardiac output; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, functional vital capacity; KCO, transfer factor; MPAP, mean pulmonary arterial pressure; 6MWD, 6-min walk distance; PAWP, pulmonary artery wedge pressure; PCH, pulmonary capillary hemangiomatosis; PCO2, partial pressure of carbon dioxide; PH, pulmonary hypertension; PO2, partial pressure of oxygen; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; RNA, ribonucleic acid; RNP, anti-ribonucleoprotein; ScI70, anti-scleroderma antibody; SSc, systemic sclerosis; WHO–FC, World Health Organization–functional class; WU, Wood unit.

aDefined by achieving the following three criteria: WHO–FC I or II, a 6-min walk distance of at least 440 m, and a cardiac index of 2.5 L/min/m² at follow-up.

bCalculated by [stroke volume (=RHC-derived cardiac output divided by heart rate) divided by [systolic pulmonary arterial pressure – diastolic pulmonary arterial pressure].
WHO-FC improved in 33%, PVR decreased in 86%, and pulmonary edema developed in 20% of the patients; (2) the %change in PVR was associated with the number of PVOD/PCH-related CT findings and %transfer factor before treatment; (3) pulmonary edema tended to develop in patients with low pulmonary arterial compliance before treatment; (4) the mean posttreatment survival was approximately 4 years, and the 1- and 3-year survival rates were 93% and 65%, respectively; and (5) coexisting SSc did not affect the clinical presentation of PVOD/PCH.

Only a few studies have reported the efficacy of pulmonary vasodilators in patients with PVOD/PCH. In an early report by Holcomb et al., clinical improvements were observed in 3 (27%) of 11 patients. In another study, Montani et al. reported that only 3 (5%) of 64 patients exhibited satisfactory clinical responses. Consistent with these studies, in the present study, WHO-FC improved in 33% of patients, and none of the 15 patients met the criteria of a satisfactory clinical response. In contrast, two studies exclusively using continuous prostaglandin I$_2$ treatment reported improved WHO-FC in 7 of 12 patients (58%) and in 8 of 8 (100%) patients. Although the disease severity varied in these studies, the clinical benefit of oral pulmonary vasodilators may be limited compared with that of carefully administered intravenous prostaglandin I$_2$.

To date, few studies have reported the response of pulmonary hemodynamics to oral pulmonary vasodilators in PVOD/PCH. Montani et al. reported that MPAP remained unchanged whereas PVR decreased from 10 to 8 Wood units after treatment in 64 patients. However, treatment in this study included both oral and intravenous vasodilators, and the effect of oral drugs alone was not examined. Similarly, other reports did not exclusively analyze a subset treated with oral drugs; thus, the present study is the first, except case reports, to demonstrate the hemodynamic effects of oral pulmonary vasodilators alone. In our study, both MPAP and PVR significantly improved from 42 to 32 mmHg and from 11.9 to 6.6 Wood units, respectively, indicating the relatively strong vasodilatory effect of oral drugs. Notably, there was a weak but significant association between %change in PVR and CT findings suggestive of PVOD/PCH ($p = 0.045$), suggesting that the pretreatment pulmonary CT might be useful for predicting the pulmonary vasodilatory effect of oral drugs. Likewise, the %transfer factor (%Kco) tended to be higher in those with better hemodynamic responses to vasodilating treatment ($p = 0.064$), similarly suggesting a possible role of %Kco for predicting vasodilatory effects. Of note, in our study, specific drugs such as phosphodiesterase-5 inhibitors, endothelin receptor antagonist, or their combined use were not shown to provide greater vasodilatory effect over other drugs or monotherapy. More studies are needed to predict the subset of patients with PVOD/PCH that is more likely to have a favorable hemodynamic response to oral vasodilators.

Pulmonary edema is the most critical side effect of vasodilator use in PVOD/PCH. In previous reports, the incidence of pulmonary edema varied widely, ranging from $<10\%$ to 20%–60%, and up to 100%. In the present study, pulmonary edema occurred in 20% of patients, suggesting that the risk of pulmonary edema associated with oral pulmonary vasodilators is not particularly high. However, as mentioned above, the incidence of drug-induced pulmonary edema varied widely among reports, possibly due to differences in the treatment regimens, severity of PVOD/PCH, and definition of pulmonary edema. More studies are needed to determine how frequently pulmonary edema occurs in response to oral vasodilators.

**FIGURE 3** Response to oral pulmonary vasodilator. (a) Changes in the WHO-functional class, (b) PaO$_2$, (c) mean pulmonary arterial pressure (MPAP), and (d) pulmonary vascular resistance (PVR) before and after the use of oral pulmonary vasodilators. PaO$_2$, partial pressure of arterial oxygen; WHO, World Health Organization; WU, Wood units.
**Table 3** Comparison of clinical parameters between good, moderate, and poor hemodynamic responses to oral pulmonary vasodilators

|                                | Patients with poor hemodynamic response (%PVR change bottom 5) | Patients with moderate hemodynamic response (%PVR change middle 5) | Patients with good hemodynamic response (%PVR change top 5) | p-values |
|--------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------|----------|
| **N**                          | 5                                                             | 5                                                               | 5                                                          |          |
| **Age (year)**                 | 67 (61–77)                                                    | 69 (54–81)                                                       | 68 (59–73)                                                 | 0.691    |
| **Male, n (%)**                | 2 (40%)                                                       | 1 (20%)                                                         | 1 (20%)                                                    | 1        |
| **Duration from the onset of PH (months)** | 12 (7–32)                                                | 11 (4–22)                                                        | 31 (9–52)                                                  | 0.403    |
| **Systemic sclerosis, n (%)**  | 1 (20%)                                                       | 3 (60%)                                                         | 2 (40%)                                                    | 0.8      |
| **WHO–FC (I/II/III/IV)**       | 0/1/4/0                                                       | 0/0/3/2                                                         | 0/0/5/0                                                    | 0.286    |
| **6MWD (m)**                   | 327 (240–532) (n = 3)                                        | 150 (150–150) (n = 1)                                           | 176 (140–287) (n = 4)                                      | 0.132    |
| **BNP (pg/ml)**                | 47 (23–1400)                                                  | 434 (145–1528)                                                  | 487 (138–712)                                              | 0.543    |
| **PO2 (torr)**                 | 68 (58–75)a                                                   | 58 (48–60)                                                       | 66 (54–73)                                                 | 0.164    |
| **Pulmonary function test**    |                                                               |                                                                 |                                                            |          |
| %DLCO (%)                      | 23 (16–32)                                                    | 25 (22–31)                                                       | 29 (24–40)                                                 | 0.326    |
| %KCO (%)                       | 22 (12–35)                                                    | 31 (24–36)                                                       | 40 (30–45)                                                 | 0.064    |
| Chest CT findings suggestive of PVOD/PCH |                                    |                                                                 |                                                            |          |
| Interlobular septal thickening, n (%) | 5 (100%)                                              | 4 (80%)                                                          | 4 (80%)                                                    | 1        |
| Centrilobular ground–glass opacities, n (%) | 5 (100%)                                              | 3 (60%)                                                          | 5 (100%)                                                   | 0.286    |
| Mediastinal lymph node enlargement, n (%) | 5 (100%)                                           | 4 (80%)                                                          | 4 (80%)                                                    | 1        |
| Number of findings suggestive of PVOD/PCH (1/2/3) | 0/0/5                                                 | 0/4/1                                                            | 0/2/3                                                      | 0.045    |
| **Pulmonary hemodynamics**     |                                                               |                                                                 |                                                            |          |
| PAWP (mmHg)                    | 3 (3–9)                                                       | 7 (4–10)                                                        | 8 (3–11)                                                   | 0.598    |
| MPAP (mmHg)                    | 40 (39–48)                                                    | 42 (33–48)                                                       | 43 (32–54)                                                  | 0.932    |
| RAP (mmHg)                     | 2 (1–8)                                                       | 8 (6–11)                                                         | 4 (1–8)                                                    | 0.160    |
| CO (L/min)                     | 3.1 (2.9–3.7)                                                 | 3.4 (2.6–4.7)                                                   | 3.0 (2.7–3.3)                                              | 0.492    |
| CI (L/min/m²)                  | 2.1 (1.9–2.9)                                                 | 2.0 (1.7–3.1)                                                   | 1.8 (1.7–2.2)                                              | 0.403    |

(Continues)
develops in various populations treated with different vasodilators.

The possible risk factors for the development of pulmonary edema have been examined in previous studies, and no such factors have been identified. Interestingly, in our study, the pulmonary arterial compliance tended to be low in patients with drug-induced pulmonary edema, suggesting that some parameters of the pulmonary vasculopathy may serve as unique predictors. Alternatively, prior studies have reported that pulmonary edema develops in an average of 9 days or a median of 1 month after the commencement of vasodilator therapy. In the present study, the onset of pulmonary edema ranged from 3 to 20 days posttreatment. As such, after using pulmonary vasodilators, careful observation is necessary for a few days to approximately 1 month for the early identification of pulmonary edema and a prompt response. Further investigation is needed to determine the risk factors, time of onset, and management of pulmonary edema in patients with PVOD/PCH treated with vasodilators.

The prognosis of PVOD/PCH is reportedly very poor. For example, in one early study, the 1-year survival rate was 28%; in another, the mean survival time was 12 months. However, the survival has improved according to more recent studies. For example, the 1-year survival rate was approximately 70% in 94 PVOD/PCH cases. In our study, the 1-year survival rate was 93%, and mean survival time was 3.9 years; these findings are better than those in early reports and at least comparable to those in recent studies. One possible reason for the better prognosis in recent reports, including ours, may be milder disease severity. In fact, in an early study by Holcomb et al., the MPAP of the patients was 65 mmHg, whereas in two recent studies, it was lower at 58 mmHg and 46 mmHg. In the present study, MPAP at diagnosis was 42 mmHg, suggesting that the disease may have been milder or in its early stages. It should also be noted that the diagnostic criteria for PVOD/PCH have been inconsistent between reports. For example, in the report by Holcomb et al., the pathological diagnosis of PVOD/PCH was obtained in all 11 patients, whereas diffusion capacity of the lung for carbon monoxide was >60% in 5 of 11 patients. This contrasts with the recent studies, including ours, where diffusion capacity of the lung for carbon monoxide of <60% was included in the inclusion criteria. Additionally, the difference may have been due to variation in treatments. In previous reports, oral calcium channel blockers or intravenous prostaglandin I_2_ were primarily used, whereas in recent reports, current oral pulmonary vasodilators have been more prevalent. Finally, the involvement of reporting/publication bias should be considered. Taken together, more information is needed to determine whether the prognosis of
PVOD/PCH has indeed improved in recent years, and if so, what factors were involved.

SSc is often complicated by PVOD/PCH-like lesions in the pulmonary vasculature. The coexistence of these two conditions is also important for treatment. Indeed, patients with SSc who have PVOD/PCH-like findings on CT often develop pulmonary edema with the use of pulmonary vasodilators and have poor

| TABLE 4 | Comparison of clinical parameters before oral vasodilating therapy of patients with and without pulmonary edema |
|---------|---------------------------------------------------------------------------------|
|         | Patients with pulmonary edema | Patients without pulmonary edema | p (with vs. without pulmonary edema) |
| N       | 3                               | 12                              |                                      |
| Age (year) | 74 (66–79)                     | 68 (60–74)                     | 0.471                               |
| Male/female | 0/3                             | 4/8                             | 0.517                               |
| Body mass index (kg/m²) | 18.6 (16.0–27.5)              | 22.9 (21.2–26.2)              | 0.312                               |
| Duration from the onset of PH (months) | 12 (6–31)                     | 14 (6–39)                      | 0.885                               |
| Systemic sclerosis, n (%) | 2 (67%)                         | 4 (33%)                        | 0.525                               |
| Use of pulmonary vasodilators, single/combination | 2/1                            | 7/5                            | 1                                    |
| Use of phosphodiesterase-5 inhibitor, n (%) | 3 (100%)                       | 7 (58%)                        | 0.506                               |
| Use of endothelin receptor antagonists, n (%) | 1 (33%)                        | 9 (75%)                        | 0.242                               |
| WHO-FC (I/II/III/IV) | 0/0/3/0                        | 0/1/9/2                        | 1                                    |
| BNP (pg/ml) | 702 (32–2456)                  | 302 (48–664)                   | 0.471                               |
| PO₂ (torr) | 68 (58–69)                     | 60 (53–68)                     | 0.387                               |

Pulmonary function test

- %DLCO (%) | 29 (22–34) | 26 (22–35) | 0.885 |
- %KCO (%) | 37 (16–37) | 32 (23–39) | 0.885 |

Chest CT findings suggestive of PVOD/PCH

- Interlobular septal thickening, n (%) | 2 (67%) | 11 (92%) | 0.371 |
- Centrilobular ground-glass opacities, n (%) | 3 (100%) | 10 (83%) | 1 |
- Mediastinal lymph node enlargement, n (%) | 3 (100%) | 10 (83%) | 1 |

- Number of findings suggestive of PVOD/PCH (1/2/3) | 0/1/2 | 0/5/7 | 0.815 |

Pulmonary hemodynamics

- PAWP (mmHg) | 7 (3–8) | 6 (3–9.8) | 0.884 |
- MPAP (mmHg) | 53 (39–57) | 41 (36.8–46) | 0.169 |
- RAP (mmHg) | 7 (1–10) | 5 (2–8) | 0.717 |
- CO (L/min) | 3.5 (2.8–4.0) | 3.1 (2.9–3.4) | 0.470 |
- CI (L/min/m²) | 2.6 (1.8–3.2) | 2 (1.8–2.3) | 0.312 |
- PVR (WU) | 14.5 (8.0–17.4) | 10.8 (9.3–12.9) | 0.386 |
- Pulmonary arterial compliance (ml/mmHg) | 0.8 (0.7–1.0) | 1.2 (0.8–1.6) | 0.083 |

Abbreviations: BNP, brain-type natriuretic peptide; CI, cardiac index; CO, cardiac output; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, functional vital capacity; KCO, transfer factor; MPAP, mean pulmonary arterial pressure; 6MWD, 6-min walk distance; PAWP, pulmonary artery wedge pressure; PCH, pulmonary capillary hemangiomatosis; PCO₂, partial pressure of carbon dioxide; PH, pulmonary hypertension; PO₂, partial pressure of oxygen; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; RNA, ribonucleic acid; RNP, anti-ribonucleoprotein; Scl70, anti-scleroderma antibody; SSc, systemic sclerosis; WHO–FC, World Health Organization–functional class; WU, Wood unit.

aData obtained under 3 L/m of nasal oxygen in one patient.

bCalculated by (stroke volume [=RHC-derived cardiac output divided by heart rate]) divided by (systolic pulmonary arterial pressure – diastolic pulmonary arterial pressure).
prognoses. However, a detailed comparison of PVOD/PCH with and without SSc has not yet been conducted. It can be speculated that the disease-specific pathophysiology of SSc may unfavorably affect the clinical presentations and outcome in SSc-associated PVOD/PCH. Notably, however, there were no significant differences in any PH-related parameters between the two groups with or without SSc. Further analyses are needed to clarify the possible impact of SSc on the development, clinical presentation, and outcomes of PVOD/PCH.

STUDY LIMITATIONS

This was a retrospective single-center study involving a small number of patients, hampering robust comparisons between groups with different treatments, treatment responses, with or without pulmonary edema, and survival. In particular, the comparison between the three groups with poor, moderate, and good hemodynamic response was an arbitrary analysis. Indeed, with the small sample size in this study, we were not able to identify robust predictors of hemodynamic response to PAH drugs. Second, because of the retrospective nature of the study, important parameters, such as partial pressure of arterial oxygen levels after treatment, were lacking in some patients. Third, the patients with SSc enrolled in this study were not representative of a general population of SSc because those with interstitial lung disease were excluded. This was necessary for a precise diagnosis of PVOD/PCH and should be considered when interpreting the results. Last, the pathological diagnosis was confirmed in only 4 of 15 patients, and the genetic analysis was performed in only 5 of 15 patients; therefore, detailed analyses based on these results could not be performed.

CONCLUSIONS

We retrospectively analyzed the clinical data of 15 patients with PVOD/PCH and found that oral pulmonary vasodilators caused clinical improvement in 33%, hemodynamic improvement in 87%, and pulmonary edema in 20% of the patients. The outcome was better than previously reported, and SSc did not affect the clinical outcome. The number of participants was small in the present study; however, considering the extreme rarity of the disease, the reported findings are useful for better characterization, future basic/clinical research, and better treatment and outcome of PVOD/PCH.

AUTHOR CONTRIBUTIONS

Junichi Nakamura and Ichizo Tsujino: conceived the original study design, collected and analyzed the data, and drafted the manuscript. Hideki Shima, Ayako Sugimoto, Toshitaka Nakaya, Takahiro Sato, Hiroshi Ohira, Taku Watanabe, and Masaru Suzuki: collected the data and reviewed the manuscript draft. Toshitaka Nakaya: analyzed the computed tomography images. Ryo Hisada and Masaru Kato: collected data from patients with SSc and reviewed them; and Satoshi Konno: supervised the entire study and reviewed the manuscript.
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obtained using the opt retrospective nature of this study, informed consent was no. 016
The present study was approved by the Institutional of interest.
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CONFLICTS OF INTEREST
Ichigo Tsujino

ETHICS STATEMENT
The present study was approved by the Institutional Review Board of Hokkaido University Hospital (approval
no. 016-0461, approval date: April 6, 2017). Owing to the retrospective nature of this study, informed consent was
obtained using the opt-out method. The study was performed in accordance with the 1964 Declaration of
Helsinki and its later amendment.

DATA AVAILABILITY STATEMENT
The corresponding author will respond to all readers’ inquiries regarding data that are related with the present
study and not presented in this manuscript.

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PULMONARY CIRCULATION

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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