

Effectiveness of phosphodiesterase-5 inhibitor therapy for portopulmonary hypertension

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JH Fisher, SR Johnson, C Chau, AT Kron, JT Granton. Effectiveness of phosphodiesterase-5 inhibitor therapy for portopulmonary hypertension. *Can Respir J* 2015;22(1):42-46.

BACKGROUND: Portopulmonary hypertension is associated with significant morbidity and mortality. Phosphodiesterase-5 inhibitor therapy is efficacious in other causes of WHO group I pulmonary arterial hypertension.

OBJECTIVE: To evaluate the efficacy and safety of phosphodiesterase-5 inhibitor therapy in patients with portopulmonary hypertension.

METHODS: A single-centre retrospective cohort study that included patients with a diagnosis of portopulmonary hypertension was performed. The primary outcome was change in pulmonary vascular resistance after six months of phosphodiesterase-5 inhibitor therapy. A secondary evaluation investigated the effect on other hemodynamic measurements, 6 min walk distance, functional class, safety outcomes and survival.

RESULTS: Of 1385 patients screened, 25 patients with portopulmonary hypertension were identified, of whom 20 received a phosphodiesterase-5 inhibitor. After six months, there was a significant decrease in pulmonary vascular resistance ($-236 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ [95% CI $-343 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ to $-130 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$]; $P<0.001$), mean pulmonary artery pressure (-8.9 mmHg [95% CI -13.7 mmHg to -4.2 mmHg]; $P=0.001$) and an increase in Fick cardiac output (0.9 L/min [95% CI 0.1 L/min to 1.6 L/min]; $P=0.02$). There was no change in 6 min walk distance. The proportion of subjects with a WHO functional class III or IV was significantly reduced at six months compared with baseline (18% versus 61%; $P=0.002$). Safety outcomes did not reveal any adverse events.

CONCLUSIONS: Phosphodiesterase-5 inhibitor therapy improved hemodynamics and functional class at six months in a cohort of patients with portopulmonary hypertension.

Key Words: *Phosphodiesterase inhibitors; Pulmonary hypertension; Pulmonary vascular resistance*

Portopulmonary hypertension (PoPH) is a serious complication of chronic liver disease that is associated with significant morbidity and mortality. PoPH is defined by the presence of pulmonary arterial hypertension (PAH) associated with portal hypertension in the absence of an alternative cause for PAH (1). PoPH is classified as 'group 1' pulmonary hypertension (2). This group includes other causes of PAH, including idiopathic, heritable and PAH due to drugs and connective tissue diseases (2). The pulmonary histopathological findings in PoPH and idiopathic PAH are identical (3). The median survival of untreated PoPH has been reported to be as low as six months (4). In fact, recently published United States registry data and previous retrospective cohort data demonstrated higher rates of death in patients with PoPH compared with those with idiopathic or heritable PAH (5,6). Furthermore, the presence of severe PoPH has been shown to dramatically increase mortality post-liver transplant (7).

Several randomized control trials of targeted therapies, including prostaglandin analogues, endothelin-receptor antagonists and phosphodiesterase-5 (PDE5) inhibitors, have been shown to improve hemodynamics, exercise capacity, WHO functional class, quality of life and, in some instances, mortality in PAH (8-11). Sildenafil and

L'efficacité de l'inhibiteur de la phosphodiesterase de type 5 contre l'hypertension portopulmonaire

HISTORIQUE : L'hypertension portopulmonaire s'associe à une morbidité et une mortalité importantes. L'inhibiteur de la phosphodiesterase de type 5 est efficace contre d'autres causes d'hypertension pulmonaire artérielle de groupe 1 selon la classification de l'OMS.

OBJECTIF : Évaluer l'efficacité et l'innocuité de l'inhibiteur de la phosphodiesterase de type 5 chez les patients faisant de l'hypertension pulmonaire.

MÉTHODOLOGIE : Des chercheurs ont effectué une étude rétrospective monocentrique de cohorte qui incluait des patients présentant une hypertension portopulmonaire diagnostiquée. Le résultat primaire était une modification de la résistance pulmonaire après la prise d'inhibiteur de la phosphodiesterase de type 5 pendant six mois. Une évaluation secondaire en évaluait l'effet sur d'autres mesures hémodynamiques, le test de marche de 6 minutes, la catégorie fonctionnelle, les résultats d'innocuité et la survie.

RÉSULTATS : Des 1 385 patients ayant subi un dépistage, 25 patients étaient atteints d'hypertension portopulmonaire, dont 20 ont reçu un inhibiteur de la phosphodiesterase de type 5. Au bout de six mois, on a constaté une diminution importante de la résistance vasculaire pulmonaire ($-236 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ [95 % IC $-343 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ à $-130 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$]; $P<0,001$), une tension artérielle pulmonaire moyenne ($-8,9 \text{ mmHg}$ [95 % IC $-13,7 \text{ mmHg}$ à $-4,2 \text{ mmHg}$]; $P=0,001$) et une augmentation du débit cardiaque selon le principe de Fick ($0,9 \text{ L/min}$ [95 % IC $0,1 \text{ L/min}$ à $1,6 \text{ L/min}$]; $P=0,02$). Il n'y avait pas de changement au test de marche de 6 minutes. La proportion de sujets ayant une classification fonctionnelle III ou IV de l'OMS avait considérablement diminué au bout de six mois (18 % par rapport à 61 %; $P=0,002$). Les résultats d'innocuité n'ont révélé aucun événement indésirable.

CONCLUSIONS : L'inhibiteur de la phosphodiesterase de type 5 a amélioré l'hémodynamie et la catégorie fonctionnelle à six mois dans une cohorte de patients faisant de l'hypertension portopulmonaire.

adalafil (two PDE5 inhibitors) have been shown to improve exercise capacity, WHO functional class and hemodynamics in randomized controlled trials involving patients with symptomatic PAH (11-13). However, patients with PoPH were excluded from these trials and the data available for targeted therapy in this group are limited. Accordingly, the objectives of the present study were to evaluate the effectiveness of PDE5 inhibitor monotherapy on pulmonary hemodynamics, symptoms and exercise capacity in a cohort of patients with PoPH.

METHODS

Patients

All patients followed at the University Health Network Pulmonary Hypertension Program (Toronto, Ontario) between 1998 and 2012 were screened for eligibility. Patients were included if they had a diagnosis of PAH, had a diagnosis of portal hypertension and were ≥ 18 years of age at the time of diagnosis. The cohort was then subdivided into those treated with PDE5 inhibitors at any time after diagnosis and those not receiving PDE5 inhibitor therapy. PAH was defined as mean pulmonary artery pressure (mPAP) $\geq 25 \text{ mmHg}$ at rest, pulmonary

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capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure ≤ 15 mmHg (14), and pulmonary vascular resistance (PVR) > 240 dyn \cdot s \cdot cm $^{-5}$ on right heart catheterization. Given that volume overload can be present in cirrhotic patients, the transpulmonary gradient was used to determine the presence of PAH if the PCWP or left ventricular end-diastolic pressure was > 15 mmHg. A transpulmonary gradient > 12 mmHg was chosen to indicate PAH (15). Portal hypertension was determined based on an abdominal ultrasound report specifically stating the presence of portal hypertension or esophageal varices observed on endoscopy. Patients were excluded from the present study if they: had another etiology for PAH (eg, HIV, anorexigen use, connective tissue disease, interstitial lung disease, severe chronic obstructive pulmonary disease or cardiac abnormalities); had another indication for PDE5 inhibitor use (eg, erectile dysfunction, Raynaud's phenomenon); or were < 18 years of age. The study protocol was approved by the University Health Network Research Ethics Board (12-0082-AE).

Exposure

The exposure was treatment with PDE5 inhibitor monotherapy any time after the diagnosis of PoPH. A minimum duration of treatment or minimum dose was not prespecified.

Outcome

mPAP and PVR are commonly used to assess hemodynamics and liver transplantation mortality risk in PoPH (16). An mPAP between 35 mmHg and 50 mmHg, in addition to a PVR ≥ 250 dyn \cdot s \cdot cm $^{-5}$, has been associated with a 50% mortality rate following liver transplantation (16). Because PVR encompasses both pulmonary pressure and cardiac output, the authors elected to use change in PVR after six months of PDE5 inhibitor monotherapy as the primary outcome measure. Secondary outcomes were change in PVR after 12 and 24 months, change in mPAP, cardiac output, PCWP, WHO functional class, plasma-brain natriuretic peptide (BNP) level, 6 min walk distance (6-MWD), and safety outcomes after six, 12 and 24 months of PDE5 inhibitor monotherapy. Safety outcomes included headache, flushing, dyspepsia, gastritis, back pain, loose stools, limb pain or myalgias, cough, epistaxis, pyrexia, insomnia and visual disturbance (11). Time to death (all-cause mortality) or transplantation (liver, lung or both) was evaluated. Patients alive on January 1, 2012 were censored. Dates of death were obtained from the clinic chart, electronic medical record or obituary. The date of death was used from the obituary if there was a correct match on at least four of six of first name, last name, date of birth or age at death, location (city/town), timing (after last clinic visit) and use of the terms 'portopulmonary hypertension' or 'pulmonary hypertension' in the obituary. This method of obtaining vital data has been successfully implemented in other studies (17).

Data collection and administration

A single abstractor (JHF) obtained data from charts and hospital electronic records using a standardized abstraction form. The date of birth, sex, dates of liver disease and PoPH diagnosis, etiology of liver disease, date of PDE5 inhibitor initiation, comorbidities, treatments, functional class, hemodynamic measures, BNP level, 6-MWD, Child-Pugh score, model for end-stage liver disease score, dates of death, lung or liver transplant and safety outcomes were recorded.

Data were double-entered into a computerized database. The duplicate files were cross-referenced for discordant data points to minimize data entry error. All discordant data points were verified against the original data abstraction form.

Statistical analysis

Descriptive statistics were used to summarize the data. The Wilcoxon matched pairs signed-rank test was used to evaluate mean differences in hemodynamic parameters. WHO functional class was dichotomized as classes I and II versus classes III and IV. Pearson's χ^2 test with Yates' continuity correction was used to evaluate differences in proportions. Survival was evaluated using Kaplan-Meier functions. Using Bonferroni

TABLE 1
Baseline echocardiographic findings in two individuals with elevated pulmonary capillary wedge pressure (PCWP)

	Patient	
	1 (PCWP 22 mmHg)	2 (PCWP 16 mmHg)
LV function	Normal	Normal
LA size	Mildly enlarged	Enlarged (severity not listed)
Mitral valve	Mild regurgitation	Mild regurgitation
Aortic valve	No stenosis or regurgitation	No stenosis or regurgitation
RV function	Severely reduced	Normal
RV size	Severely enlarged	Moderately enlarged
RA size	Severely enlarged	Enlarged (severity not listed)
Tricuspid valve	Mild to moderate regurgitation	Moderate regurgitation
RVSP	98 mmHg	55 mmHg

LA Left atrium; LV Left ventricle; RA Right atrium; RV Right ventricle; RVSP RV systolic pressure

correction to account for multiple comparisons, $P \leq 0.003$ was considered to be statistically significant. A sensitivity analysis was conducted for change in PVR using the mean PVR at six months to impute for missing data. Analyses were performed using RStudio version 0.97.248 (RStudio, USA).

RESULTS

Patients

A review of 1385 patients seen at the University Health Network Pulmonary Hypertension Program identified 25 patients with PoPH. Twenty (80%) were treated with a PDE5 inhibitor. Of these, two patients had a PCWP > 15 mmHg on diagnostic right heart catheterization (22 mmHg and 16 mmHg); however, the transpulmonary gradient was significantly increased in both (40 mmHg and 21 mmHg, respectively) and they were subsequently included in the analysis. Echocardiographic findings are shown in Table 1. The initial therapy was sildenafil 20 mg three times daily in 15 patients, sildenafil 25 mg three times daily in four patients and tadalafil 40 mg daily in one patient. The median time from diagnosis of PoPH to initiation of PDE5 inhibitor was two months (interquartile range one to three months). One patient received 11 days of inhaled epoprostenol sodium (Flolan, GlaxoSmithKline, USA) initiated at the same time as tadalafil. Given the short duration of therapy, the authors believed that the inhaled Flolan was unlikely to impact six-month PVR and, thus, this patient was included in the primary analysis. No other patients received prostaglandin analogues or endothelin receptor antagonists. Physician explanations for not initiating a PDE5 inhibitor in the untreated group included: PoPH was too mild ($n=2$); awaiting approval for starting therapy in a trial ($n=2$); and not a candidate for vasodilator therapy ($n=1$). The authors were unable to firmly determine why this one patient was believed not to be a candidate for vasodilator therapy by the treating physician. Baseline characteristics of the treated and untreated groups are summarized in Table 2. More patients were male (60% in the treated group and 80% in the untreated group) and the most common etiology of liver disease was alcohol use (55% in the treated group and 60% in the untreated group). Less common etiologies for liver disease were congenital hepatic fibrosis ($n=1$), diffuse biliary strictures post transplant ($n=1$), combined alcohol and hepatitis C ($n=1$), and combined alcohol and hemochromatosis ($n=1$) in the treated group and cryptogenic ($n=1$) in the untreated group. Four patients in the treated group had mild chronic obstructive pulmonary disease that was not believed to be sufficient to cause PAH. Forced expiratory volume in 1 s (FEV_1) was normal in three of these patients. The fourth patient had a concomitant restriction, with an FEV_1 of 1.65 L (63%), forced vital capacity (FVC) of 2.86 L (63%) and FEV_1/FVC ratio of 67. The restriction was believed to be possibly related to obesity (body mass index 34.7 kg/m 2),

TABLE 2
Patient baseline characteristics

Baseline characteristics	Untreated (n=5)	Treated (n=20)
Male sex	4 (80)	12 (60)
Age at pulmonary hypertension diagnosis, years, median (IQR)	58 (55, 60)	55 (47.5, 60.5)
Age at liver disease diagnosis, years, median (IQR)	49 (43.3, 55.8)	47 (39, 52.5)
Etiology of liver disease		
Alcohol	3 (60)	11 (55)
NASH	0 (0)	2 (10)
Viral hepatitis	1 (20)	2 (10)
Autoimmune	0 (0)	1 (5)
Other	1 (20)	4 (20)
MELD score, median (IQR)	14 (11, 15)	15 (13, 18)
Child-Pugh class		
A	1 (20)	3 (15)
B	1 (20)	7 (35)
C	1 (20)	3 (15)
Not available	2 (40)	7 (35)
Comorbidities		
Coronary artery disease	0 (0)	4 (20)
Systemic hypertension	3 (60)	9 (45)
Diabetes mellitus	1 (20)	8 (40)
Hyperlipidemia	1 (20)	6 (30)
Peripheral vascular disease	0 (0)	0 (0)
Cancer	0 (0)	5 (25)
Chronic obstructive pulmonary disease	1 (20)	4 (20)
Chronic kidney disease	0 (0)	1 (5)
Congestive heart failure	0 (0)	1 (5)
Beta blocker use	2 (40)	7 (35)

Data presented as n (%) unless otherwise indicated. IQR Interquartile range; MELD Model for end-stage liver disease; NASH Nonalcoholic steatohepatitis

with no other etiology identified. Computed tomography of the chest did not show any significant parenchymal lung disease. Baseline hemodynamic parameters for both groups are outlined in Table 3.

Primary outcome

Nineteen of 20 treated patients underwent a follow-up right heart catheterization after PDE5 inhibitor initiation (17 at six months, one at 12 months and one at 24 months); one patient in the treated group died before their scheduled right heart catheterization, and the authors were unable to determine the cause of death. One patient in the treated group underwent a right heart catheterization at six, 12 and 24 months. Only one untreated patient underwent a follow-up right heart catheterization. After six months of PDE5 inhibitor therapy, there was a significant decrease in mean PVR by $-236 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ (95% CI $-343 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ to $-130 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$; $P<0.001$). A sensitivity analysis using the mean six-month PVR to impute for missing data improved the precision but did not change the magnitude of the treatment effect (mean change in PVR $-209 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ [95% CI $-304 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ to $-115 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$]; $P<0.001$). One patient in the treated group had worsening in PVR at six months (Figure 1).

Secondary outcomes

Improvements were also observed in other hemodynamic parameters in the treated group on six-month follow-up right heart catheterization (Table 3). There was no significant change in PCWP. Hemodynamic data were available for only two patients at 12 and 24 months (Table 4). Individual PVR response is shown in Figure 1. The mean (\pm SD) plasma BNP level was $134.6\pm 83.1 \text{ pg/mL}$ at baseline ($n=10$) and significantly decreased after six months of PDE5 inhibitor therapy (mean difference -51.9 pg/mL [95% CI -94.6 pg/mL to -9.2 pg/mL]; $P=0.02$, $n=10$). The

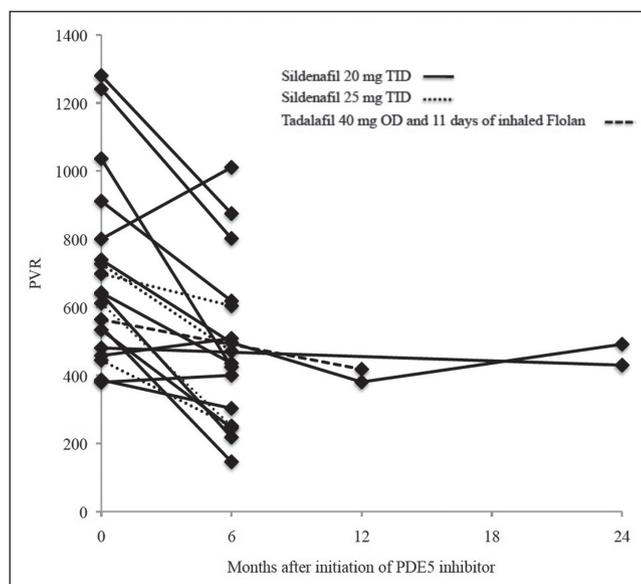


Figure 1) Individual pulmonary vascular resistance (PVR) response to phosphodiesterase-5 (PDE5) inhibitors. X-axis represents time after PDE5 inhibitor initiation; y-axis represents PVR expressed as $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$. TID Three times daily; OD Once daily. Flolan GlaxoSmithKline, USA

improvements in plasma BNP level were sustained but not statistically significant at 12 and 24 months (mean difference -63.0 pg/mL [95% CI -137.6 pg/mL to 11.6 pg/mL]; $P=0.07$, $n=8$; and -29.6 pg/mL [95% CI -159.4 pg/mL to 100.1 pg/mL]; $P=0.42$, $n=6$, respectively).

There was an improvement in symptoms observed after PDE5 inhibitor initiation, with the proportion of subjects with a WHO functional class of III or IV significantly less at six months compared with baseline (18% versus 61%; $P=0.002$). There was no significant change in 6-MWD at six, 12 or 24 months (mean difference 6.9 m [95% CI -31.2 m to 45.0 m ; $P=0.69$, $n=16$]; 18.0 m [95% CI -21.6 m to 57.6 m ; $P=0.33$, $n=15$]; and 4.0 m [95% CI -70.2 m to 78.2 m ; $P=0.89$, $n=12$], respectively).

Safety

PDE5 inhibitors were well tolerated by the study cohort; dyspepsia, loose stools, back pain and myalgias were the only observed side effects and occurred in $<10\%$ of patients. No serious medication-related adverse events were observed; however, the cause of death for the patient who died before undergoing a follow-up right heart catheterization was indeterminable.

Survival

Survival status as of January 1, 2012 was determined for all study patients. The probability of one-year survival was 84.4% (95% CI 70% to 100%), two-year survival was 72% (95% CI 53% to 97%) and four-year survival was 57% (95% CI 34% to 97%). One patient in the treated group was able to undergo successful liver transplant after PDE5 inhibitor initiation; however, five patients went from being considered to be 'inoperable' to 'operable' based on hemodynamic criteria ($\text{mPAP} < 35 \text{ mmHg}$ and $\text{PVR} < 250 \text{ mmHg}$). In the transplanted patient, echocardiogram subsequently showed normalization of right ventricular systolic pressure and the PDE5 inhibitor was discontinued one-year post-transplant. The patient remained alive at the time of censoring (2.5 years post-liver transplant) with no indication of PAH recurrence.

DISCUSSION

We found that PDE5 inhibitor therapy improved hemodynamics, BNP levels and WHO functional class after six months. PDE5 inhibitors were well tolerated by our study cohort, with no major adverse events

TABLE 3
Hemodynamic data at baseline and six months post-phosphodiesterase-5 inhibitor treatment

Outcome	Baseline		Six months (treated [n=17])	
	Untreated (n=5)	Treated (n=20)	Mean difference (95% CI)	P
Pulmonary vascular resistance, dyn·s·cm ⁻⁵	450.7±212.7	683.3±259.0	-236.1 (-342.6 to -129.6)	<0.001
Mean pulmonary artery pressure, mmHg	38.4±11.8	47.5±10.2	-8.9 (-13.7 to -4.2)	0.001
Fick cardiac output, L/min	5.3±1.4	4.7±1.2	0.9 (0.1 to 1.6)	0.02
Pulmonary capillary wedge pressure, mmHg	10.8±4.8	10±5.9	0.1 (-3.2 to 3.4)	0.94

Data presented mean ± SD unless otherwise indicated

TABLE 4
Individual hemodynamic data in the treated group at baseline, 12 and 24 months post-phosphodiesterase inhibitor treatment

Outcome	Patient 1			Patient 2			Patient 3		
	Baseline	12 months	24 months	Baseline	12 months	24 months	Baseline	12 months	24 months
PVR, dyn·s·cm ⁻⁵	739.2	380.3	491.2	480.3	-	429.8	563.6	417.7	-
mPAP, mmHg	46	33	33	46	-	40	34	34	-
Fick cardiac output, L/min	4.9	6.1	4.6	5.3	-	5.8	4.4	5.0	-
PCWP, mmHg	1	4	5	14	-	9	3	8	-

mPAP Mean pulmonary artery pressure; PCWP Pulmonary capillary wedge pressure; PVR Pulmonary vascular resistance

observed. To our knowledge, this is one of the largest cohorts to date investigating PDE5 inhibitor monotherapy in patients with PoPH. Previously published case reports have described the use of PDE5 inhibitors in PoPH as both targeted therapy and a bridge to liver transplant. Bremer et al (18) published a case report involving a 55-year-old man with PoPH who had a sustained reduction in pulmonary and portal pressures at six months with the use of tadalafil followed by maintenance sildenafil. Makisalo et al (19) described the use of sildenafil in a cirrhotic patient with severe PoPH as a bridge to liver transplant. This patient had a reduction in pulmonary pressures to a level that allowed for a successful liver transplant, which had previously been considered to be contraindicated. Hollatz et al (20) described a group of 11 patients with PoPH that underwent successful liver transplant after treatment with primarily sildenafil and/or subcutaneous treprostinil. Seven patients had been started initially on sildenafil monotherapy; however, five eventually had a second agent added. Another observational study followed 14 patients with moderate to severe PoPH who were treated with sildenafil (21). However, only eight of these patients received sildenafil as monotherapy and the remaining six were treated with inhaled prostaglandin analogue therapy with the subsequent addition of sildenafil. In the 12 patients who completed the study, 6-MWD was improved at both three months and one year. A reduction in PVR and mPAP was shown in a group of nine patients after treatment with sildenafil for variable durations (22).

The magnitude of the treatment effect observed on change in PVR in our study was similar to that reported in randomized control trial data of sildenafil for the treatment of other causes of WHO group 1 PAH (11) and two previous small observational studies in patients with PoPH (20-22). However, direct comparison of our study to previous observational data is difficult because many of the patients in other studies received combination therapy rather than a PDE5 inhibitor alone. One patient exhibited worsening in PVR after six months of therapy. We are unable to explain the lack of response in this individual. Time from diagnosis of PoPH to initiation of PDE5 inhibitor was four months, making it possible that PVR worsened before starting therapy. The patient did continue to consume alcohol; however, follow-up data on liver disease severity were unavailable. Sildenafil has been shown to significantly improve 6-MWD in patients with other causes of WHO group 1 PAH (11), but the effect on 6-MWD in patients with PoPH has varied among different studies (20,21,23). We did not show a significant improvement in 6-MWD with PDE5 inhibitor therapy; however, there was no decline over 24 months, suggesting at the very least that patients did not experience worsening in their exercise capacity. Again, a direct comparison of treatment effect on 6-MWD between our study and previous data is problematic, given that many patients in previous studies received an

additional therapy, including epoprostenol, iloprost, treprostinil and/or bosentan (20,21). In the study that reported a significant improvement in 6-MWD, the baseline PVR was 387 dyn·s·cm⁻⁵ higher and baseline 6-MWD was 73 m less than in our cohort, which may partially account for the different result (21). Furthermore 6-MWD improvements may be difficult to demonstrate in some patients with PoPH, given the potential coexistence of ascites, deconditioning, sarcopenia, anemia and encephalopathy, which may affect 6-MWD independent of hemodynamic changes.

Survival at two years in our study cohort was similar to that reported in PoPH patients enrolled in The Registry to Evaluate Early And Long-term pulmonary arterial hypertension disease management (REVEAL) (6), and better than that previously described in a group of untreated patients (4). However, survival estimates vary widely among studies, ranging between 14% and 68% at five years, depending on the cohort and whether patients received any targeted PAH treatments or liver transplant (24,25).

There were several limitations to our study. Given that this was a retrospective observational study, we were at risk for selection bias and untreated patients may be systematically different from the patients who received therapy. Only patients with private insurance, compassionate coverage from the drug company or government, or the ability to pay out of pocket were started on treatment. There may be important unmeasured characteristics that differ between such individuals and those who do not have drug coverage or the ability to pay, thus potentially altering outcomes. Interestingly, the untreated group had lower baseline PVR and were slightly older than the treated group. It is unclear whether response to therapy would be different in this population. We did not have follow-up hemodynamic data on untreated patients and, thus, did not have a control group for comparison. Hemodynamic data at 12 and 24 months were only available for two patients. We were also unable to determine cause of death. Although the use of endothelin inhibitors in PoPH has been evaluated (26), we were concerned that these agents were potentially hepatotoxic. Therefore, we do not have comparator data to this class of medications, nor did we evaluate the effects of combination oral therapy in our cohort. Despite this, our study results are encouraging, suggesting that patients with PoPH may derive significant benefit from PDE5 inhibitor therapy. The extent to which treatment improves eligibility or outcomes in liver transplantation remains unclear.

The French Registry cohort of patients with PAH (27) suggests that PoPH is not uncommon and accounts for approximately 10% of PAH cases. However, data regarding treatment with targeted PAH therapies in this group of patients are limited and, in Canada, there are no formally approved medications. The subsequent decision to initiate therapy, as well as the patient's ability to pay for nonapproved medications is,

therefore, quite problematic. PDE5 inhibitors are an attractive first-line therapy in patients with PoPH given the ease of administration and lack of hepatotoxicity and edema that can be observed with other PAH therapies (10,28-30). In addition, genetic polymorphisms in PDE5 have been associated with an increased risk for PoPH, lending support to the use of therapies targeting cyclic GMP (31). However, a randomized controlled trial of such targeted therapy is lacking and clearly needed in this group of patients.

We found that PDE5 inhibitor therapy was well tolerated and improved PVR, mPAP and WHO functional class in a cohort of patients with PoPH. A randomized controlled trial is needed to confirm efficacy and safety in this patient population.

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