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Sildenafil treatment for portopulmonary hypertension

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ABSTRACT: Portopulmonary hypertension (POPH) is regarded as a subtype of pulmonary arterial hypertension (PAH); however, established PAH therapies have not been evaluated for this condition.

The current authors treated 14 patients (four male, 10 female; mean (range) age 55 (39–75) yrs) with moderate (n=1) or severe (n=13) POPH caused by alcoholic liver disease (n=7), chronic viral hepatitis (n=3), autoimmune hepatitis (n=3), and hepatic manifestation of hereditary haemorrhagic teleangiectasia (n=1) with oral sildenafil. Eight patients were newly started on pulmonary vasoactive treatment, while six patients were already on treatment with inhaled prostanoids (iloprost, n=5; treprostinil, n=1). During treatment with sildenafil, mean±SD 6-min walk distance increased from 312±111 m to 397±99 m after 3 months, and 407±97 m after 12 months. Mean±SD pro-brain natriuretic peptide levels decreased from 582±315 ng·mL^{-1} to 230±278 ng·mL^{-1}, and to 189±274ng·mL^{-1} after 3 and 12 months, respectively. Two patients died after 1 and 2 months from liver failure and cardiac failure, respectively. There was a similar response to sildenafil treatment after 3 and 12 months in patients on monotherapy and those on combination therapy.

In conclusion, sildenafil might be effective in monotherapy and in combination therapy with inhaled prostanoids in portopulmonary hypertension, leading to significant improvement by 3 months and sustained response over 12 months.

KEYWORDS: Inhaled prostanoids, portopulmonary hypertension, pulmonary circulation, sildenafil

Patients with liver diseases are at risk of developing pulmonary vascular complications [1]. Among these, portopulmonary hypertension (POPH) is a rare but severe complication affecting 2–10% of patients with liver cirrhosis. It is associated with increased mortality due to obstructive pulmonary vasculopathy and has a major impact on treatment options for underlying liver disease [2]. Development of POPH has been associated with portal hypertension, but it can occur at any stage of liver diseases, with increasing incidence dependent on the severity of hepatic impairment [3]. Patients with POPH are at high risk of severe complications during liver transplantation [4].

POPH is regarded as a subtype of pulmonary arterial hypertension (PAH) [5]. However, newly developed treatment strategies for PAH have been neither studied nor approved for POPH. Furthermore, POPH has been explicitly excluded from recent published randomised controlled trials on PAH [6].

For editorial comments see page 466.

Currently available compounds for pulmonary vasoactive treatment have been successfully used in POPH, even enabling successful liver transplantation [7, 8]. So far, case reports and a case series have been published showing clinical, functional and haemodynamic benefit on treatment with intravenous and inhaled prostanoids, oral bosentan or combination therapy [9–13].

The phosphodiesterase-5 inhibitor sildenafil is currently licensed for the treatment of PAH. It has the advantage of being an oral compound with pulmonary vasoselective action but no hepatotoxicity [14]. The successful use of sildenafil in POPH has recently been reported in two case studies [15, 16].

The current authors evaluated long-term sildenafil treatment of POPH, the primary objectives being safety and efficacy as either monotherapy or in combination with inhaled prostanoids.

PATIENTS AND METHODS

In the current authors' tertiary referral centre for pulmonary vascular diseases, all patients with PAH associated with liver disease were evaluated

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to ascertain: 1) the degree of liver cirrhosis and the underlying aetiology of liver disease; 2) symptoms related to PAH according to World Health Organization (WHO) classification; 3) exercise capacity using 6-min walking distance (6-MWD) according to American Thoracic Society guidelines [17]; and 4) haemodynamic parameters using right-heart catheterisation.

Pulmonary vasoactive treatment was started when patients were in WHO functional stage III–IV, with an impaired exercise tolerance and moderate-to-severe pre-capillary pulmonary hypertension with increase of mean pulmonary arterial pressure (mPAP) >35 mmHg [1], and a pulmonary vascular resistance (PVR) >500 dyne·s·cm^{-5} [18].

None of the patients in the present study were being treated with β-blocking agents. Patients on prostanoid treatment received either iloprost 6 inhalations·day^{-1} with a total daily dose of 30 μg (n=5), or treprostinil 4 inhalations·day^{-1} with a total daily dose of 120 μg (n=1) at mouthpiece using an ultrasonic inhalation device. Sildenafil treatment was started with increasing dosage, reaching 50 mg three times daily within 3 weeks in all patients. Follow-up included: clinical assessment; measurement of 6-MWD; laboratory studies including liver function tests and pro-brain natriuretic peptide (pro-BNP) measurement; and right-heart catheterisation after 3 months and 12 months.

As data are normally distributed, results are shown as mean±SD. To detect statistical significant differences between groups, two-sided unpaired t-tests were used. For the assessment of treatment effects, two-sided paired t-tests were used. For subgroup analysis, ANOVA (α=0.05) and *post hoc* analysis were applied. Bonferroni correction was used for correction of multiple comparisons [19].

RESULTS

Among 32 patients with POPH, 20 patients with advanced disease (*i.e.* moderate or severe stage of the disease according to recent guidelines [1]) were identified. Of these, 12 patients were already receiving therapy with inhaled iloprost (n=7), inhaled treprostinil (n=2) or endothelin-receptor blockers (n=3). Sildenafil treatment was considered in newly diagnosed patients and in patients not stable on current therapy. Six patients were stable on treatment with endothelin-receptor blockers (n=3) or inhaled prostanoids (iloprost, n=2; treprostinil, n=1) and were not included in the study.

Sildenafil treatment was started in 13 patients with severe and one patient with moderate POPH but in WHO functional class III (four male, 10 female; mean age 55±12 yrs). Six patients had already been on active treatment with inhaled prostanoids (iloprost, n=5; treprostinil, n=1) for mean (range) 20 (3–42) months, but required additional treatment. Underlying aetiologies included liver cirrhosis caused by alcohol liver disease (n=7), or associated with viral hepatitis (n=3), autoimmune hepatic diseases (n=3) or hepatic involvement in hereditary haemorrhagic teleangiectasia (HHT; n=1). Patients were in either clinical stage Child A (n=7), B (n=6) or C (n=1).

Concerning pulmonary hypertension, patients were in WHO functional classes III (n=10) and IV (n=4) with a mean 6-MWD at baseline of 307±109 m.

Pre-capillary pulmonary hypertension was confirmed on right-heart catheterisation with mPAP 55±11 mmHg, cardiac index of 2.2±0.8 L·min^{-1}·m^{-2} and PVR of 1130±688 dyne·s·cm^{-5}. One patient (patient 5) in WHO class III with mPAP 59 mmHg and PVR 438 dyne·s·cm^{-5} was also included in the study.

Within 3 months of treatment beginning, two patients had died. The patient with hepatic involvement of HHT (patient No. 13) was already in an advanced stage of liver cirrhosis when referred for assessment of POPH. The patient died in progressive liver failure 1 month after the start of sildenafil therapy. There were no additional causes of liver disorder. Notably, there were no signs of a bleeding event.

Patient No. 14, with severe POPH associated with viral liver cirrhosis, initially improved on treatment with inhaled iloprost; however, she required combination therapy with sildenafil owing to the progression of the disease. The patient died in cardiac failure 2 months after starting combination therapy. Again, there were no signs of a bleeding event.

The other 12 patients completed 3 months' follow-up, with an increase in 6-MWD from 312±111 m to 397±99 m (p=0.001). There was a significant decrease in mPAP, from 55±11 mmHg to 46±10 mmHg (p=0.01), an increase in cardiac index from 2.2±0,8 L·min^{-1} to 2.8±1.0 L·min^{-1} (p=0.06), and a significant decrease in PVR from 1,070±597 dynes·s·cm^{-5} to 698±358 dyne·s·cm^{-5} (p<0.05; table 1). Pro-BNP levels decreased from 582±315 ng·mL^{-1} to 230±278 ng·mL^{-1} (p=0.06). Liver function test, arterial partial pressure of oxygen (P_{O_2}) and haemoglobin levels remained stable (table 2).

After 12 months' follow up, 6-MWD was 407±97 m (p<0.0001 from baseline), and pro-BNP levels had decreased further to 189±274 mg·mL^{-1} (p<0.05 from baseline). Haemodynamic parameters showed mPAP of 51±7 mmHg, cardiac index of 2.5±0.6 L·min^{-1}·m^{-2} and PVR of 797±358 dyne·s·cm^{-5}, and were not significantly different from baseline. Liver function test remained stable, as did oxygenation and haemoglobin levels (tables 1 and 2). There were no deaths among patients who survived the first 3 months.

Although patients who were receiving prostanoid therapy prior to the study period had significantly worse baseline haemodynamic parameters, there was no statistically significant difference between patients with combination therapy and patients with first-line sildenafil monotherapy concerning 6-MWD at baseline and at 3 and 12 months' follow-up (table 3; fig. 1).

Patients with Child A liver cirrhosis had a better response to sildenafil therapy, with a significant increase in 6-MWD after 3 months' therapy; however, by 12 months there was no statistical significant difference between the 6-MWD of Child A and Child B patients (fig. 2). During the whole study period, there were no reported bleeding events or episodes of visual disturbance in patients.

DISCUSSION

POPH comprises a distinct aetiology of PAH. However, it was not investigated in recent randomised controlled trials on treatment for pulmonary hypertension [6, 14]. Consequently, the treatment of POPH is dependent on compassionate use of compounds currently available to treat PAH. The available

TABLE 1 Individual patient characteristics, baseline haemodynamics and response to therapy

Patient	Sex	Age yrs	Liver cirrhosis	Child stage	Treatment	mPAP		CI			PVR			6-MWD		
						Base mmHg	3 months mmHg	12 months mmHg	Base L·min^{-1}	3 months L·min^{-1}	12 months L·min^{-1}	Base dyne·s·cm^{-5}	3 months dyne·s·cm^{-5}	12 months dyne·s·cm^{-5}	Base m	3 months m	12 months m
2	F	46	Alcoholic	A	sil	57	49	56	2.5	3.4	2.4	1074	621	984	385	468	396
3	F	58	Alcoholic	A	sil	48	52	54	1.4	2.0	1.6	1143	851	998	334	442	403
4	M	48	Alcoholic	B	sil	36	20	30	2.5	2.4	2.3	552	359	423	312	410	420
5	M	48	Alcoholic	B	sil	47	38	42	2.7	4.3	3.2	548	269	343	368	398	450
6	M	60	Viral	B	sil	59	56	56	3.6	2.9	3.0	438	530	540	430	416	434
7	F	75	PBC	B	sil	51	52	54	3.5	3.8	3.3	543	521	554	329	370	425
8	F	59	Alcoholic	A	sil/ilo	58	52	52	2.3	1.7	1.9	1263	1467	1245	58	130	143
9	F	63	Alcoholic	A	sil/ilo	71	51	56	2.3	2.8	3.1	867	509	594	360	480	494
10	F	45	Immune	A	sil/ilo	50	49	53	1.4	1.8	2.2	1362	1047	1050	262	421	435
11	M	49	Viral	A	sil/ilo	76	44	48	1.3	2.4	2.5	2616	891	780	150	390	417
12	F	75	Immune	B	sil/ilo	49	42	52	1.8	4.6	2.4	984	311	725	443	519	534
Mean±SD		55±11				59	49	54	1.7	1.8	1.6	1446	997	1333	317	322	335
13##	F	39	HHT	C	sil	55±11	46±10#	51±7	2.2±0.8	2.8±1.0#	2.5±0.6	1070±597	698±358¶	797±323+	312±111	397±99§	407±97/
14##	F	69	Viral	B	sil/tre	46			3.3			513			363		
						64			1.0			2467			183		

mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; 6-MWD: 6-min walking distance; F: female; sil: sildenafil; M: male; PBC: primary biliary cirrhosis; ilo: inhaled iloprost; HHT: hereditary haemorrhagic teleangiectasia; tre: inhaled treprostinil; #: p=0.01 *versus* baseline; ¶: p=0.02 *versus* baseline; +: p=0.09 *versus* baseline; §: p=0.001 *versus* baseline; /: p=0.0001 *versus* baseline; ##: patient died during study. 1 mmHg = 0.133 kPa.

data on the efficacy and safety of pulmonary vasoactive therapy in this patient population are sparse. In the current retrospective study, a significant clinical, functional and haemodynamic improvement was found over 3 months' treatment with oral sildenafil in patients with severe POPH. Successful treatment of POPH has been reported using prostanoids or endothelin-receptor antagonists, with observation times of 3–12 months [9–13]. Subcutaneous, *i.v.* or inhaled prostanoids are associated with considerable side-effects or require significant patient commitment, and the endothelin-receptor antagonist bosentan is associated with an increased risk of hepatotoxicity (occurring in ~10% of patients) [20]. Sildenafil combines the advantage of oral treatment for severe PAH with an excellent risk-profile regarding hepatic side-effects in these patients with impaired liver function.

In the current study, two patients died, 1 and 2 months after initiation of sildenafil treatment, respectively. One patient died owing to liver failure in advanced liver cirrhosis due to HHT. This patient was not eligible for liver transplantation due to severe pulmonary hypertension [2, 4]. The second patient suffered from liver cirrhosis due to viral hepatitis. Despite combination therapy with inhaled iloprost and sildenafil, she developed progressive pulmonary vascular disease and died in right-heart failure.

Although six patients already received inhaled prostanoids with effective dosing, additional pulmonary vasoactive therapy was required for functional stabilisation. Combination of sildenafil add-on therapy with inhaled prostanoids resulted in a favourable improvement after 3 and 12 months, similar to that shown by patients being treated with sildenafil monotherapy. The effects seen in the current study were comparable to those seen in patients with other forms of PAH [21, 22]. Differences in response to treatment with regard to the origin of liver disease were found neither in the current study nor in previous reports [1–4]. In the current study, patients with a milder degree of liver cirrhosis showed a significant improvement in exercise capacity after 3 months' sildenafil therapy compared with patients in advanced stages of liver disease (fig. 2). Although this effect might be related to the small sample size, it should be considered in forthcoming investigations.

Although there was a slight deterioration in haemodynamic parameters after 12 months, patients remained in a stable clinical and functional condition. In addition, pro-BNP levels remained stable. In the current study, a sildenafil dose 2.5 times as high as the currently approved dosage for treatment of PAH was used. Sildenafil dosage was not increased further owing to the potential for bleeding.

None of the patients in the current study experienced bleeding events or required blood transfusions while on chronic sildenafil treatment. Notably, there were no reported episodes of gastrointestinal haemorrhage, as has been reported previously [23, 24]. The two deceased patients showed no signs of a fatal bleeding event and died from liver failure and cardiac failure, respectively.

Goal-directed therapy is the current challenge in PAH, and specific targets might be achievable with growing evidence for, and availability of, combination therapy [25].

TABLE 2 Characteristics of 12 patients completing 3 and 12 months' follow-up

	Baseline	3 months	p-value *versus* baseline	12 months	p-value *versus* baseline
NYHA class	3.3±0.5	2.6±0.5	0.001	2.8±0.4	0.08
Pro-BNP ng·mL^{-1}	582±315	230±278	0.06	189±274	0.03
***P*$_{O_2}$ mmHg**	72±9	65±24	0.2	74±8	0.5
Bilirubin mg·dL^{-1}	1.8±1.2	1.2±0.9	0.02	1.1±0.7	0.06
Haemoglobin g·dL^{-1}	14.1±2.0	13.8±1.4	0.7	14.3±2.0	0.7

Data are presented as mean±SD, unless otherwise stated. NYHA: New York Heart Association; pro-BNP: pro-brain natriuretic protein; P_{O_2}: partial pressure of oxygen. 1 mmHg = 0.133 kPa.

TABLE 3 Baseline parameters comparing monotherapy and combination therapy in the whole study population

	Monotherapy	Combination therapy	p-value
Subjects n	8	6	
Male/female n	3/5	1/5	
Age yrs	52±12	60±11	0.2
Child A/B/C n	3/4/1	4/2/0	
NYHA	3.3±0.5	3.3±0.5	0.9
6-MWD m	316±122	296±101	0.9
Pro-BNP ng·mL^{-1}	396±392	722±189	0.2
mPAP mmHg	50±7	61±11	0.04
CI L·min^{-1}·m^{-1}	2.7±0.7	1.6±0.4	0.005$^{\#}$
PVR dyne·s·cm^{-5}	759±338	1625±747	0.01$^{\#}$
***P*$_{O_2}$ mmHg**	68±12	75±8	0.23
Bilirubin mg·dL^{-1}	2.1±1.8	2.3±1.2	0.56
Haemoglobin g·dL^{-1}	14.1±2.2	14.2±1.5	0.89

Data are presented as mean±SD, unless otherwise stated. NYHA: New York Heart Association; 6-MWD: 6-min walking distance; pro-BNP: pro-brain natriuretic protein; mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; P_{O_2}: partial pressure of oxygen; $^{\#}$: $p \leqslant 0.01$. 1 mmHg = 0.133 kPa.

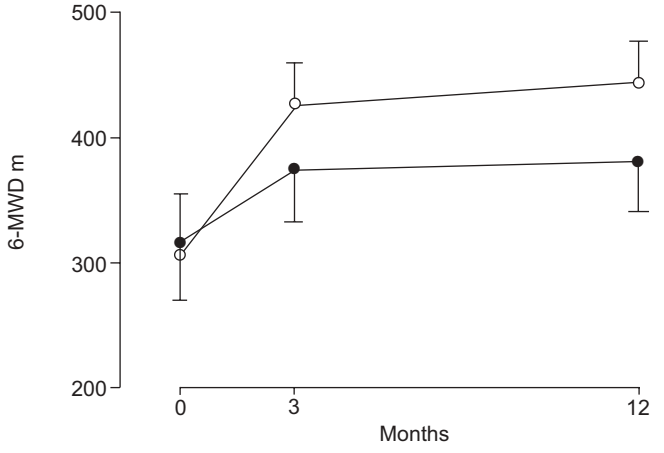

FIGURE 1. A 6-min walking distance (6-MWD) after 3 and 12 months' follow-up treatment, comparing sildenafil monotherapy (●; n=7) and sildenafil and inhaled prostanoids combination therapy (○; n=5). Data are presented as mean±SEM. There was no statistically significant difference between treatment groups.

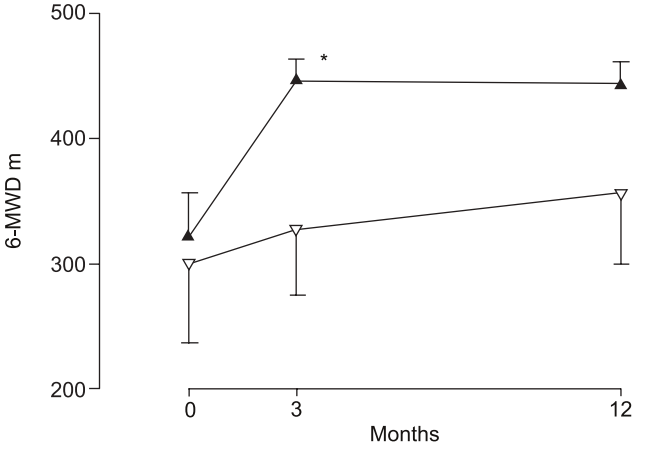

FIGURE 2. Follow-up after 3 and 12 months' sildenafil treatment, comparing degrees of hepatic impairment. Data are presented as mean±SEM. Child A: ▲, n=7; Child B: ▽, n=5. There was a statistically significant difference between the two groups at 3 months (*post hoc* ANOVA). *: $p<0.01$ *versus* baseline.

In the patient sample of the current study, starting combination therapy with oral sildenafil on top of chronic inhaled prostanoid treatment leads to a significant and sustained haemodynamic and functional improvement without significant side-effects. However, further additional therapy including *i.v.* epoprostenol might be required when liver transplantation is planned or patients are not stable on combination therapy [1].

There are major limitations in the current study. The rather low number of patients with heterogeneous aetiology of liver disease might indicate a selection bias. Subgroup analyses or potential side-effects require further investigation.

Although the current study was not sufficient to deduce general treatment recommendations, the subjects were

recruited from patients referred for assessment and therapy for pulmonary hypertension to a large specialised centre for pulmonary vascular diseases. In the current authors' opinion, the response to sildenafil treatment was sufficiently pronounced and homogeneous to produce significant results.

In conclusion, sildenafil is a safe and well-tolerated therapy in portopulmonary hypertension which may lead to significant clinical, functional and haemodynamic improvement after 3 months and to a sustained response over 12 months either as monotherapy or in combination with inhaled prostanoids.

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