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Oral pulmonary vasoactive drugs achieve hemodynamic eligibility for liver transplantation in portopulmonary hypertension

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ABSTRACT

Background and aims: Portopulmonary hypertension (POPH) hampers survival of patients with cirrhosis and portal hypertension and may preclude liver transplantation (LT). Management of such patients with oral pulmonary vasoactive drugs (PVD) has not been standardized. Our aim was to assess the efficacy and safety of oral PVD for management of POPH.

Methods: All patients treated by oral PVD (bosentan, ambrisentan, sildenafil, tadalafil) for POPH were retrospectively studied. Significant response was defined for the patients who reached the following LT eligibility criteria: mean pulmonary artery pressure (MPAP) <35 mmHg or MPAP between 35 and 50 mmHg with pulmonary vascular resistance (PVR) <250 dyn s cm^{-5}.

Results: 20 patients were followed for 38 (19–57) months. Oral PVD improved MPAP (−8 [−19, +2] mmHg), PVR (−201 [−344, −68] dyn s cm^{-5}) and 6-min walk distance (+52 [−51, +112] m). Fifty-three percent of evaluable patients reached eligibility to LT criteria, of whom 5 were transplanted. Baseline MPAP > 51 mmHg and/or PVR > 536 dyn s cm^{-5} predicted non response to treatment. Five-years survival was 53%. No worsening of cirrhosis or serious adverse effect was recorded.

Conclusion: Oral pulmonary vasoactive drugs are safe in cirrhotic patients with POPH. These treatments improved hemodynamic conditions allowing patients access to liver transplantation eligibility.

1. Introduction

Portopulmonary hypertension (POPH) is an uncommon and severe complication of portal hypertension most frequently associated with cirrhosis. POPH is defined by the association of portal hypertension and pulmonary artery hypertension (PAH) according to hemodynamic criteria assessed by right-heart catheterization [1]: mean pulmonary artery pressure (MPAP) ≥25 mmHg, pulmonary vascular resistance (PVR) ≥240 dyn s cm^{-5} and a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. POPH accounts for 7–10% of cases of PAH [2], occurs in 1–6% of patients with portal hypertension [3] and up to 10% of patients awaiting liver transplantation [4]. Prognosis of patients with cirrhosis and portal hypertension is largely hampered by POPH, as five-year survival is 14% without treatment [5]. Moreover, patients with POPH have a higher risk of death than patients with other forms of PAH [6]. Liver transplantation (LT) was suggested as an attractive treatment because it can cure the underlying liver disease [1]. Yet PAH increases post-transplant mortality because of the high surgical risk linked to right-heart failure [1], with higher mortality in patients with the more severe POPH [5]. Swanson et al. have shown that 5-year survival was only 25% in patients who underwent LT alone and 45% when they received only medical treatment; associating prior POPH medical therapy to LT improved 5-year survival to 67% [5].

By associating vasodilatation, anti-platelet effect and vascular remodeling, prostacyclin analogues such as epoprostenol, treprostinil and inhaled iloprost are classically used for idiopathic PAH [7]. Their use was extended for the management of POPH in patients with cirrhosis and in liver transplant recipients. Recently, Awdish et al. have shown that early initiation of intravenous

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prostacyclin improved 5-year survival to 71% [8]. In PAH, the recent development of pulmonary vasoactive drugs (PVD) such as endothelin receptors antagonist (ERA) and 5-phosphodiesterase inhibitor (PDI) made it possible to circumvent complications and compliance issues related to long-term use of intravenous and inhaled therapies. Bosentan [9] or Ambrisentan [10] have shown satisfactory results for treatment of idiopathic PAH. Adding sildenafil to epoprostenol improved hemodynamic measurements and quality of life [11]. However, because of restrictive inclusion criteria in clinical trials, little information is available regarding the use of these new therapeutic options, alone or in combination, in the setting of cirrhosis and liver transplantation.

The aim of this study was to report the efficacy and safety of oral treatments of PAH in patients with POPH and cirrhosis. Special attention was paid to the impact of these treatments on liver transplantation accessibility.

2. Material and methods

2.1. Patients

All patients referred to the liver diseases or cardiology department between 2005 and 2015 for evaluation and management of POPH were retrospectively screened. POPH was defined as the association of portal hypertension, MPAP ≥25 mmHg, PVR ≥ 240 dyn s cm^{-5} and PCWP < 15 mmHg evaluated by right-heart catheterization. Portal hypertension was defined by the presence of endoscopic or radiologic signs, such as esophageal or gastric varices, splenomegaly, ascites, portosystemic shunts. All patients who were treated with oral PVD as endothelin receptors antagonists (Bosentan or Ambrisentan), 5-phosphodiesterase inhibitors (Sildenafil or Tadalafil), alone, in combination of oral treatment, or in addition to eproprostenol infusion, were included. Patients with other causes of PAH were excluded by chest CT, pulmonary function tests, lung scintigraphy, HIV serology, autoimmunity tests.

Clinical and biological data were collected (ascites, gastro-esophageal varices, hepatic encephalopathy, bilirubin, albumin, INR, prothrombin time, Child-Pugh class, MELD score) at baseline and after oral PVD initiation. Survival, adverse events, complication of cirrhosis, hospitalization and treatment modification were recorded from the introduction of oral PVD to March 2015.

2.2. Evaluation of response to oral PVD

Baseline criteria were recorded: 6-min walking distance (6-MWD), spirometry, NTpro-BNP. Baseline hemodynamic data were assessed by right-heart catheterization.

Clinical and biological data (6-MWD, NTpro-BNP) were collected after oral PVD initiation, as well as hemodynamic data, assessed by mean echocardiography or right-heart catheterization, every six to twelve month during follow-up.

2.3. Treatment endpoints

Primary outcome measure was the change in RVP and cardiac index between initiation of treatment and the end of follow-up. Secondary outcome measure was change of 6-MWD and NTpro-BNP.

To assess treatment efficacy with a clinically relevant endpoint in the setting of patients with cirrhosis, we considered "Response to treatment" if the patient had reached the following liver transplantation eligibility criteria for POPH [12]: MPAP < 35 mmHg or 35 ≤ MPAP < 50 mmHg with PVR < 250 dyn s cm^{-5} with therapy.

Table 1
Demographic and biological data for the 20 patients.

Male/female	13/7
Age (years)	51 [48–59]
BMI (kg/m^2)	27.3 [23.5–30.3]
Child Pugh (n (%))	
A	8 (40)
B	10 (50)
C	2 (10)
MELD score	12 [9–14]
Bilirubin (μmol/l)	37 [20–58]
INR	1.33 [1.19–1.55]
Albumin (g/l)	35 [32.2–37.3]
Creatinine (μmol/l)	71 [60–90]

Results are expressed as n or median (25th–75th percentile).

2.4. Statistical analysis

Results are expressed as percentage or median and Interquartile Range (IQR). Correlations between quantitative variables were estimated using Spearman's rank correlation coefficient. Comparisons between groups were performed using the $\chi 2$ test, Fisher's exact test, and the Wilcoxon test as appropriate. A p value <0.05 was considered statistically significant. Optimal cutoffs were determined using receiver operating characteristic (ROC) curves. Statistical analysis was performed using JMP® software version Pro 11.0 (SAS, Cary, NC).

3. Results

3.1. Patients

Twenty patients with POPH treated orally were referred to our center during the study period. Demographic data are shown in Table 1. All patients have cirrhosis. The etiology of cirrhosis was alcoholic liver disease (ALD) for 13 (65%) of them, association of ALD and non-alcoholic fatty liver disease (NAFLD) for 3 (15%), hepatitis C virus (HCV) for 2 (10%), association of ALD and HCV for 1 (5%) and autoimmune hepatitis (AIH) for 1 (5%). Twenty percent of patients had a MELD score >16. Four patients had refractory ascites, 5 had hepatic encephalopathy, and 10 had medium or large varices.

Ten patients (50%) had liver transplantation indication according to international guidelines [13]: 5 (50%) for hepatocellular carcinoma, 3 (30%) for refractory ascites, 1 (10%) for chronic hepatic encephalopathy and 1 (10%) for severe liver failure.

Median follow-up from diagnosis of POPH was 38 months [19–57].

3.2. Baseline characteristics

Characteristics at first evaluation for POPH, assessed by right-heart catheterization for 20 included patients, are shown in Table 2. One patient did not have right-heart catheterization before initiation of treatment because of the initial severity of liver failure and was treated based on the obvious POPH at first cardiac echography. This patient was excluded from the efficacy analysis but not from the tolerance and survival analysis. Median time for second evaluation by right-heart catheterization was 3 months [1–5].

Median MPAP was 44 mmHg [39–51], PCWP was 11 mmHg [8–13] and PVR was 480 dyn s cm^{-5} [312–604]. Dyspnea according to NYHA scale was 3 for 65% of patients, 2 for 20% and 15% of patients did not complain of dyspnea. Median arterial pressure in oxygen (PaO_2) was 77 mmHg [62–80] and 7 patients had PaO_2 ≤75 mmHg.

Hemodynamic profile was not different between patients with or without LT indication.

Table 2
Characteristics at baseline and at the last hemodynamic evaluation of portopulmonary hypertension.

	Baseline	Last follow-up	Median change after treatment	p-value
MPAP (mmHg)	44 [39–51][a]	40 [29–47][b]	−8 [−19, +2]	0.01
Cardiac Index (L min^{-1} m^{-2})	5.6 [4.3–6.7][a]	6.7 [5.2–7.9][b]	+0.95 [+0.14, +2]	0.002
PVR (dyn s cm^{-5})	480 [312–604][a]	284 [212–455][b]	−201 [−344,–68]	<0.0001
PWCP (mmHg)	11 [8–13][a]	11 [9–13][b]	−1 [−4, +5]	0.5
6-MWD (m)	415 [335–451]	406 [330–464]	+52 [−51, +112]	0.1
NT-proBNP (ng mL^{-1})	267 [136–671]	117 [56–198]	−164 [−608, +42]	0.005

Results are expressed as median (25th–75th percentile).
[a] For 19 patients (initial right-heart catheterization was not performed in 1 patient).
[b] For 18 patients (follow-up right-heart catheterization was not performed in 2 patients). MPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PWCP: pulmonary wedge capillary pressure; 6-MWD: 6-min walking distance.

3.3. Efficacy of oral therapies for POPH

Ten patients were treated with sildenafil (50%), 5 with bosentan (25%), 3 with the association of bosentan and sildenafil (15%), 1 with the association of bosentan and tadalafil (5%) and 1 with ambrisentan (5%). Two patients had associated IV epoprostenol treatment during their management.

Evolution of hemodynamic, biological and clinical parameters after medical treatments is shown in Table 2. Two patients were followed by echocardiography only and did not have right-heart catheterization after oral treatment initiation. These patients were excluded from the efficacy analysis but not from the tolerance and survival analysis.

With oral therapies, 9 of the 17 (53%) initial patients with follow-up cardiac catheterization data had reached liver transplantation eligibility criteria [12] and were considered responder; median time of treatment to achieve eligibility for LT was 12 months [1–24]; median time of second right-heart catheterization was 3 months [1–5]; non responders were evaluated more rapidly than responders (1 month [1–3] versus 5 months [3–6]). Thirty-five per cent of evaluable patients have MPAP decrease of at least 30%, and 64% have PVR decrease of at least 30%.

In non responders PVR decreased by 140 dyn s cm^{-5} [−332, −57], $p = 0.01$, as well as their cardiac index by 1.3 L min^{-1} m^{-2} [−2, −0.3], $p = 0.02$, and NTproBNP by 194 ng ml^{-1} [−1002, +44], $p = 0.04$. However, MPAP was similar at baseline and after treatment initiation: 49 mmHg [43–58] versus 45 [41–56], p = 0,4.

3.4. Predictive factors of response to treatment

Baseline MPAP was lower in responders than non-responder patients (40 mmHg [38–46] vs. 49 mmHg [43–58]), p = 0.04, as shown in Table 3. A baseline MPAP cut-of of 51 mmHg could predict the response to treatment with a sensibility and a negative predictive value of 100%, a specificity of 50% and a positive predictive value of 69% (area under the curve = 0.79). Baseline PVR was lower in responders (464 dyn s cm^{-5} [291–513] vs. 557 [437–804], $p = 0.04$). A baseline PVR cut-off of 536 dyn s cm^{-5} could predict the response to treatment with a sensitivity of 89%, a negative predictive value of 83%, a positive predictive value of 73% and a specificity of 63% (area under the curve = 0.73). Among patients with MPAP > 51 mmHg, all have PVR > 536 dyn s cm^{-5}, and no one was considered as responder. There was no difference in the severity of underlying liver disease estimated by Child-Pugh class and MELD score between the two groups. Among the 17 evaluable patients, response probability was not different depending on the PVD used.

3.5. Liver transplantation and survival

The overall flow-chart is shown in Fig. 1. Among the ten patients who had LT indication, 3 were not listed for LT because they did not reach LT eligibility criteria since they had MPAP > 35 mmHg and PVR > 250 dyn s cm^{-5} after treatment. Six patients with LT indication were considered as responders to oral PVD and were listed for LT; 5 were transplanted and 1 patient died from a septic shock waiting for LT. One patient was listed and had LT despite not fulfilling LT eligibility criteria. This decision was made upon multidisciplinary approach, given the significant improvement of POPH, the comforting cardiac function at echography, the young age and the concurrent liver failure.

Table 3
Baseline Predictive factors of response to oral PVD in 17 patients who underwent initial and follow-up right-heart catheterization.

	Non responders (n = 8)	Responders (n = 9)	*p*
Male/Female (n)	5/3	6/3	0.4
Age (years)	52 [47–60]	51 [49–60]	1
Etiology of cirrhosis			
ALD	4	7	0.4
ALD + NAFLD	1	2	
HCV	1		
ALD + HCV	1		
AIH	1		
Child Pugh score	7 [6–8]	7 [5–10]	0.5
MELD score	11 [10–13]	12 [9–17]	0.6
BMI (kg/m^2)	26.6 [21.3–29.6]	28.3 [25.5–33.7]	0.1
MPAP (mmHg)	49 [43–58]	40 [38–46]	0.04
PVR (dyn s cm^{-5})	557 [437–804]	464 [291–513]	0.04
Cardiac Index (L min^{-1} m^{-2})	5.2 [4.3–6.7]	5.8 [4.9–7.2]	0.3
NT-proBNP (ng mL^{-1})	505 [132–1200]	205 [98–374]	0.1

Results are expressed as n or median (25th–75th percentile). ALD: alcoholic liver disease, NAFLD: non alcoholic fatty liver disease, HCV: hepatitis C liver disease, AIH: auto immune hepatitis. PVR: pulmonary vascular resistance.

Among the 9 patients who reached LT eligibility criteria, 5 have been transplanted during the study period. Four patients were not listed for LT and not transplanted: 3 of them because they had no indication for LT and one because he has cardiologic contraindication for LT (unrelated to POPH). Among these 4 patients without LT, 1 died from a lung cancer, 1 from a rapidly progressive hepatocellular carcinoma, 1 from a septic shock, and 1 was still alive at the end of the study.

All transplanted patients continued oral PVD after LT (3 patients with sildenafil alone, 1 with bosentan and eproprostenol, 1 with association of sildenafil and ambrisentan, 1 with the association of bosentan and tadalafil). Three of them were weaned from PVD treatment following LT after a median of 24 months [10–25], others remained stable on therapy. Median MPAP, PVR and CI after LT were respectively 23 mmHg [18–36], 196 dyn s cm^{-5} [176–354], and 5.2 L min^{-1} m^{-2} [4.5–6.7]. Median follow-up after LT was 41 months [5–80]. One transplanted patient died 2 months after LT from a septic shock.

Eight patients included for efficacy analysis did not reach LT eligibility criteria and were considered as non responders. Among

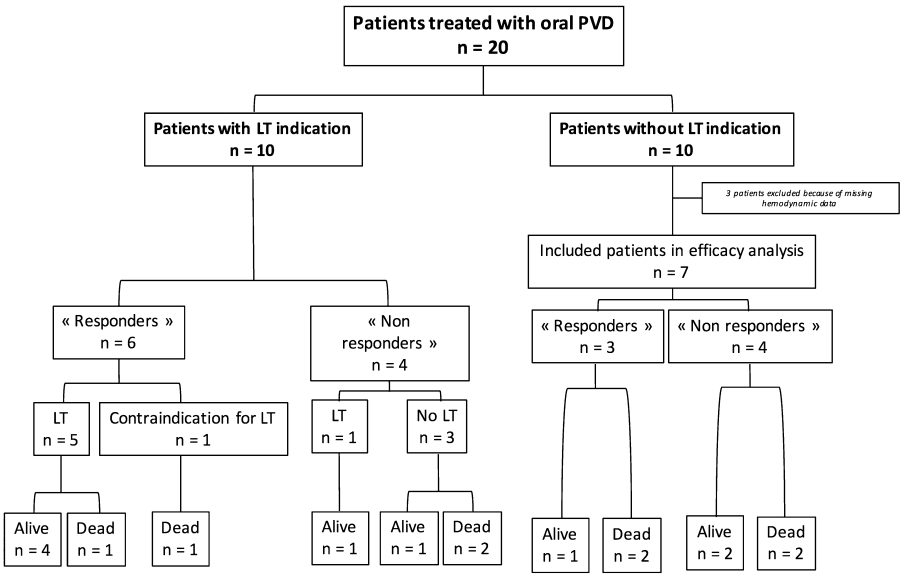

Fig. 1. Flow-chart of patients treated with oral pulmonary vasoactive drugs for portopulmonary hypertension between 2005 and 2015.

them 4 had LT indication: 1 had LT as previously described; for the 3 others patients, POPH treatment was not burdened because two of them had progressive HCC outside Milan criteria and one improved liver function and had no longer LT indication. Among the 4 patients considered as non responders who had no LT indication, 2 were still alive and being followed at the end of study, and 2 died from acute heart failure and acute-on-chronic liver failure.

Among the three patients who were not included in efficacy analysis because of lacking of hemodynamic data, one was still alive at the end of the study, two died during follow-up, 1 from a lung cancer and 1 from unknown cause.

Detailed data describing patients at baseline, and after initiation of PVD, eligibility to LT and survival are shown in Table 4.

As shown in Fig. 2, survival rates were 85% at 12 months, 70% at 24 months, 65% at 36 months, 53% at 48 and 60 months and 35% at 96 months.

There was no difference in survival between responders and non-responders to oral PVD.

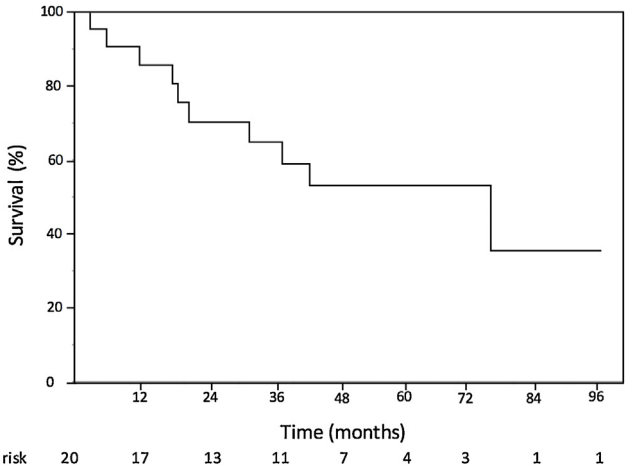

Fig. 2. Survival curves (Kaplan–Meier estimate) of patients orally treated for portopulmonary hypertension.

3.6. Tolerance of oral therapies for POPH

Only two patients had to switch from bosentan to sildenafil, one of them for nausea, and one for moderate cytolysis.

No patient had worsening or onset of ascites or variceal hemorrhage during the period of treatment. Bilirubin was similar between baseline and after oral PVD (37 μmol/L [20–58] versus 26 [23–36], $p = 0.1$), as well as prothrombin time (67% [56–74] versus 66 [49–75], $p = 0.2$), and creatinine (71 μmol/L [60–97] versus 80 [61–96], $p = 0.4$). Continuation of oral PVD after LT was well tolerated without further adverse event. Immunosuppressive regimen did not have to be modified.

4. Discussion

Our retrospective study report a significant cohort of patients treated by oral therapies for POPH and suggest that this strategy is safe and effective: (1) oral treatments significantly improved hemodynamic and clinical parameters, leading to response according to liver transplantation eligibility criteria (MPAP lower than 35 mmHg or $35 \leq$ MPAP < 50 mmHg with PVR lower than 250 dyn s cm^{-5}) in 53% of patients, (2) oral therapies were well tolerated and no serious side effects have been reported. Among patients with indication for LT and who reached LT eligibility criteria, 83% were transplanted. Overall survival was 53% at 5 years and 35% at 8 years.

There is no consensus on the specific management of POPH and treatment are inspired by PAH guidelines [7]: intravenous epoprostenol is reserved for most severe forms of disease, endothelin receptor antagonists, as bosentan or ambrisentan, and phosphodiesterase type-5 inhibitors as sildenafil or tadalafil are reserved for less severe forms. Intravenous epoprostenol was the first treatment used in management of POPH [5]. Awdish et al. [8] have shown that early initiation of epoprostenol made it possible to improve 5-year survival and reduce LT indication. However treatment with epoprostenol has many limitations due to its administration route and side-effects. Recent advance has profoundly changed treatment options in PAH [14], allowing more convenient treatment with fewer side effect. But theoretical liver toxicity, especially of endothelin receptor antagonists, has long hampered their use in patients with POPH. Indeed, bosentan could cause liver injury in 2–18% of patients treated for PAH [15].

Table 4
Detailed baseline clinical, hemodynamic and survival data for the 20 included patients.

	Sexe	Age	Etiology of cirrhosis	Child- Pugh	MELD	Indication for LT	Pulmonary vasoactive drugs	Baseline MPAP	Last MPAP	Baseline PVR	Last PVR	Baseline CI	Last CI	Access to LT eligibility	LT	Outcome (dead/alive)	Total follow-up (months)
1	M	53	ALD + NAFLD	6	8	No	Sildenafil + bosentan	42	44	422	269	5.3	10.1	No	No	Dead	76
2	M	50	ALD	6	11	HCC	Sildenafil + bosentan	53	45	880	520	4.12	5.67	No	No	Dead	12
3	M	51	ALD	5	9	No	Bosentan	50		864		3.62			No	Dead	43
4	F	49	ALD + NAFLD	6	8	No	Bosentan	38	34	312	296	5.9	5.9	Yes	No	Alive	47
5	M	49	ALD + NAFLD	7	9	No	Ambrisentan	51	24	604	168	5.56	7.6	Yes	No	Dead	38
6	M	62	ALD	5	12	No	Bosentan	39	29	255		9.1	9.73	Yes	No	Dead	19
7	M	51	ALD	12	20	Refractary ascites	Sildenafil	42	47	272	210	9.3	13.3	Yes	No	Dead	21
8	F	47	ALD	9	18	No	Sildenafil	30		240		6.4			No	Dead	18
9	M	50	ALD	7	10	HCC	Bosentan	44	53	558	473	2.73	4.76	No	No	Alive	60
10	M	60	ALD	7	11	No	Sildenafil	45	47	480	353	6.76	8.6	No	No	Alive	72
11	F	58	ALD	6	12	No	Sildenafil	55	63	624	616	5.1	5.3	No	No	Alive	36
12	M	46	HCV + ALD	9	13	No	Sildenafil	39	40	320	272	8.18	7.67	No	No	Dead	3
13	F	63	HCV	8	10	Hepatic encephalopa-thy	Sildenafil	59	42	555	307	6.35	7.3	No	No	Dead	32
14	M	54	HCV	9	11	No	Sildenafil		58		560		6.3		No	Alive	43
15	F	30	AIH	8	17	Severe liver failure	Sildenafil + bosentan	65	39	864	400	5	5.6	No	Yes	Alive	53
16	F	37	ALD	5	12	HCC	Bosentan + epoprostenol	46	27	472	176	5.75	7.1	Yes	Yes	Alive	79
17	M	61	ALD	7	12	HCC	Sildenafil	40	18	536	176	4.33	4.4	Yes	Yes	Alive	45
18	M	59	ALD	12	21	Refractory ascites	Sildenafil	37	36	310	216	6.7	4.7	Yes	Yes	Alive	19
19	F	48	ALD	5	9	HCC	Sildenafil + epoprostenol	37	19	464	216	4.13	4.73	Yes	Yes	Alive	96
20	M	54	ALD	7	14	Refractory ascites	Bosentan + tadalafil	46	31	490	239	5.4	7.36	Yes	Yes	Dead	6

ALD: alcoholic liver disease, NAFLD: non alcoholic fatty liver disease, AIH: auto immune hepatitis, HCV: hepatitis C liver disease, LT: liver transplantation; MPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; CI: cardiac index.

The largest cohort of patients treated for POPH came from the REVEAL registry consisting of 1652 patients with PAH, whose 174 with POPH [16]. This observational study showed that (i) patients with POPH was less treated that patients with idiopathic or familial PAH, (ii) ERA was the least used molecule, (iii) PDI was more used that prostacyclin analogues although there was no evidence of efficacy in this indication in literature. Some case reports have suggested that sildenafil and bosentan could improve hemodynamic (MPAP), clinical (6-MWD) and biological (NT-proBNP) parameters, and even allow LT [17–20]. Few studies with small groups of patients have specifically studied PDI use. Gough et al. have shown that sildenafil monotherapy significantly decreased PVR, and decreased MPAP below 35 mmHg in 4 of 9 patients, and allowed LT for 1 patient [21]. Similar results were shown by Hemmes et al. who studied 10 patients [22]. Bosentan was studied by Hoeper et al. [23] and Savale et al. [24] in respectively 18 and 34 patients. They have shown significant and maintained improvement of PVR and MPAP. Ambrisentan was also evaluated, showing efficacy on hemodynamic and clinical parameters in 13 patients [25]. A prospective study is currently ongoing on macitentan, a new ERA, specifically in group of patients with POPH.

One strength of our report is the description of long-term efficacy of oral medications for management of POPH. Indeed median follow-up was more than 3 years while most studies have evaluated short-term response [21–23]. Moreover while previous study described the use of single oral regimen, we also report the use of combination of treatment that was safe in our experience and allowed further improvement in the control of POPH. The main weakness of our report is the retrospective design with its inherent drawbacks. However because these patients are handled by a multidisciplinary cardiology and hepatology team working in liver transplantation for many years, follow-up was relatively homogenous and conservative.

A major issue in the treatment of POPH is the more or less associated liver failure [26]. It is noteworthy that we describe efficacy and tolerance of oral therapies in patients with severe liver disease. Indeed, 60% of patients were Child-Pugh class B or C, some had large varices, ascites or significant hepatic encephalopathy. Whichever the drug used, bosentan, sildenafil, ambrisentan or tadalafil, no significant worsening of cirrhosis related to treatment had occurred. This confirmed the safety of such treatments in patients with cirrhosis. Bosentan was well tolerated in previous studies; but Hoeper et al. [23] have evaluated exclusively Child-Pugh class A cirrhosis. Similarly, Savale et al. [24] included mostly Child A cirrhosis or portal thrombosis without underlying cirrhosis. On a small cohort of 11 severe patients (4 Child-Pugh class C and 7 class B), Gough et al. [21] have shown sildenafil was well tolerated, even in patients with ascites, hepatic encephalopathy or recurrent gastrointestinal bleeding, except for one patient.

One aim of POPH treatment may be to allow LT in a patient with LT indication. Fix et al. reported that treatment enabled 5 of 19 patients to reach LT eligibility criteria and 2 patients to be transplanted [27]. Ashfaq et al. [28] showed positive results with 12 of 16 patients improving to a MPAP lower than 35 mmHg and 11 patients were transplanted, 9 could stop treatment of PAH after LT. However, treatment in both studies was based upon epoprostenol. Our results show that oral treatment allowed 53% of our included patients to reach LT eligibility criteria, and lead 5 patients to liver transplantation among the ten who had initially LT indication. Three of these patients were even able to stop oral therapies after LT without recurrence of POPH. Therefore we could consider that our results are relatively similar but with a more convenient treatment management thanks to oral therapy. These results are in line with previously published study showing that with sildenafil, 4 of 9 and 3 of 10 patients reached LT eligibility in the studies by Gough et al. and Hemmes et al. respectively [21,22], and one patient safely underwent LT in each.

Regarding overall survival, comparison with other reports must be interpreted very cautiously because of the retrospective design for most of the studies, and the selection and follow-up bias. In our study survival was 85% at one year, which is relatively similar to that reported by both the French [26] and the US registry [16] of POPH. At 5 years, survival was 53% which is slightly higher than 40% as described in the US registry [16] and lower than 68% as described in the French registry [26]. Of note, most of the treated patients in both registry had epoprostenol regimen, therefore our results suggest that oral treatment may have similar survival benefits with more convenient treatment management. We have not shown difference of survival according to response to treatment, probably because most of patients died from unrelated to POPH causes.

Guidelines for PAH management suggest PVR and MPAP are prognosis factors [7], and treatment strategy is determined by disease severity, assessed by functional score and hemodynamic data. In our report, we have suggest baseline MPAP and PVR were predictive for non-response to oral treatment for POPH, suggesting that patients with MPAP > 50 mmHg and PVR > 530 dyn s cm^{-5} should be preferentially treated by more aggressive therapy.

While Savale et al. showed that patients with Child-Pugh class B cirrhosis have a better hemodynamic response than those with Child-Pugh class A cirrhosis [24], our results showed liver disease severity had no effect on the response to treatment.

In conclusion, our results show that oral treatment of POPH seems safe and effective regardless of the severity of underlying liver disease. Improvement in mean pulmonary artery pressure and pulmonary vascular resistance allowed 53% of patients to reach liver transplantation eligibility criteria. No significant complication of cirrhosis was related to the introduction of treatment and five-year survival was 53%. Response to treatment could be predicted by baseline MPAP and PVR. Larger and prospective studies are required to confirm these data and lead to guidelines.

Conflict of interest

None declared.

References

[1] Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. Liver Transplantation 2012;18:881–91.
[2] Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. Chest 2010;137:376–87.
[3] Hadengue A, Benhayoun MK, Lebrec D, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991;100:520–8.
[4] Krowka MJ, Swanson KL, Frantz RP, et al. Portopulmonary hypertension: results from a 10-year screening algorithm. Hepatology 2006;44:1502–10.
[5] Swanson KL, Wiesner RH, Nyberg SL, et al. Survival in portopulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. American Journal of Transplantation 2008;8:2445–53.
[6] Kawut SM, Taichman DB, Ahya VN, et al. Hemodynamics and survival of patients with portopulmonary hypertension. Liver Transplantation 2005;11:1107–11.
[7] Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The European Respiratory Journal 2009;34:1219–63.
[8] Awdish RL, Cajigas HR. Early initiation of prostacyclin in portopulmonary hypertension: 10 years of a transplant center's experience. Lung 2013;191:593–600.
[9] Sitbon O, McLaughlin VV, Badesch DB, et al. Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. Thorax 2005;60:1025–30.
[10] Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010–9.
[11] Simonneau G, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Annals of Internal Medicine 2008;149:521–30.

[12] Krowka MJ, Plevak DJ, Findlay JY, et al. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. Liver Transplantation 2000;6:443–50.
[13] Martin P, DiMartini A, Feng S, et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the study of liver diseases and the American Society of Transplantation. Hepatology 2014;59:1144–65.
[14] McLaughlin VV, Shah SJ, Souza R, et al. Management of pulmonary arterial hypertension. Journal of the American College of Cardiology 2015;65: 1976–97.
[15] Fattinger K, Funk C, Pantze M, et al. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. Clinical Pharmacology & Therapeutics 2001;69:223–31.
[16] Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL registry. Chest 2012;141:906–15.
[17] Austin MJ, McDougall NI, Wendon JA, et al. Safety and efficacy of combined use of sildenafil, bosentan, and iloprost before and after liver transplantation in severe portopulmonary hypertension. Liver Transplantation 2008;14:287–91.
[18] Cadden IS, Greanya ED, Erb SR, et al. The use of sildenafil to treat portopulmonary hypertension prior to liver transplantation. Annals of Hepatology 2009;8:158–61.
[19] Grander W, Eller P, Fuschelberger R, et al. Bosentan treatment of portopulmonary hypertension related to liver cirrhosis owing to hepatitis C. European Journal of Clinical Investigation 2006;36(Suppl. 3):67–70.
[20] Makisalo H, Koivusalo A, Vakkuri A, et al. Sildenafil for portopulmonary hypertension in a patient undergoing liver transplantation. Liver Transplantation 2004;10:945–50.
[21] Gough MS, White RJ. Sildenafil therapy is associated with improved hemodynamics in liver transplantation candidates with pulmonary arterial hypertension. Liver Transplantation 2009;15:30–6.
[22] Hemnes AR, Robbins IM. Sildenafil monotherapy in portopulmonary hypertension can facilitate liver transplantation. Liver Transplantation 2009;15:15–9.
[23] Hoeper MM, Seyfarth HJ, Hoeffken G, et al. Experience with inhaled iloprost and bosentan in portopulmonary hypertension. The European Respiratory Journal 2007;30:1096–102.
[24] Savale L, Magnier R, Le Pavec J, et al. Efficacy, safety and pharmacokinetics of bosentan in portopulmonary hypertension. The European Respiratory Journal 2013;41:96–103.
[25] Cartin-Ceba R, Swanson K, Iyer V, et al. Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. Chest 2011;139:109–14.
[26] Le Pavec J, Souza R, Herve P, et al. Portopulmonary hypertension: survival and prognostic factors. American Journal of Respiratory and Critical Care Medicine 2008;178:637–43.
[27] Fix OK, Bass NM, De Marco T, et al. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. Liver Transplantation 2007;13:875–85.
[28] Ashfaq M, Chinnakotla S, Rogers L, et al. The impact of treatment of portopulmonary hypertension on survival following liver transplantation. American Journal of Transplantation 2007;7:1258–64.