Digestive and Liver Disease xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

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

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ARTICLE INFO

Article history:
Received 9 June 2016
Accepted 12 October 2016
Available online xxx

Keywords:
Cirrhosis
Liver transplantation
Portal hypertension
Pulmonary artery hypertension

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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http://dx.doi.org/10.1016/j.dld.2016.10.010
1590-8658/

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.

Please cite this article in press as: Legros L, et al. Oral pulmonary vasoactive drugs achieve hemodynamic eligibility for liver transplantation in portopulmonary hypertension. Dig Liver Dis (2016), http://dx.doi.org/10.1016/j.dld.2016.10.010