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Safety and Efficacy of Ambrisentan for the Treatment of Portopulmonary Hypertension

Rodrigo Cartin-Ceba, MD; Karen Swanson, DO; Vivek Iyer, MD; Russell H. Wiesner, MD; and Michael J. Krowka, MD, FCCP

Background: Ambrisentan is a selective endothelin-receptor antagonist that is approved by the US Food and Drug Administration for the treatment of pulmonary arterial hypertension. We describe hemodynamic responses and clinical outcomes of patients with portopulmonary hypertension (POPH) treated with ambrisentan.

Methods: In this observational study, we prospectively identified and followed consecutive adult patients with POPH who received monotherapy with ambrisentan ≤ 10 mg daily from January 2007 until December 2009. Liver enzymes were assessed monthly. Pulmonary hemodynamic responses were assessed using echocardiograms and right-sided heart catheterizations.

Results: We identified 13 patients (seven men) with POPH and began monotherapy with ambrisentan. The median age was 57 (interquartile range [IQR], 52-60). Patients were followed for a median of 613 days (IQR, 385-1,011). The median model for end-stage liver disease score was 10 (IQR, 8.5-15); eight patients had Child-Turcotte-Pugh A classification. Median time on ambrisentan therapy was 390 days (IQR, 363-611). Two patients died, one of advanced hepatocellular carcinoma and one of septic shock following pneumonia. The mean pulmonary artery pressure decreased from a baseline median of 58 mm Hg (IQR, 37-63) to 41 mm Hg (IQR, 27-48) ($P = .004$). The pulmonary vascular resistance median was reduced from 445 dynes/s/cm^5 (IQR, 329-834) to 174 dynes/s/cm^5 (IQR, 121-361) ($P = .008$). There was no difference in the longitudinal analysis of liver function tests (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and international normalized ratio) after 12 months of therapy. One patient underwent successful liver transplantation and normalized pulmonary hemodynamic responses after transplantation.

Conclusions: In this small cohort of patients with moderate to severe pulmonary hypertension in the setting of POPH, we have shown that ambrisentan monotherapy can significantly improve pulmonary hemodynamic responses without adverse effect on hepatic function.

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Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; ERA = endothelin-receptor antagonist; ET-1 = endothelin 1; ETA = endothelin A; INR = international normalized ratio; IQR = interquartile range; LT = liver transplantation; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAOP = pulmonary artery occlusion pressure; POPH = portopulmonary hypertension; PVR = pulmonary vascular resistance; RHC = right-sided heart catheterization; RVSP = right ventricular systolic pressure; WHO = World Health Organization

Portopulmonary hypertension (POPH) is an uncommon complication of patients with portal hypertension, predominantly in patients with cirrhosis.[1] The prevalence of POPH in patients with liver disease ranges from 4% to 10% in the largest published series.[2] As a subgroup of the recent Dana Point 2008 Clinical Group 1 classification of pulmonary arterial hypertension (PAH),[3] POPH is characterized by increased pulmonary vascular resistance (PVR) causing obstruction to arterial pulmonary flow as determined by right-sided heart catheterization (RHC).[4,5] It has been suggested that POPH portends a poor

prognosis, especially if liver transplantation (LT) is attempted when the mean pulmonary artery pressure (mPAP) is > 35 mm Hg.[5-7] The 5-year survival rate of untreated patients with POPH is dismal (~14%) but can improve significantly when medical treatment is provided, with recent data reporting a 5-year survival rate of 68%.[2] There have been no controlled, randomized studies to date addressing medical treatment of POPH.[8,9]

Treatment of POPH has been based on data extrapolated from clinical trials performed in patients with idiopathic PAH. IV epoprostenol is currently

the best-studied drug for the treatment of POPH, and patients have shown hemodynamic improvement in the largest series published to date.[1] However, IV epoprostenol is not an easy treatment to administer, with its 24-h continuous IV delivery system requiring drug mixture and central venous access and having possible infectious complications. Oral therapy options have been successfully used in the treatment of POPH in small groups of patients, including the phosphodiesterase-5 inhibitor sildenafil and the dual endothelin-receptor antagonist (ERA) bosentan. Sildenafil is prescribed three times a day, and bosentan can cause a transient increase in liver function enzymes in $\leq 11\%$ of patients, which can be particularly worrisome in patients with POPH.[10] Ambrisentan is a newer ERA with potential advantages: highly selective ERA antagonism, once-daily doses, and rare elevation in liver enzymes. We aimed to describe the hemodynamic responses and clinical outcomes of patients with POPH and treated with ambrisentan at the Mayo Clinic, in Rochester, Minnesota, from January 2007 to December 2009.

Materials and Methods

The Mayo Clinic institutional review board approved the Pulmonary Vascular Complications of Liver Disease (PVCLD) data collection. We prospectively identified and followed consecutive adult (≥ 18 years old) patients with POPH evaluated at the Mayo Clinic from January 2007 to December 2009 who were treated with ambrisentan as monotherapy (group 1, World Health Organization [WHO] functional class 2 or 3). Three patients refused the suggested IV prostacyclin therapy; no patient seen during this time span was started on IV, subcutaneous, or inhaled prostacyclin; and no patient was started on a phosphodiesterase inhibitor. The diagnosis of pulmonary hypertension was suggested in these patients with well-documented liver disease following routine screening using Doppler echocardiography (right ventricular systolic pressure [RVSP] > 50 mm Hg).[11] Each patient subsequently underwent clinically indicated outpatient RHC for pulmonary and systemic hemodynamic assessment. The POPH was defined according to the following criteria[12]: portal hypertension and/or clinical diagnosis of chronic liver disease (diagnosis of portal hypertension was made based on the presence of esophageal and/or gastric varices observed during upper endoscopy, and the clinical diagnosis of chronic liver disease was made by a hepatologist taking into consideration laboratory, clinical, ultrasonographic, endoscopic,

and histopathologic data where available), mPAP > 25 mm Hg at rest, PVR > 240 dynes/s/cm[5], and pulmonary artery occlusion pressure (PAOP) < 15 mm Hg or a transpulmonary gradient > 12 mm Hg.

As part of standard of care clinical practice, patients received ambrisentan 5 mg po daily for 4 weeks, with a dosage increase to 10 mg po daily thereafter in the absence of side effects and with adequate tolerability. Liver function test results (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and total bilirubin) were assessed monthly. Clinical characteristics were abstracted from electronic medical records and included demographic data, laboratory data (including baseline and monthly liver function test results, renal function, and B-type natriuretic peptide [BNP] levels), model for end-stage liver disease score, Child-Turcotte-Pugh classification, WHO functional class, smoking status, pulmonary function test results (spirometry, lung volumes, and diffusing capacity), etiologic characteristics of portal hypertension, etiologic characteristics of cirrhosis, medications, and date and cause of death. Data abstracted also included systemic BP and heart rate, baseline and follow-up echocardiographic data (ejection fraction, RVSP, and right ventricle size and function). Baseline and follow-up hemodynamic data were assessed using RHC (mPAP, PAOP, PVR, cardiac output) accomplished ≤ 15 months after the start of therapy. Patients were followed from the time of initiation of ambrisentan therapy to December 2009.

Statistical Analysis

All continuous data are summarized as medians and interquartile range (IQR) or means and SD. Categorical data are summarized as percentages. Differences in medians between groups were tested using the Wilcoxon sign rank test. Differences in proportions were compared using the χ^2 test or the Fisher exact test. For longitudinal data, analysis was performed with repeated measures and analysis of variance. JMP statistical software, version 8.0 (SAS; Cary, North Carolina) was used for all analyses. A P value $< .05$ was considered statistically significant.

Results

During the observation period, we identified 13 patients with POPH who were started on ambrisentan as monotherapy. Baseline clinical characteristics of the cohort are described in Table 1. All patients were considered to have at least moderate POPH, with an mPAP > 35 mm Hg. The patients were followed for a median of 613 days (IQR, 385-1,011). One patient stopped the medication after 2 weeks of therapy because of bilateral periorbital bleeding, peripheral edema, and a weight gain of 8 pounds, which resolved after discontinuing ambrisentan. After excluding this patient, 11 of 12 patients were put on the maximum dosage of 10 mg/d. Patients who refused parental prostacyclin therapy had PVR calculations of 1,134, 656, and 456 dynes/s/cm[5]. The median duration for ambrisentan therapy was 390 days (IQR, 363-611). The main cause of the portal hypertension was cirrhosis (11 patients, 85%); the other two cases were caused by portal vein thrombosis and Budd-Chiari syndrome. The most common cause of

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cirrhosis was alcohol use (six patients, 46%), followed by hepatitis C (three patients, 23%) and one patient each with autoimmune hepatitis and nonalcoholic fatty liver disease. One patient was on anticoagulation therapy with warfarin (Budd-Chiari syndrome), and six patients were receiving oral β-blockers for portal hypertension before the diagnosis of POPH and were continued on these medications. Two patients died during the study period, one of advanced hepatocellular carcinoma 3 months after starting therapy with ambrisentan and one of septic shock following pneumonia 4 weeks after starting therapy with ambrisentan. The median time to RHC after initiation of ambrisentan therapy was 325 days (IQR 280-370). Postambrisentan mPAP data, measured 3 to 18 months after therapy, were available in eight patients.

Figure 1 illustrates the individual measurements of mPAP, PVR, and cardiac output at the baseline and after ambrisentan therapy, and it shows the differences in eight individuals for whom the RHC data were available. There is a statistically significant reduction in the mPAP from a median of 58 mm Hg (IQR, 37-63) to a median of 41 mm Hg (IQR, 27-48, $P = .004$). A reduction in PVR was noted in all individuals ($P = .008$), and the PVR was normalized in five of eight patients (Fig 1). The difference in the median PVR before and after ambrisentan therapy was 291 dynes/s/cm^5, which is a 61% absolute reduction in the calculated resistance (Table 2). Cardiac
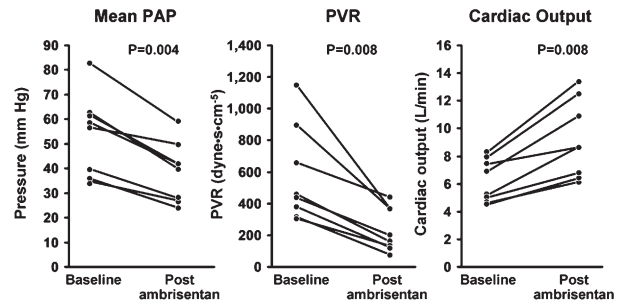

FIGURE 1. Individual mean PAP, PVR, and cardiac output at the baseline and after therapy with ambrisentan (median therapy of 390 days). PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance.

output increased after ambrisentan treatment in all eight subjects, as shown in Figure 1 ($P = .008$). Table 2 summarizes the hemodynamic data as assessed by RHC in addition to the WHO functional class before and after therapy with ambrisentan. No differences were observed in the PAOP between the baseline and posttreatment data ($P = .46$). The median WHO functional class was reduced from 3 (IQR, 2-3) to 1.5 (IQR, 1-2, $P = .008$) after 1 year of therapy. The systemic systolic and diastolic BPs did not present clinical or statistically significant changes at the baseline and after therapy with ambrisentan, as shown in Figure 2A. The RVSP (echocardiogram, all patients had available data) presented a statistically significant reduction from the baseline over a 1-year period after initiation of ambrisentan ($P = .04$); however, the effect was mainly observed after the first 3 months, with a plateau in pressures, as observed in Figure 2A. The BNP levels (all patients had available data) presented a more sustained drop during 12 months of follow-up after initiation of therapy (Fig 2B).

There were no statistical differences in the levels of AST, ALT, and total bilirubin at the baseline and after therapy with ambrisentan over a 12-month follow-up period (Fig 3A). The levels of creatinine and the international normalized ratio (INR) did not present statistically significant variations during the 12-month follow-up period after ambrisentan initiation (Fig 3B).

At the time of this analysis, one patient with significant encephalopathy underwent successful cadaveric LT after 4 months of ambrisentan therapy (mPAP decreased from 35 to 27 mm Hg, PVR improved from 314 to 73 dynes/s/cm^5, and cardiac output improved from 6.8 to 10.9 L/min). Ambrisentan at a reduced dose (5 mg) was continued and then stopped, with no adverse effect on the concomitant use of tacrolimus 3 months post-LT. A repeat echocardiogram demonstrated normal RVSP and normal right ventricular size and function. The rest of the patients are currently undergoing evaluation for LT.

Table 1—Baseline Characteristics of 13 Patients With Portopulmonary Hypertension

Clinical Characteristics	Patients (N = 13)
Age, y, median (IQR)	57 (52-60)
Male gender, No. (%)	7 (54)
White, No. (%)	12 (92)
BMI, kg/m², median (IQR)	28.4 (24.3-32.1)
Smoking history, No. (%)	9 (69)
Alcoholic cirrhosis, No. (%)	6 (46)
Cirrhosis, No. (%)	11 (85)
MELD score, median (IQR)	10 (8.5-15)
Child-Turcotte-Pugh A classification, No. (%)	8 (62)
FEV$_1$/FVC, median (IQR)	74 (67-76)
FEV$_1$, % predicted, median (IQR)	83 (72-93)
FVC, % predicted, median (IQR)	93 (75-104)
TLC, % predicted, median (IQR)	96 (90-107)
Dlco, % predicted, median (IQR)	65 (46-92)
Baseline echocardiographic RVSP, mm Hg, median (IQR)	78 (66-96)
Baseline echocardiographic LVEF, %, median (IQR)	66 (63-69)
WHO functional class, median (IQR)	3 (2-3)

Dlco = diffusing capacity of lung for carbon monoxide; IQR = interquartile range; LVEF = left ventricular ejection fraction; MELD = model for end-stage liver disease; RVSP = right ventricular systolic pressure; TLC = total lung capacity; WHO = World Health Organization.

Clinical Characteristics	Baseline	After Ambrisentan Treatment	Percentage Change	P Value
mPAP, mm Hg, median (IQR), n = 8	58 (37-63)	41 (27-48)	−29	.004
PVR, dynes/s/cm⁵, median (IQR), n = 8	445 (329-834)	174 (121-361)	−61	.008
PAOP, mm Hg, median (IQR), n = 8	12 (8-14)	14 (13-19)	+14	.46
Cardiac output, L/min, median (IQR), n = 8	6 (4.7-7.7)	8.6 (6.5-12)	+27	.008
WHO functional class, median (IQR), n = 11	3 (2-3)	1.5 (1-2)	−50	.008

mPAP = mean pulmonary artery pressure; PAOP = pulmonary artery occlusion pressure; PVR = pulmonary vascular resistance. See Table 1 for expansion of other abbreviations.

Discussion

This single-institution observational study demonstrates that monotherapy with ambrisentan is effective and safe for the treatment of patients with POPH, as evidenced by significant improvements in hemodynamic measurements (mPAP, PVR, and cardiac output), biomarkers (BNP), and symptoms (WHO functional class) with no deterioration in systemic BP, liver function test results, or renal function. Ambrisentan was well tolerated, with only one patient stopping the medication because of side effects not related to elevation of liver function. Ambrisentan therapy allowed one other patient to be successfully bridged to LT.

Concomitant with the hemodynamic improvement, our cohort of patients showed a significant improvement in their symptoms, as shown by the functional class change before and after therapy with this newer ERA. We believe that it is also very important to comment that these beneficial hemodynamic and symptomatic changes were followed by excellent tolerability, with no significant change in systemic BP and no elevation of hepatic transaminase, total bilirubin, INR, or creatinine levels. The two deaths observed in this cohort were unrelated to ambrisentan use and were secondary to complications of the patients' underlying chronic liver disease.

Survival in patients with POPH has improved with medical treatment,[2] which has traditionally included the use of prostanoids, phosphodiesterase inhibitors, and ERAs such as bosentan and ambrisentan. Plasma levels of endothelin 1 (ET-1) are elevated (up to 10-fold) in patients with PAH and are strongly correlated with increased mean right atrial pressure and severity of the disease.[13] Two receptor subtypes mediate the effects of ET-1: endothelin A (ETA) receptors and endothelin B receptors. Under normal physiologic conditions, the receptor types have broadly opposing functions. Activation of ETA receptors mediates vasoconstriction, proliferation, hypertrophy, cell migration, and fibrosis, whereas activation of endothelin B receptors stimulates the release of potent vasodilators (nitric oxide and prostacyclin), which exhibit antiproliferative properties and prevent apoptosis.[13] Therefore, selective antagonism over ETA receptors

is desired in patients with PAH. Bosentan is an oral agent approved by the US Food and Drug Administration in 2002 for treatment of PAH. It has minimal selectivity over the ETA receptors, and elevation of hepatic aminotransferase levels is a common phenomenon in patients treated with bosentan, occurring in ≤ 11% of patients receiving 125 mg bid.[14] This is of significant concern in patients with POPH because of their preexisting liver disease. Bosentan has been used successfully in the treatment of POPH in a number of case reports with minimal or no significant elevation in liver enzymes.[15-18] In addition, the largest series of patients with POPH treated with bosentan (mainly Child-Turcotte-Pugh A classification) showed a significant reduction in PVR with no adverse effects on liver function enzymes.[19,20]

As opposed to bosentan, ambrisentan is a highly selective ETA receptor antagonist.[21] It has proven efficacy (via 6-min walk tests and hemodynamic responses) in the treatment of patients with PAH in two large, well-designed, 12-week, placebo-controlled, phase 3 trials.[22] Despite these beneficial data, patients with POPH were not included in these studies, and no study has reported the use of ambrisentan in patients with POPH. Besides its selective ETA antagonism, ambrisentan also has the advantages of once-daily doses, minimal drug interactions (especially with common medications used in patients with pulmonary
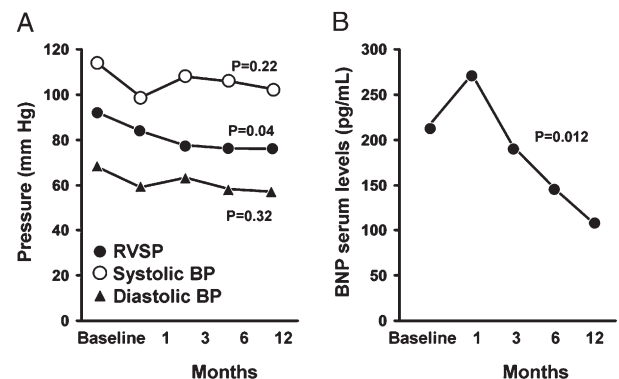

FIGURE 2. A, Systemic systolic and diastolic BP and RVSP assessed by echocardiogram. B, BNP levels. Assessments were performed at the baseline and after 12-month follow-up postinitiation of ambrisentan therapy. BNP = B-type natriuretic peptide; RVSP = right ventricular systolic pressure.
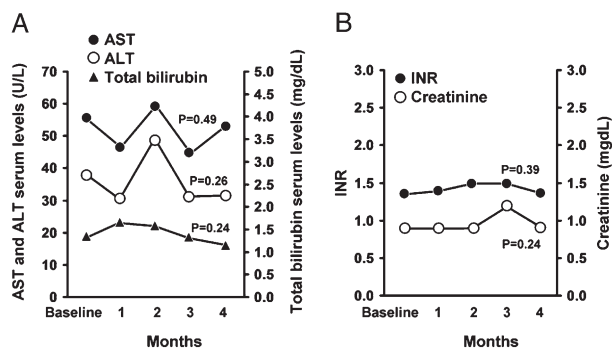
FIGURE 3. A, Liver function tests results for AST, ALT, and total bilirubin. B, Liver function tests results for INR and creatinine. Tests were performed at the baseline and after 12-month follow-up postinitiation of ambrisentan therapy. ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio. See Figure 2 legend for expansion of other abbreviations.

hypertension such as sildenafil and warfarin), and minimal effect on liver function.

The implications of using ambrisentan to facilitate successful LT require further study. Our case was instructive in that the patient had significant encephalopathy and moderate POPH. He and his family were unable to learn the process of using 24-h continuous prostacyclin, and his family would only accept an oral therapeutic option. The appropriate transplant candidates, severity of POPH, and potential combination therapy with a prostanoid or phosphodiesterase inhibitor are clinically important issues that can be patient specific. It is of interest to note that improvement in mPAP with ambrisentan (or any pulmonary-modulating therapy) in patients with POPH can reach the threshold of 35 mm Hg that many centers prefer to see before proceeding to LT. In selected cases, however, the improvement in PVR can be fairly dramatic and even normalize, as seen in five of our patients. In the setting of improved or normal right ventricular function, such elevated mPAP (> 35 mm Hg) and normal PVR may well be a high-flow phenomenon and would not, by itself, be a contraindication to LT, in our opinion.

We acknowledge several limitations. First, our study was observational and the treatment regimen was not randomized and did not follow a protocol during the treatment of patients with POPH. Patient selection for treatment could have been potentially biased because it was often dependent on physician/patient choice rather than a protocol. However, no patients were excluded from consideration of oral ambrisentan because they were started on prostacyclin or phosphodiesterase therapy. In addition, our study presents a relatively small group of patients, although this is, to our knowledge, the largest group of patients with POPH treated with ambrisentan. Other points include the predominantly white population studied and the

fact that the study was performed at a tertiary referral center and the findings may not be generalizable to other settings. In conclusion, in this small cohort of patients with moderate to severe pulmonary hypertension and POPH, we have shown that ambrisentan monotherapy can significantly improve pulmonary hemodynamic responses without adverse effect on hepatic function.

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