Eur Respir J 2013; 41: 96–103
DOI: 10.1183/09031936.00117511

Efficacy, safety and pharmacokinetics of bosentan in portopulmonary hypertension

Laurent Savale*,#,¶,f, Romain Magnier+,f, Jérôme Le Pavec*,#,¶, Xavier Jaïs*,#,¶, David Montani*,#,¶, Dermot S. O'Callaghan*,#,¶, Marc Humbert*,#,¶, Jasper Dingemanse§, Gérald Simonneau*,#,¶ and Olivier Sitbon*,#,¶

ABSTRACT: Data on treatment of patients with portopulmonary hypertension (PoPH) are limited, as they are usually excluded from randomised controlled trials with pulmonary arterial hypertension (PAH)-specific therapies. This study investigated the short- and long-term efficacy/safety of bosentan in these patients, as well as its pharmacokinetics.

All 34 consecutive patients with PoPH treated with first-line bosentan (December 2002 to July 2009) were retrospectively evaluated. Assessments included the New York Heart Association functional class (NYHA FC), blood tests, haemodynamics, 6-min walk distance (6MWD) and event-free status. The pharmacokinetics of bosentan in five patients with Child–Pugh (C-P) class B cirrhosis were compared with idiopathic PAH patients.

Significant improvements from baseline were observed in NYHA FC, 6MWD and haemodynamics, and were largely maintained during follow-up. Patients with C-P class B cirrhosis (n=9) had significantly larger haemodynamic improvement after mean±SD 5±2 months. Mean follow-up time was 43±19 months; four patients died and seven patients had significant elevation of liver enzymes (annual rate 5.5%). Plasma concentrations of bosentan were higher in patients with C-P class B cirrhosis than those observed in idiopathic PAH.

These data confirm the benefit of bosentan treatment for patients with PoPH. Haemodynamic improvements were particularly pronounced in patients with more severe cirrhosis. The safety profile of bosentan was consistent with previous studies.

KEYWORDS: Bosentan, cirrhosis, endothelin receptor antagonists, hypertension, portopulmonary hypertension, pulmonary

Portopulmonary hypertension (PoPH) is defined as pulmonary arterial hypertension (PAH) associated with portal hypertension, with or without advanced hepatic disease. The disease is classified as group 1 pulmonary hypertension (PH) in the current PH classification [1]. Although it shares many characteristics with idiopathic PAH (IPAH), including pathophysiological changes in lung microvasculature, the haemodynamics of PoPH can be somewhat different at baseline with higher cardiac output and lower pulmonary vascular resistance.

According to estimates, 2–6% of patients with portal hypertension and ~1–2% of those with cirrhosis have PoPH [2–5]. PoPH is a relatively common cause of PH, representing 15% of patients enrolled in the French PAH registry [6]. Estimates of survival in patients with PoPH have varied widely among published studies [7–10]. The US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) database, in which data from >2,700 patients were collected, identified PoPH as an independent predictor of increased mortality among PAH patients (hazard ratio 3.6, 95% CI 2.4–5.4) [11]. In contrast, LE PAVEC *et al*. [7] found that 1-, 3- and 5-yr survival rates among patients followed at the French National Referral Centre (Hôpital le Kremlin Bicêtre, Bicêtre, France) were 88%, 75% and 68%, respectively, suggesting that these patients may in fact have less severe outcomes [7]. Poorer prognosis was associated with Child–Pugh (C-P) class B or C cirrhosis, high right atrial pressure and low cardiac index. Differences in the severity of liver disease at time of first assessment among the different series may in part explain the discordance of findings.

In contrast with other types of associated PAH, patients with PoPH have been excluded from the large clinical trials in PAH and there have been no controlled studies of PAH-specific therapies exclusively in PoPH. The majority of data on

AFFILIATIONS
*Université Paris-Sud 11, Faculté de Médecine,
#AP-HP, Centre de Référence de l'Hypertension Pulmonaire Sévère, Hôpital Bicêtre, Le Kremlin Bicêtre,
¶INSERM U999 ''Hypertension Artérielle Pulmonaire, Physiopathologie et Innovation Thérapeutique'', Centre Chirurgical Marie-Lannelongue, Le Plessis-Robinson, and
+Service de Pneumologie, Centre Hospitalier Universitaire, Caen, France.
§Actelion Pharmaceuticals Ltd, Dept of Clinical Pharmacology, Allschwil, Switzerland.
fThese authors contributed equally to this article.

CORRESPONDENCE
O. Sitbon
Service de Pneumologie
Hôpital Bicêtre
78 rue du général Leclerc
94270 Le Kremlin Bicêtre
France
E-mail: olivier.sitbon@bct.aphp.fr

Received:
July 10 2011
Accepted after revision:
May 14 2012
First published online:
May 31 2012

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

treatment of PoPH, therefore, derive from case series and case reports. A number of such reports suggest that the dual endothelin receptor antagonist (ERA) bosentan is well tolerated and effective in this population [12–18]. In a small study, treatment with bosentan proved to be efficacious and well tolerated in patients with C-P class A cirrhosis [19, 20]. Furthermore, the pharmacokinetics of bosentan and its metabolites in patients with C-P class A did not differ to a relevant extent from those in healthy subjects [21]. However, to date, there has been only one case report of treatment with bosentan in a single patient with more advanced liver disease [17]. This lack of data is mainly due to safety concerns associated with impaired metabolism and potentially increased risk of liver abnormalities in patients with advanced liver diseases. Indeed, bosentan is not approved for C-P class B and C patients.

This present study provides data on both the short- and long-term efficacy of the use of bosentan in patients with PoPH, as well as safety, tolerability and some pharmacokinetic data. It is the first study to investigate the effect of treatment in patients with PoPH and cirrhosis, which included C-P class B patients.

PATIENTS AND METHODS

Study subjects

This was a retrospective study that aimed to describe the short- and long-term outcome of unselected patients with PoPH treated with first-line bosentan, including patients with noncirrhotic portal hypertension and patients with C-P class A and B cirrhosis.

Data were analysed from a total of 34 consecutive patients with PoPH treated with first-line bosentan between December 2002 and July 2009 at the French Reference Center for severe PH.

PAH was diagnosed by means of right heart catheterisation (RHC) showing a mean pulmonary arterial pressure (P_{pa}) at rest of >25 mmHg, a pulmonary capillary wedge pressure <15 mmHg, and a pulmonary vascular resistance (PVR) of >3 Wood units [22]. Acute vasodilator testing with inhaled nitric oxide (10 ppm) was performed in all patients, as previously described [23]. The presence of primary lung disease and post-embolic PH was excluded by performing pulmonary function tests, computed tomography of the chest and ventilation/perfusion lung scanning.

The diagnosis of portal hypertension was based on haemodynamic measurement of a hepatic venous pressure gradient of >5 mmHg, or the presence of oesophageal varices at endoscopy or portal vein thrombosis diagnosed by Doppler abdominal ultrasound. Cirrhosis was documented by history of liver biopsy findings or typical clinical and/or biological signs.

According to French legislation, ethics committee agreement and provision of informed consent are not required for retrospective collection of data corresponding to current practice. The database was, however, compiled anonymously within the restrictive requirements of the Commission Nationale Informatique et Liberté, the organisation dedicated to privacy, information technology, and civil rights in France. The present study was approved by the local institutional review board (CHU Bicêtre, France). Informed consent was obtained for the pharmacokinetic study. Five patients with C-P class B cirrhosis and three patients with IPAH were included in the pharmacokinetic substudy (AC-052-114), which was approved by the ethics committee.

Treatment

All patients received nonspecific supportive therapies in accordance with current guidelines, diuretics to control signs and symptoms of right heart failure (including peripheral oedema), and long-term oxygen therapy if hypoxaemia was present [24]. Anticoagulants are not usually administered in the presence of severe hepatocellular insufficiency and/or thrombocytaemia due to hypersplenism.

Bosentan was prescribed according to the European Summary of Product Characteristics at 62.5 mg *b.i.d.* for 4 weeks, followed by 125 mg *b.i.d.* thereafter. All patients had liver enzyme concentrations less than three-fold the upper limit of normal (ULN) before initiation of bosentan. For seven patients (four with C-P class B cirrhosis and three with C-P class A cirrhosis), the dosing regimen was maintained at 62.5 mg *b.i.d.* because of mildly increased liver enzyme concentrations less than three-fold the ULN at baseline. Liver function tests were performed every 2 weeks during the first 6 weeks and monthly thereafter. In the event of elevated liver enzymes, bosentan was stopped or the dosage was reduced, in accordance with current recommendations [25].

Assessments

All patients underwent a complete baseline evaluation before starting bosentan therapy, including assessment of modified New York Heart Association functional class (NYHA FC), physical examination, routine blood tests, non-encouraged 6-min walk distance (6MWD) and resting haemodynamic variables measured by RHC. Patients were reassessed for all parameters at short- and long-term time-points. Haemodynamic assessment was repeated 3–6 months after bosentan initiation, then every year or in case of clinical worsening. Noninvasive assessments were also repeated every 4–6 months. The first and last evaluation on bosentan monotherapy were analysed for the study.

Event-free status was defined as the survival time without introduction of prostacyclin analogues and/or phosphodiesterase type-5 inhibitor therapy, discontinuation of bosentan or acute right heart failure requiring hospitalisation for intravenous diuretics and/or dobutamine infusion.

Pharmacokinetics

Five patients with C-P class B cirrhosis were included in a pharmacokinetic substudy and compared with three patients with IPAH. Blood samples for the determination of plasma concentrations of bosentan and its three metabolites (Ro 47-8634, Ro 48-5033 and Ro 64-1056) were taken at regular intervals (predose, and 1, 2, 3, 4, 5, 6, 9 and 12 h after drug intake) over a dosing interval after patients had been on stable bosentan treatment for at least ⩾14 days. Ro 48-5033 is the only pharmacologically active metabolite. Plasma concentrations were determined with a validated liquid chromatography–tandem mass spectrometry assay [26]. The pharmacokinetic variables were assessed by noncompartmental analysis (WinNonlin; Pharsight, Mountain View, CA, USA).

All patients with C-P class B cirrhosis were included in the pharmacokinetic substudy 14 days after the start of treatment with bosentan at 62.5 mg *b.i.d.* Two patients with IPAH were treated with bosentan at 125 mg *b.i.d.* and one at 62.5 mg *b.i.d.* at the time of the pharmacokinetic substudy. Pharmacokinetic variables were normalised to a dose of 125 mg *b.i.d.* This is justified in view of the small dose range investigated in this study and because the pharmacokinetics of bosentan are proportional to dose over a wide dose range [27].

Analysis

Results are expressed as mean±SD or as median. Baseline and post-baseline values for 6MWD and haemodynamic variables were compared using a two-sided paired t-test. For the subgroup of patients for whom baseline data, data after 4 months and data at last evaluation were available, comparisons were made using ANOVA. Changes in NYHA FC were compared using the Chi-squared test. A p-value <0.05 was to be considered statistically significant. Analyses of event-free status were performed using an intention-to-treat approach and the Kaplan–Meier method. The date of initiation of bosentan therapy was the starting point for determining the follow-up duration and estimating survival. Patients lost to follow-up were censored as of the date of the last bosentan prescription.

RESULTS

Between December 2002 and July 2009, 77 patients with newly diagnosed PoPH were evaluated in our centre. Among them, 10 did not receive any PAH-specific therapy, 17 were treated with first-line sildenafil, 11 with *i.v.* epoprostenol, one with inhaled iloprost and four with combination therapy (bosentan in association with sildenafil or epoprostenol). Finally, 34 patients were given first-line bosentan monotherapy and constituted the patient population of this study. Patient demographics at baseline, as well as aetiologies of liver disease, are shown in table 1. Six patients had portal thrombosis without cirrhosis. Among the 28 patients with cirrhosis, 19 were classified into C-P class A and nine into class B. Five patients with C-P class B cirrhosis were included in the pharmacokinetic substudy. No patient displayed positive acute vasodilator response to inhaled nitric oxide at first haemodynamic assessment.

Short-term efficacy

Short-term evaluation was performed after mean±SD 5±2 months after bosentan initiation. Significant improvements from baseline were observed in 6MWD, NYHA FC and haemodynamic variables (table 2). Pulmonary haemodynamic data significantly improved with an increase in cardiac index and a decrease in PVR by a mean of 39% and 31%, respectively.

The short-term haemodynamic response was significantly better in patients with C-P class B cirrhosis compared with those with C-P class A cirrhosis or with noncirrhotic portal hypertension (fig. 1). Individual data for patients with C-P class B cirrhosis after first evaluation of treatment are shown in table 3. Notably, PVRs were either near-normalised or normalised (<3 Wood units) in a subset of patients with cirrhosis C-P class B after 4 months of bosentan treatment.

TABLE 1 Baseline demographic, clinical, biological and haemodynamic characteristics

Patients	34
Demographics	
Age yrs	50±12
Male/female	16/18
NYHA FC I/II/III/IV	0/4/28/2
6MWD m	352±104
Haemodynamics	
P_{ra} mmHg	10±7
Mean P_{pa} mmHg	50±10
P_{pcw} mmHg	10±4
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.8±0.7
PVR Wood units	8.7±3.3
S_{v,O_2} %	63±9
Liver status	
Portal vein thrombosis	6
Cirrhosis Child–Pugh stage A/B	19/9
Aetiology of cirrhosis	
Alcoholic cirrhosis	20
Chronic hepatitis C infection	4
Mixed aetiology (alcohol + hepatitis C)	3
Autoimmune hepatitis	1
Biological data	
AST $IU \cdot L^{-1}$	42±16
ALT $IU \cdot L^{-1}$	32±12
Total bilirubin $\mu mol \cdot L^{-1}$	25±13
Platelet count $\times 10^6$ cells$\cdot L^{-1}$	108±49

Data are presented as n or mean±SD. NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; P_{pa}: pulmonary artery pressure; P_{pcw}: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; S_{v,O_2}: mixed venous oxygen saturation; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

After first evaluation, bosentan monotherapy was continued in 27 patients and sildenafil was added in seven. All these seven patients had cirrhosis C-P class A.

Long-term efficacy

24 patients were assessed at least three times under bosentan monotherapy. The last evaluation of these patients was conducted 35±16 months (range 12–75 months) after bosentan initiation. The remaining 10 patients did not undergo long-term evaluation on monotherapy with bosentan for the following reasons: seven patients received sildenafil in addition to bosentan after the first evaluation, sildenafil was introduced to replace bosentan in one patient because of liver toxicity and two patients were receiving bosentan monotherapy but had only one evaluation at cut-off. In patients who were evaluated at least three times, improvements in haemodynamic variables observed in the short term were largely maintained, with significant improvement in NYHA FC and increase over baseline in cardiac index and PVR (table 2). 6MWD significantly improved from baseline in this group of patients at final assessment. Individual data for patients with C-P class B after 37±25 months of treatment are shown in table 3.

TABLE 2 Functional class, exercise capacity and haemodynamics at baseline and on bosentan monotherapy and follow-up evaluations in patients treated exclusively by bosentan monotherapy

	Patients evaluated more than once[#]		Patients evaluated at least three times[¶]		
	Baseline	First evaluation[+]	Baseline	First evaluation	Last evaluation[§]
NYHA FC I/II/III/IV	0/4/28/2	1/23/10/0***	0/3/19/2	1/16/7/0***	4/12/7/1**
6MWD m	352±104	403±86***	358±108	413±92	431±122*
P_{ra} mmHg	10±7	6±4*	8±6	5±4	6±5
Mean P_{pa} mmHg	50±10	43±13***	49±10	40±12*	43±14
CI L·min^{-1}·m^{-2}	2.8±0.7	3.7±1***	2.7±0.6	3.8±0.8***	3.7±0.9***
PVR Wood units	8.7±3.2	5.7±3***	8.7±3	4.9±1.9***	5.6±2.9***
S_{v,O_2} %	63±9	69±6*	63±10	70±6*	67±10

Data are presented as n or mean±SD. NYHA FC: New York Heart Association functional class; 6MWD: 6-min walk distance; P_{ra}: right atrial pressure; P_{pa}: pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; S_{v,O_2}: mixed venous oxygen saturation. [#]: n=34; [¶]: n=24; [+]: first evaluation performed on bosentan monotherapy 5±2 months after treatment initiation (range 4–12 months); [§]: last evaluation performed on bosentan monotherapy 35±16 months after treatment initiation (range 12–75 months). *: p<0.05 *versus* baseline; **: p<0.01 *versus* baseline; ***: p<0.001 *versus* baseline.

Effect of bosentan therapy on overall and event-free survival

At the cut-off date (May 31, 2010), the mean follow-up period was 43±19 months. Event-free survival estimates were 82%, 63% and 47% at 1, 2 and 3 yrs, respectively. Event-free survival curves were similar in patients with noncirrhotic portal hypertension or C-P class A cirrhosis and patients with more severe C-P class B cirrhosis (fig. 2a).

12 patients required additional PAH-specific therapies during the follow-up period. All of them received sildenafil in combination with bosentan.

Four patients died during follow-up at 21, 36, 61 and 67 months, respectively. Three had cirrhosis C-P class A and 1 had cirrhosis C-P class B. The cause of death was right heart failure for three patients and hepatocellular carcinoma for one patient (fig. 2b).

Safety

A significant elevation of liver enzymes (>3× the ULN) was observed in seven patients, corresponding to an annual rate of 5.5%. Among these seven patients, bosentan was discontinued in three patients with C-P class A cirrhosis after 6, 15 and 33 months, and two others with C-P class B cirrhosis after 16 and 58 months due to increased liver enzymes. Bosentan was discontinued in three patients who received moderately high dosage (62.5 mg *b.i.d.*) because of a moderately elevated level of liver enzymes at baseline of 1–3× the ULN. In all cases, sildenafil was introduced to replace bosentan. Annual rate of increase in liver enzymes was 4.1% (95% CI 0.2–8%) in patients with noncirrhotic portal hypertension and with cirrhosis C-P class A, and 12.4% (95% CI 0.7–25.6%) in patients with cirrhosis C-P class B (not statistically significant). In six cases, normalisation of hepatic transaminase levels was observed during the 3 months following bosentan dose reduction or discontinuation. In one other case, persistently abnormal liver enzyme levels were attributed to underlying hepatocellular carcinoma.

Pharmacokinetics

Figure 3 shows the dose-normalised plasma concentration–time profiles of bosentan in five PoPH patients with C-P class B

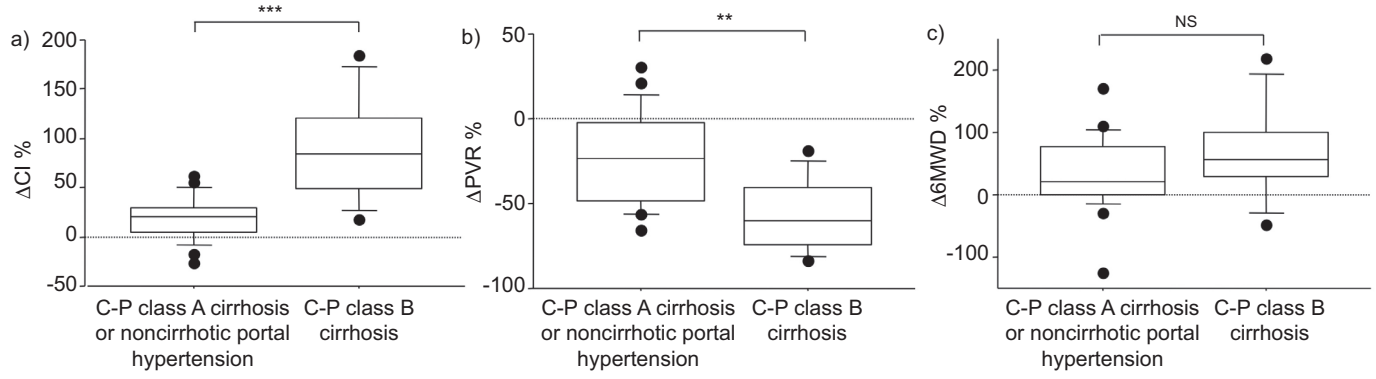

FIGURE 1. Comparison of change (Δ) in a) cardiac index (CI), b) pulmonary vascular resistance (PVR) and c) 6-min walk distance (6MWD) in patients with noncirrhotic portal hypertension or cirrhosis Child–Pugh (C-P) class A (n=23) and patients with cirrhosis C-P class B (n=8) 4 months after the initiation of bosentan according to the severity of the underlying liver disease. Results show that patients with C-P B cirrhosis have a greater haemodynamic improvement after 4 months of bosentan. NS: nonsignificant. **: p<0.01; ***: p<0.001.

TABLE 3 Functional class, exercise capacity and haemodynamics at baseline and on bosentan therapy in patients with Child–Pugh (C-P) class B cirrhosis and follow-up evaluations in patients with C-P class B cirrhosis treated exclusively with bosentan monotherapy

Patient	Baseline				First evaluation					Last evaluation#			
	6MWD m	Mean P_{pa} mmHg	CI L·min·m^{-2}	PVR Wood units	Bosentan dose mg *b.i.d.*	6MWD m	Mean P_{pa} mmHg	CI L·min·m^{-2}	PVR Wood units	Bosentan dose mg *b.i.d.*	6MWD m	Mean P_{pa} mmHg	CI L·min·m^{-2}	PVR Wood units
1	325	64	2.1	16.4	125	465	29	5.9	2.7	125	480	56	3.9	7.7
2	500	64	2.8	9.6	125	512	34	5.4	2.3	125	510	32	5.9	2.2
3	235	41	1.6	10.5	125	453	29	3.9	3	125	460	26	4.2	2.6
4	420	42	4.1	3.6	62.5	373	31	7.2	1.5	62.5				
5	354	50	2.3	8.5	62.5	410	37	4.5	3.1	62.5	396	39	3.1	4.2
6	385	47	2.3	9.5	125	443	46	3.4	5.4	125	430	64	3.6	8.3
7	356	56	2.4	9.7	62.5	418	52	3.4	7.8	62.5				
8	465	52	1.9	11.9	62.5	395	43	2.8	7.3	62.5	465	43	2.5	8.4
9	412	42	2.4	6.8						125	385	48	4.1	5.2
Mean±SD	384±79	51±9	2.5±0.7	9.6±3.5		433±44	38±9	4.6±1.5	4.1±2.4		446±45	44±13	3.9±1.1	5.5±2.6

6MWD: 6-min walk distance; P_{pa}: pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance. #: last evaluation performed 37±25 months after bosentan initiation (range 12–75 months).

FIGURE 2. Kaplan–Meier estimates of a) event-free and b) cumulative survival in 34 patients with portopulmonary hypertension treated with first-line bosentan therapy according to the severity of the underlying liver disease. C-P: Child–Pugh.

cirrhosis and three patients with IPAH. The profiles of the three bosentan metabolites measured showed a similar course and difference between the groups (data not shown). The pharmacokinetic variables derived from the individual plasma concentration–time profiles are presented in table 4.

DISCUSSION

There are currently few data on the use of PAH-specific therapies in PoPH, particularly in patients with more advanced hepatic disease. This study was one of the largest to date in this patient population and the first to include a significant number of patients in C-P class B. Treatment with bosentan was associated with short-term improvements in functional status, 6MWD and haemodynamics that were maintained over the long term. In patients with more advanced liver disease C-P class B, haemodynamic response was greater leading to a normalisation or near-normalisation of PVR in some patients. Moreover, long-term treatment with bosentan was well tolerated in patients with mild or more severe cirrhosis.

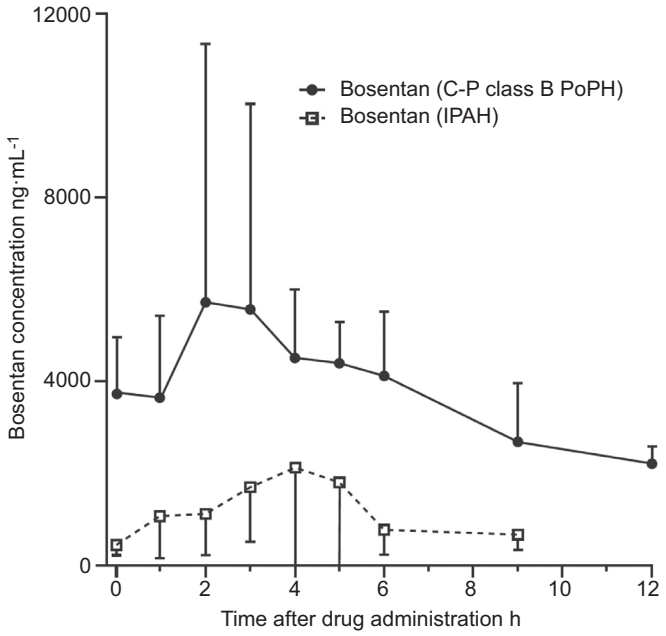

FIGURE 3. Mean±SD dose-normalised plasma concentration–time profiles of bosentan in portopulmonary hypertension (PoPH) patients with Child–Pugh (C-P) class B cirrhosis (n=5) or patients with idiopathic pulmonary arterial hypertension (IPAH) without comorbid portal hypertension (n=3). Concentrations from patients treated with doses of 62.5 mg *b.i.d.* were normalised to a dose of 125 mg.

The mean treatment duration of 47±20 months enables an adequate evaluation of the potential long-term benefits of bosentan therapy in these patients. Significant improvement in haemodynamic variables between baseline and follow-up evaluations is encouraging, as it is correlated with a better prognosis [7]. Indeed, patients with a lower cardiac index are usually at higher risk of death [7]. Therefore, improvement in cardiac index in this study suggests that bosentan may be beneficial and improve survival. In these patients with portal hypertension, bosentan seems at least as effective as previously observed in double-blind, placebo-controlled studies in patients with IPAH and PAH associated with connective tissue disease [28–30].

The pronounced improvements observed in patients with liver disease in C-P class B are of particular interest. This is an important result, because risk of mortality is higher for PoPH patients with more severe liver disease [7]. Despite the existence of a more severe liver dysfunction in patients with cirrhosis C-P class B, which is known to be a poorer prognostic factor, the event-free survival is equivalent to patients with either mild cirrhosis or noncirrhotic portal hypertension and patients with more severe cirrhosis. Normalisation or near-normalisation of haemodynamics is exceptional with PAH-specific therapy in patients with either IPAH or PAH associated with concomitant disease. This type of response is generally observed in patients with PAH associated with inflammatory conditions, such as HIV infection or connective tissue diseases [31, 32]. Inflammatory processes are more important in patients with more advanced hepatic disorders, which could explain pronounced improvement in these patients. In patients with portal hypertension, the development of portosystemic shunts, a decrease in liver phagocytic capacity and increased frequency of bacterial translocation facilitate the circulation of pulmonary cytokines, pro-angiogenic factors or bacterial endotoxins, which probably induce pulmonary vascular endothelium dysfunction and increase production of endothelin. Data from this study also suggest a role of endothelin in the pathological process of PoPH. In addition, there is evidence to suggest that endothelin-1 may be aetiologically relevant in portal hypertension and hepatic fibrotic remodelling [33–36].

Another hypothesis explaining differences of response in patients with more severe cirrhosis could be increased systemic exposure to bosentan and/or its active metabolite due to impaired metabolism in such patients. Results from the pharmacokinetic substudy presented here suggest that this is indeed the case, as the maximal concentration of bosentan was considerably higher in PoPH patients with cirrhosis C-P class B than in those with IPAH, even though patients with cirrhosis were taking lower doses of bosentan at the time of the pharmacokinetic substudy. The underlying mechanism for this difference is probably a decrease in the efficiency of organic anion transporter peptide, the transporter responsible for uptake of bosentan into hepatocytes, rather than enzymes responsible for bosentan metabolism in the liver (cytochrome

TABLE 4 Pharmacokinetic variables of bosentan and its metabolites in patients with portopulmonary hypertension (PoPH; n=5) and idiopathic pulmonary arterial hypertension (IPAH; n=3)

	t_{max} h		C_{max} ng·mL^{-1}		AUC_τ ng·mL^{-1}·h^{-1}	
	PoPH	IPAH	PoPH	IPAH	PoPH	IPAH
Bosentan	4 (2–6)	4 (3–4)	53.3 (22.4–127)	14.6 (1.27–168)	360 (212–613)	76.1 (9.07–638)
Ro 47-8634	6 (5–6)	3 (3–4)	0.753 (0.393–1.45)	0.351 (0.0439–2.81)	6.39 (3.21–12.7)	2.40 (0.427–13.5)
Ro 48-5033	2 (0–9)	3 (0–5)	13.2 (7.98–21.8)	1.46 (0.158–13.5)	106 (58.4–192)	8.57 (1.28–57.2)
Ro 64-1056	6 (5–9)	4 (3–5)	2.66 (1.43–4.97)	0.873 (0.170–4.48)	25.8 (14.7–45.1)	6.92 (1.59–30.0)

Data are presented as geometric mean (median) for t_{max} and geometric mean (95% confidence interval) for C_{max} and area under the curve for one dosing interval (AUC_τ). To enable comparison, C_{max} and AUC_τ have been dose-normalised. t_{max}: time to maximum concentration; C_{max}: maximum concentration.

P450 isoenzymes), because the extent of the increase in exposure was similar for bosentan and its metabolites. Although only three patients with IPAH were included as comparators in this study, the pharmacokinetic results obtained were very similar to those obtained in a larger group of PAH patients [27]. More detailed pharmacokinetic studies are warranted to investigate the influence of more severe forms of liver cirrhosis on the disposition of ERAs.

The use of ERAs is associated with an increased frequency of elevated aminotransferase levels, and monthly liver function tests are required for all patients treated with them. Therefore, potential concerns exist regarding their safety in patients with either cirrhosis or impaired liver function, such as those analysed in this study. Liver damage could also change the metabolism of bosentan in such patients. However, the results presented here suggest that there is no difference between patients with PoPH and those with other forms of PAH. The annual rate of liver enzyme elevations observed in this study is similar to that previously reported in the post-marketing surveillance of bosentan [37] and in other trials in PAH [28–30]. They usually develop gradually, remain asymptomatic, and are generally reversible either spontaneously or after dose reduction or discontinuation. We observed a trend for a higher annual rate of aminotransferases elevation and higher incidence of bosentan discontinuation in patients with more severe cirrhosis. In all cases, liver disturbance was reversible and without impact on liver disease evolution. However, close monitoring of liver enzymes should be conducted in patients with more severe cirrhosis C-P class B. Despite a good haemodynamic response observed in patients with advanced liver disease, bosentan should probably be used in these patients both with caution and after having considered the use of alternative treatments without liver liability as first-line therapy. In addition, the results of the pharmacokinetic substudy and responses to treatment observed in patients with more advanced liver disease may suggest that the use of bosentan at a dose of 62.5 mg *b.i.d.* may be sufficient.

A recently published observational study has reported on the effects of ambrisentan, a selective antagonist of the ET_A receptor subtype, in 13 patients with moderate-to-severe PoPH associated with mild cirrhosis (C-P class A). Treatment was associated with a significant reduction in mean P_{pa} and PVR without adverse effects on liver function tests [38]. This drug, which is considered to have a minimal effect on liver function, could also be an interesting option in patients with more severe cirrhosis. This option must be properly evaluated.

The main limitation of our study is its retrospective open-label design. Accordingly, data presented here should be interpreted with caution. Another limitation is the potential selection bias in the long-term data analysed in this study; it is possible that the patient population was enriched for patients who responded to treatment. This is especially true for the long-term analysis of 6MWD. Because of the small numbers involved and the variability of dosing, the pharmacokinetic data also must be interpreted with caution. It is unfortunate that plasma bosentan levels were not measured in all patients, especially as samples were obtained only from three control patients. However, the pharmacokinetic properties of bosentan in these control patients were in close accordance with those assessed in a larger historical control group [27]. Furthermore, the fact that bosentan plasma levels were not measured, at least in some C-P class A patients, is also a limitation of the study. The pharmacokinetics of bosentan in C-P class A patients have been studied previously [21], but these patients were not diagnosed with PoPH. Finally, plasma levels may not necessary reflect tissular drug action on the receptor. Nevertheless, this study represents a considerable advance on previously available data and provides a rationale for further studies investigating this important patient population. It is unlikely that any future studies will be placebo controlled, given the poor prognosis of patients with PAH who do not receive treatment [39]. A prospective open-label trial would provide valuable data. Furthermore, pharmacological data should be enriched by a larger study comparing the pharmacokinetics of bosentan between patients with mild cirrhosis and more severe cirrhosis.

These data confirm the benefit of bosentan in the treatment of patients with PoPH, especially with regards to haemodynamic improvements. In particular, this study suggests that the greatest positive haemodynamic responses are in patients with C-P class B cirrhosis. The safety profile of bosentan in patients with PoPH was generally consistent with previous studies including PAH patients without cirrhosis. However, special care must be taken with patients with more severe cirrhosis due to the potential liver toxicity of this treatment.

STATEMENT OF INTEREST

Statements of interest for L. Savale, X. Jaïs, D. Montani, M. Humbert, J. Dingemanse, G. Simonneau and O. Sitbon can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES

1 Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: Suppl. 1, S43–S54.

2 Hadengue A, Benhayoun MK, Lebrec D, *et al.* Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology* 1991; 100: 520–528.

3 Colle IO, Moreau R, Godinho E, *et al.* Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology* 2003; 37: 401–409.

4 Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet* 2004; 363: 1461–1468.

5 Halank M, Ewert R, Seyfarth HJ, *et al.* Portopulmonary hypertension. *J Gastroenterol* 2006; 41: 837–847.

6 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.

7 Le Pavec J, Souza R, Herve P, *et al.* Portopulmonary hypertension: survival and prognostic factors. *Am J Respir Crit Care Med* 2008; 178: 637–643.

8 Robalino BD. Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. *J Am Coll Cardiol* 1991; 17: 492–498.

9 Kawut SM, Taichman DB, Ahya VN, *et al.* Hemodynamics and survival of patients with portopulmonary hypertension. *Liver Transpl* 2005; 11: 1107–1111.

10 Krowka MJ, Miller DP, Barst RJ, *et al.* Portopulmonary hypertension: a report from the US-based REVEAL Registry. *Chest* 2012; 141: 906–915.
11 Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164–172.
12 Halank M, Miehlke S, Hoeffken G, *et al.* Use of oral endothelin-receptor antagonist bosentan in the treatment of portopulmonary hypertension. *Transplantation* 2004; 77: 1775–1776.
13 Grander W, Eller P, Fuschelberger R, *et al.* Bosentan treatment of portopulmonary hypertension related to liver cirrhosis owing to hepatitis C. *Eur J Clin Invest* 2006; 36: Suppl. 3, 67–70.
14 Hinterhuber L, Graziadei IW, Kahler CM, *et al.* Endothelin-receptor antagonist treatment of portopulmonary hypertension. *Clin Gastroenterol Hepatol* 2004; 2: 1039–1042.
15 Neuhofer W, Gulberg V, Gerbes AL. Endothelin and endothelin receptor antagonism in portopulmonary hypertension. *Eur J Clin Invest* 2006; 36: Suppl. 3, 54–61.
16 Stahler G, von Hunnius P. Successful treatment of portopulmonary hypertension with bosentan: case report. *Eur J Clin Invest* 2006; 36: Suppl. 3, 62–66.
17 Barth F, Gerber PJ, Reichen J, *et al.* Efficiency and safety of bosentan in child C cirrhosis with portopulmonary hypertension and renal insufficiency. *Eur J Gastroenterol Hepatol* 2006; 18: 1117–1119.
18 Kuntzen C, Gulberg V, Gerbes AL. Use of a mixed endothelin receptor antagonist in portopulmonary hypertension: a safe and effective therapy? *Gastroenterology* 2005; 128: 164–168.
19 Hoeper MM, Seyfarth HJ, Hoeffken G, *et al.* Experience with inhaled iloprost and bosentan in portopulmonary hypertension. *Eur Respir J* 2007; 30: 1096–1102.
20 Hoeper MM, Halank M, Marx C, *et al.* Bosentan therapy for portopulmonary hypertension. *Eur Respir J* 2005; 25: 502–508.
21 van Giersbergen PL, Popescu G, Bodin F, *et al.* Influence of mild liver impairment on the pharmacokinetics and metabolism of bosentan., a dual endothelin receptor antagonist. *J Clin Pharmacol* 2003; 43: 15–22.
22 Rodriguez-Roisin R, Krowka MJ, Herve P, *et al.* Pulmonary-hepatic vascular disorders (PHD). *Eur Respir J* 2004; 24: 861–880.
23 Sitbon O, Humbert M, Jais X, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111: 3105–3111.
24 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2009; 34: 1219–1263.
25 Cohen H, Chahine C, Hui A, *et al.* Bosentan therapy for pulmonary arterial hypertension. *Am J Health Syst Pharm* 2004; 61: 1107–1119.
26 Dell D, Lausecker B, Hopfgartner G, *et al.* Evolving bioanalytical methods for the cardiovascular drug bosentan. *Chromatographia* 2002; 55: S115–S119.
27 Dingemanse J, van Giersbergen PL. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. *Clin Pharmacokinet* 2004; 43: 1089–1115.
28 Channick R, Badesch DB, Tapson VF, *et al.* Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary hypertension: a placebo-controlled study. *J Heart Lung Transplant* 2001; 20: 262–263.
29 Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896–903.
30 Galie N, Rubin L, Hoeper M, *et al.* Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093–2100.
31 Degano B, Yaici A, Le Pavec J, *et al.* Long-term effects of bosentan in patients with HIV-associated pulmonary arterial hypertension. *Eur Respir J* 2009; 33: 92–98.
32 Jais X, Launay D, Yaici A, *et al.* Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. *Arthritis Rheum* 2008; 58: 521–531.
33 Benjaminov FS, Prentice M, Sniderman KW, *et al.* Portopulmonary hypertension in decompensated cirrhosis with refractory ascites. *Gut* 2003; 52: 1355–1362.
34 Chan CC, Wang SS, Lee FY, *et al.* Endothelin-1 induces vasoconstriction on portal-systemic collaterals of portal hypertensive rats. *Hepatology* 2001; 33: 816–820.
35 Kojima H, Sakurai S, Kuriyama S, *et al.* Endothelin-1 plays a major role in portal hypertension of biliary cirrhotic rats through endothelin receptor subtype B together with subtype A *in vivo*. *J Hepatol* 2001; 34: 805–811.
36 Tieche S, De Gottardi A, Kappeler A, *et al.* Overexpression of endothelin-1 in bile duct ligated rats: correlation with activation of hepatic stellate cells and portal pressure. *J Hepatol* 2001; 34: 38–45.
37 Humbert M, Segal ES, Kiely DG, *et al.* Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J* 2007; 30: 338–344.
38 Cartin-Ceba R, Swanson K, Iyer V, *et al.* Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. *Chest* 2011; 139: 109–114.
39 D'Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension: results from a national prospective study. *Ann Intern Med* 1991; 115: 343–349.