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Bosentan therapy for portopulmonary hypertension

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ABSTRACT: The dual endothelin receptor antagonist bosentan has been approved in several countries for pulmonary arterial hypertension, and patients with portopulmonary hypertension (PPHTN) have not specifically been excluded. However, no data have been published on the efficacy and safety of bosentan in this patient population. Here, the first clinical experiences with bosentan in patients with Child A cirrhosis and severe PPHTN are reported.

In total, 11 consecutive patients with cirrhosis and severe PPHTN in New York Heart Association Functional Classes III and IV were treated for >1 yr with bosentan.

After 1 yr of treatment with bosentan, all patients showed improved symptoms and exercise capacity. The 6-min walking distance increased from 310±102 m at baseline to 388±81 m at 1 yr. Cardiopulmonary exercise testing disclosed a significant increase in peak oxygen uptake, from 12.6±3.5 to 16.6±2.8 mL·min^{-1}·kg^{-1}. Pulmonary vascular resistance fell from 944±519 to 635±321 dynes·s·L^{-1}. The medication was well tolerated by all patients, and there was no evidence of drug-related liver injury.

In conclusion, bosentan proved to be efficacious and safe in a small number of patients with portopulmonary hypertension.

KEYWORDS: Cirrhosis, endothelin receptor antagonists, secondary pulmonary hypertension

The development of pulmonary arterial hypertension (PAH) in patients with portal hypertension is referred to as portopulmonary hypertension (PPHTN) [1]. This complication predominantly affects patients with cirrhosis of various aetiologies accompanied by portal hypertension, but may also occur in noncirrhotic portal hypertension. Thus, it appears that portal hypertension rather than liver dysfunction triggers the occurrence of pulmonary hypertension [2].

The incidence of PPHTN varies widely in the medical literature. An autopsy study found vascular changes compatible with severe pulmonary hypertension in 0.7% of patients with cirrhosis [3], whereas most clinical series have described much higher incidences, ranging 2–16% [1, 4–9]. These differences may be the result of different study populations, but also of different diagnostic criteria. In many cases, patients with cirrhosis develop only mild-to-moderate elevation of pulmonary vascular pressure in the presence of a high cardiac output and mildly elevated pulmonary vascular resistance. These patients usually show no symptoms related to pulmonary hypertension and specific treatment may not be required [2]. However, for unknown reasons, some patients develop progressively symptomatic pulmonary hypertension with right heart dysfunction. In these patients, the prognosis is poor with 1-yr mortality rates ranging 24–60% [7, 10].

The only specific treatment available for PPHTN has been intravenous epoprostenol. There are no controlled trials of epoprostenol in this patient population, but several case series suggest a positive effect on exercise capacity and haemodynamics [11–15], although it has been questioned whether epoprostenol improves survival in PPHTN [16].

The dual endothelin receptor antagonist bosentan is efficacious in patients with idiopathic PAH and PAH related to connective tissue disease [17, 18]. Elevation of hepatic aminotransferase levels is a common phenomenon in patients treated with bosentan, occurring in ~10% of patients receiving 125 mg twice daily [18]. Owing to concerns about potential liver toxicity, patients with PPHTN have been excluded from clinical studies with bosentan, and physicians have been reluctant to prescribe the drug in patients with cirrhosis. However, the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products have approved bosentan for

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all forms of PAH, not specifically excluding PPHTN, as long as liver function is stable.

The present article reports the first long-term clinical experiences with bosentan in patients with cirrhosis and severe PPHTN.

METHODS

Clinical data were retrospectively collected from all patients who were referred with newly diagnosed severe PPHTN (New York Heart Association (NYHA) Functional Class III or IV; mean pulmonary arterial pressure ($\bar{P}_{pa}$) >40 mmHg), between January 2001 and February 2003, to three German university hospitals (Hanover Medical School, Hanover; Carl Gustav Carus University of Dresden, Dresden; and University Hospital Leipzig, Leipzig). At this time, all patients with PPHTN and Child A cirrhosis were treated with bosentan, since no other drug has gained approval for the treatment of this condition in Germany. All patients were carefully informed about the lack of clinical experience with bosentan in PPHTN and safety concerns about potential liver toxicity, and gave written informed consent. There was no formal study protocol, and the patients were treated at the discretion of their local physicians. This approach was approved by the institutional review boards of all the participating centres.

Bosentan was started at a dose of 62.5 mg twice daily in all patients, and the dose was increased to 125 mg twice daily after 4–8 weeks based on clinical judgement and tolerability. Liver enzyme, including alanine aminotransferase and aspartate aminotransferase, and bilirubin levels were monitored twice monthly during the first 3 months and monthly thereafter. All patients were seen in the outpatient clinics of the university hospitals at 3-monthly intervals for a thorough clinical investigation, including assessment of NYHA Functional Class, 6-min walking distance (6MWD), and pulmonary and liver function. Right heart catheter examinations were performed in all patients within 6 months before bosentan treatment was started and after 1 yr of treatment. Cardiac output was measured by thermodilution in triplicate and averaged. Samples for arterial and mixed venous blood gas analysis were obtained during heart catheterisation without supplemental oxygen. The alveolar–arterial oxygen tension difference (P_{Aa,O_2}) was calculated by subtracting arterial oxygen tension (P_{a,O_2}) from alveolar oxygen tension (P_{A,O_2}) (with P_{A,O_2}=150-arterial carbon dioxide tension (P_{a,CO_2})/0.8). Regular cardiopulmonary exercise testing, following a standardised protocol on a cycle ergometer [19], was part of the routine programme in two centres.

Statistics

All data are presented as mean±SD. A paired t-test (two-sided) was used to compare variables at baseline and after 1 yr of treatment. A p-value of <0.05 was considered significant.

RESULTS

Between January 2001 and January 2003, bosentan treatment was initiated in 11 consecutive patients with PPHTN (at Hanover Medical School (n=4), University Hospital Leipzig (n=4) and Carl Gustav Carus University of Dresden (n=3)), who presented with stable liver function (Child–Pugh class A) but severe functional limitation due to pulmonary hypertension (NYHA Functional Class III or IV). The final dose of bosentan was 125 mg *b.i.d.* in six patients and 62.5 mg *b.i.d.*in the remaining five. The demographics and baseline characteristics of these patients are shown in table 1. The majority of the patients suffered from alcoholic liver disease, but all such patients had abandoned alcohol consumption ⩾6 months (median interval 38 months) before bosentan was introduced. The diagnosis of cirrhosis and portal hypertension was confirmed by expert hepatologists in all patients, and all patients had a history of one or more complications of portal hypertension, such as ascites, oesophagogastric varices or

TABLE 1 Demographics and baseline characteristics of patients with cirrhosis and severe portopulmonary hypertension

Patient No.	Sex	Age yrs	Aetiology	Liver biopsy	Previous complications#	Smoking		VC % pred	FEV_1/VC	$D_{L,CO}$ % pred
						Status	Consumption pack-yrs			
1	M	51	Alcohol abuse	No	V, S	CS	10	112	71	56
2	M	66	Cryptogenic	Yes	A	NS	0	81	76	40
3	M	42	Alcohol abuse	Yes	V, S	CS	25	75	75	46
4	F	48	Hepatitis C	Yes	V, S	CS	20	68	65	51
5	M	51	Alcohol abuse	No	V, S, A	CS	20	90	75	70
6	F	62	Alcohol abuse	Yes	V, VB, S, A	Ex	10	91	58	38
7	F	55	Cryptogenic	Yes	V, VB, S	NS	0	111	57	41
8	F	37	Biliary atresia	No	V, S	NS	0	101	79	66
9	M	51	Alcohol abuse	No	A, S	Ex	7	87	85	75
10	F	41	Alcohol abuse	No	V, A	CS	20	89	77	57
11¶	F	63	Alcohol abuse	No	V, A, S	NS	0	58	60	50

VC: vital capacity; FEV_1: forced expiratory volume in one second; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung; M: male; F: female; V: oesophagogastric varices; S: splenomegaly; A: ascites; VB: variceal bleeding; CS: current smoker; NS: nonsmoker; Ex: ex-smoker; % pred: percentage of the predicted value. #: of portal hypertension; ¶: patient suffered from cirrhosis, pulmonary hypertension and a sinus venous defect with right-to-left shunting.

hypersplenism (table 1). Preliminary data from one patient (No. 2) have already been published as a case report [20].

At baseline, pulmonary function testing revealed mild-to-moderate impairment of $D_{L,CO}$ in the majority of the patients as five patients had $D_{L,CO}$ of ⩽50% of the predicted value and four of 50–70% pred. In addition, mild airflow obstruction, with a forced expiratory volume in one second/vital capacity ratio of <70%, was present in four patients (table 1). The results of pulmonary function testing remained virtually unchanged after 1 yr of bosentan treatment (data not shown).

Outcome, functional classification and exercise capacity

No patient underwent transplantation or died during the observation period. All 11 patients reported subjective improvement in exercise capacity after initiation of bosentan treatment, and six patients improved by one functional class. The 6MWD increased from 310±102 m at baseline to 388±81 m after 1 yr (p=0.0004). Data from cardiopulmonary exercise testing were available from seven patients and revealed a significant increase in peak oxygen uptake, from 12.6±3.5 to 16.6±2.8 mL·min^{-1}·kg^{-1} (p=0.01), as well as an increase in oxygen pulse, from 6.7±1.2 to 9.3±2.1 mL (p=0.01). Ventilatory efficiency (minute ventilation/carbon dioxide production) at the anaerobic threshold showed a tendency to decrease from 57.7±22.1 to 46.9±11.7, but this change was not significant (p=0.31). The individual NYHA classification at baseline and after 1 yr of treatment together with the change in 6MWD and variables obtained from cardiopulmonary exercise testing are shown in table 2.

Haemodynamic studies and blood gas analyses

The individual results of the haemodynamic studies are shown in table 3. Treatment with bosentan caused a nonsignificant fall in $\bar{P}_{pa}$ from 53±9 to 48±14 mmHg (p=0.23). Cardiac output rose, from 4.6±1.8 to 5.7±1.6 L·min^{-1} (cardiac index 2.5±1.0 and 3.1±0.8 L·min^{-1}·m^{-2}, respectively; p=0.02),

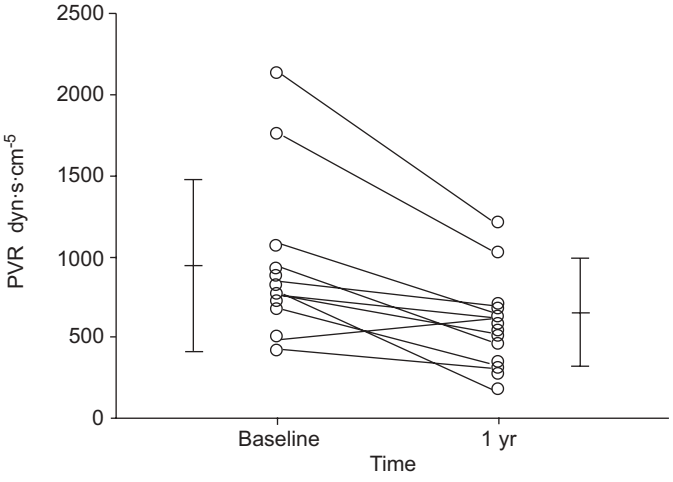

FIGURE 1. Impact of bosentan treatment on pulmonary vascular resistance (PVR) in 11 patients with portopulmonary hypertension. Separate points represent individual patients; horizontal and vertical bars represent mean±SD.

resulting in a significant fall in pulmonary vascular resistance, from 944±519 to 635±321 dynes·s·cm^{-5} (p=0.007; fig. 1). The increase in cardiac output was due to a rise in stroke volume from 57±20 to 70±23 mL (p=0.01), whereas the cardiac frequency remained unchanged (data not shown). Mixed venous oxygen saturation was 60±9% at baseline and 63±11% at 1 yr (p=0.4). The right atrial pressure fell slightly, from 9±6 to 7±7 mmHg, a change that was also nonsignificant (p=0.35). The mean systemic artery pressure dropped from 91±9 to 83±14 mmHg (p=0.09).

As shown in table 3, blood gas analyses disclosed a significant worsening of arterial oxygenation. The P_{a,O_2} fell from 8.6±1.7 kPa (65±13 Torr) at baseline to 7.7±1.5 kPa (58±11 Torr) after 1 yr (p=0.006); P_{a,CO_2} was unchanged; and the P_{Aa,O_2};

TABLE 2 Effects of bosentan treatment on functional classification, 6-min walking distance (6MWD), peak oxygen uptake ($V'_{O_2,max}$) and peak oxygen pulse (V'_{O_2}/f_c)

Patient No.	NYHAFC		6MWD m		$V'_{O_2,max}$ mL·min^{-1}·kg^{-1}		V'_{O_2}/f_c mL	
	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr	Baseline	1 yr
1	III	II	400	450	17.1	22.9	8.6	12.7
2	III	III	360	370	14.1	14.7	7.5	8.7
3	III	III	250	360	8.3	15.8	6.1	11.4
4	III	II	358	396	12.7	15.6	6.3	7.4
5	III	II	264	455	7.5	15.7	5.3	9.7
6	III	II	327	407	13.2	15.5	7.5	8.2
7	III	III	280	375	15.0	16.1	5.9	7.2
8	III	III	392	448	NA	NA	NA	NA
9	III	III	476	504	NA	NA	NA	NA
10	III	III	168	280	NA	NA	NA	NA
11	IV	III	140	224	NA	NA	NA	NA
Mean±SD			310±102	388±81	12.6±3.5	16.6±2.8	6.7±1.2	9.3±2.1
p-value				0.0004		0.013		0.012

NYHAFC: New York Heart Association Functional Class; V'_{O_2}: oxygen uptake; f_c: cardiac frequency; NA: not assessed.

TABLE 3 Effects of bosentan treatment on haemodynamics and blood gas analyses

Patient No.	P_{ra} mmHg		$\bar{P}_{pa}$ mmHg		CO L·min^{-1}		CI L·min^{-1}·m^{-2}		P_{pcw} mmHg		PVR dyn·s·cm^{-5}		SV mL		Sv_{O_2} %		$\bar{P}_a$ mmHg		P_{a,O_2} Torr		P_{a,CO_2} Torr		P_{Aa,O_2} Torr	
	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr
1	3	0	55	56	4.8	6.3	2.4	3.1	7	3	800	673	70	77	68	66	79	76	86	61	33	34	23	46
2	5	3	54	18	5.0	8.1	2.6	4.2	8	5	741	128	71	85	65	69	97	64	74	63	32	29	36	51
3	20	3	45	49	4.5	6.7	2.0	3.2	5	6	717	509	43	87	51	74	74	64	74	71	29	35	40	35
4	14	11	69	76	2.3	4.0	1.5	2.8	9	14	2085	1247	47	67	48	64	91	76	76	65	35	39	30	36
5	11	4	53	50	4.7	5.4	2.3	2.5	11	10	714	592	57	82	64	64	103	103	65	57	30	32	47	52
6	11	2	49	42	5.1	6.7	3.0	4.0	8	12	642	322	69	81	67	69	94	96	60	58	33	33	49	51
7	4	2	50	35	3.4	4.3	2.3	2.7	12	10	893	549	35	46	58	55	92	104	47	46	28	31	68	65
8	3	7	50	45	9.2	7.8	5.0	4.3	2	8	417	378	96	107	74	72	84	84	60	58	32	35	50	48
9	0	4	43	57	5.6	5.5	2.9	2.8	4	7	552	725	66	64	67	68	91	92	67	68	35	32	39	42
10	16	21	70	50	2.9	3.3	1.5	1.8	6	6	1772	1051	27	30	51	56	103	79	72	57	33	38	37	45
11	14	21	49	50	3.4	4.2	1.9	2.3	5	8	1048	806	47	39	50	35	90	79	43	31	40	39	57	70
Mean±SD	9±6	7±7	53±9	48±14	4.6±1.8	5.7±1.6	2.5±1.0	3.1±0.8	7±3	8±3	944±519	635±321	57±20	70±23	60±9	63±11	91±9	83±14	65±3	58±11	33±3	34±3	43±13	49±11
p-value		0.35		0.23		0.02		0.02		0.31		0.007		0.014		0.40		0.09		0.006		0.12		0.04

P_{ra}: right atrial pressure; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CO: cardiac output; CI: cardiac index; P_{pcw}: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SV: stroke volume; Sv_{O_2}: mixed venous oxygen saturation; $\bar{P}_a$: mean arterial pressure; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; P_{Aa,O_2}: alveolar–arterial oxygen tension difference; BL: baseline. 1 Torr=0.133 kPa.

increased from 5.7±1.7 kPa (43±13 mmHg) to 6.5±1.5 kPa (49±11 mmHg; p=0.04). However, no patient complained of increasing dyspnoea at rest or during exertion.

Side-effects

Bosentan treatment was well tolerated by all of the patients. Although there was a decline in mean systemic artery pressure, there were no clinical signs or symptoms of hypotension and no episodes of syncope. Most notably, there was no evidence for drug-induced liver toxicity. Hepatic aminotransferase activities were normal or slightly abnormal (less than twice the upper limit of normal) in all patients at baseline and remained practically stable throughout the whole observation period (table 4). The same was true for bilirubin levels, which were 29±12 μmol·L^{-1} at baseline and 26±10 μmol·L^{-1} after 1 yr (p=0.19). Parameters of liver synthesis, *i.e.* international normalised ratio and serum albumin activity levels remained unchanged (table 4). No encephalopathy and no episodes of variceal bleeding were observed. One patient developed increasing amounts of ascites 7 months after the introduction of bosentan. The patients had previously suffered from several episodes of ascites, and clinical judgement was that this complication was due to worsening of portal hypertension rather than causally linked to bosentan treatment.

DISCUSSION

For many years the only specific drug treatment available for PPHTN has been continuous intravenous epoprostenol [1, 2, 11, 21]. The present data suggest that the dual endothelin receptor antagonist bosentan may offer a safe and effective noninvasive alternative. All patients in the present series suffered from severe pulmonary hypertension at baseline (NYHA Functional Class III or IV; mean 6MWD 310 m; $\bar{P}_{pa}$ 53 mmHg; cardiac index (CI) 2.7 L·min^{-1}·m^{-2}; pulmonary vascular resistance 944 dyn·s·cm^{-5}; right atrial pressure 7 mmHg; and mixed venous oxygen saturation 60%). In an earlier series of 49 patients with PPHTN of similar severity ($\bar{P}_{pa}$ 59 mmHg and CI 3.3 L·min^{-1}·m^{-2}), who did not receive specific treatment for pulmonary hypertension, ROBALINO and MOODIE [10] reported a 1-yr mortality of >60%. Another series of 39 patients with PPHTN from France with comparable haemodynamics ($\bar{P}_{pa}$ 56 mmHg and CI 2.7 L·min^{-1}·m^{-2}) found a 1-yr mortality of 24% [7]. During the 1-yr observation period reported here, no patient died, which is remarkable given the grave prognosis of this condition. However, the present data do not provide sufficient evidence to conclude that bosentan improves survival in PPHTN.

All patients in the present case series experienced functional improvement, with increasing exercise tolerance; six patients improved by one functional class. The 6MWD increased by a mean of 78 m, and, in those patients who were followed by cardiopulmonary exercise testing, there was a substantial increase in peak oxygen uptake and oxygen pulse, suggesting improved cardiopulmonary function during exercise. In addition, treatment with bosentan improved cardiopulmonary haemodynamics at rest; after 1 yr of bosentan treatment, $\bar{P}_{pa}$ had fallen by 10% from baseline, cardiac output had increased by 22% and pulmonary vascular resistance had fallen by 32%.

TABLE 4 Indicators of liver and kidney function

Patient No.	Child–Pugh class		Ascites		Encephalopathy		INR		SCr µmol·L^{-1}		sAl g·L^{-1}		SBR µmol·L^{-1}		ALT µmol·L^{-1}·s^{-1}		AST µmol·L^{-1}·s^{-1}	
	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr	BL	1 yr
1	A	A	None	None	Absent	Absent	1.08	1.16	66	80	44	43	18	28	0.75	0.85	0.75	0.85
2	A	B	None	Mod	Absent	Absent	1.22	1.21	99	109	47	32	16	16	0.44	0.28	0.44	0.28
3	A	A	None	None	Absent	Absent	1.73	1.12	111	68	40	46	21	12	0.31	0.31	0.31	0.31
4	A	A	None	None	Absent	Absent	OAC	OAC	70	54	36	45	33	25	0.41	0.33	0.41	0.33
5	A	A	None	None	Absent	Absent	1.05	1.01	107	101	36	37	50	33	0.54	0.80	0.54	0.80
6	A	A	None	None	Absent	Absent	1.10	1.15	52	45	30	32	19	17	0.43	0.42	0.43	0.42
7	A	A	None	None	Absent	Absent	OAC	OAC	72	79	40	46	20	16	0.29	0.51	0.29	0.51
8	A	A	None	None	Absent	Absent	OAC	OAC	53	47	30	30	28	33	0.73	1.08	0.73	1.08
9	A	A	None	None	Absent	Absent	1.01	1.03	67	88	43	49	33	32	0.57	0.60	0.57	0.60
10	A	A	None	None	Absent	Absent	OAC	OAC	85	75	39	44	40	41	0.68	0.92	0.68	0.92
11	A	A	None	None	Absent	Absent	OAC	OAC	113	102	46	41	45	34	0.47	0.42	0.47	0.42
Mean ± SD									81±23	77±22	39±6	40±7	29±12	26±10	0.36±0.15	0.41±0.16	0.51±0.16	0.59±0.28
p-value										0.43		0.54		0.19		0.24		0.13

The Child–Pugh class, a measure of severity of liver disease, is based on points assigned for the degree of ascites (1: absent; 2: slight; and 3: severe), serum concentrations of bilirubin (SBR; 1: <34 µmol·L^{-1}; 2: 34–51 µmol·L^{-1}; and 3: >51 µmol·L^{-1}) and albumin (sAl; 1: >35 g·L^{-1}; 2: 28–35 g·L^{-1}; and 3: <28 g·L^{-1}), the international normalised ratio (INR; 1: <1.7; 2: 1.8–2.3; and 3: >2.3) and the degree of encephalopathy (1: none; 2: grade 1–2; and 3: grade 3–4). A total score of 5–6 is considered Child class A, 7–9 class B and 10–15 class C. The normal range for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) is 0.10–0.52 µmol·L^{-1}·s^{-1}. SCr: serum creatinine; OAC: oral anticoagulation (INR assumed to be 1 for calculation of Child–Pugh score); BL: baseline; Mod: moderate.

The present data confirm previous studies on the efficacy of bosentan in other forms of PAH [17–19, 22, 23]. Together, these observations support the hypothesis that endothelin is a pathogenetically relevant mediator in pulmonary hypertension of various aetiologies. A recent study found significantly elevated plasma endothelin-1 levels in patients with PPHTN compared to cirrhotic patients with portal hypertension but without pulmonary hypertension [8]. In addition, a large body of evidence suggests that endothelin-1 may also be involved in the pathogenesis of portal hypertension [24–28]. A recent case report of a patient with PPHTN (who was included in the present study) described normalisation of portal venous pressures with bosentan treatment [20]. Thus, the beneficial effects of bosentan in PPHTN could be related to a reduction in both pulmonary and portal hypertension. Unfortunately, no systematic follow-up information exists on portal hypertension in the present patients, but this aspect should be addressed in forthcoming trials.

There are serious safety concerns regarding the administration of bosentan in patients with coexisting liver disease since potential hepatotoxicity is a well-recognised side-effect of bosentan [18]. Presumably, the underlying mechanism is inhibition by bosentan and its metabolites of a bile salt transporter pump [29]. In order to prevent serious liver damage, regulatory agencies demand that hepatic aminotransferase levels be checked every 4 weeks before a new prescription of bosentan is filled. With these precautions in place, there have been no reports of serious or permanent liver damage associated with bosentan. It was hypothesised that the same precautions should prevent drug-related liver toxicity and worsening of liver function in patients with underlying liver disease. To date, this hypothesis seems to be correct, but it is important to note that great caution is still necessary when bosentan is given to patients with liver disease. It must be emphasised that all of the present patients exhibited stable liver function (Child class A). In these patients, it has been shown that metabolism of bosentan is not impaired [30]. In patients with more advanced liver disease, metabolism of bosentan might be impaired, leading to increased plasma concentrations and potentially resulting in enhanced toxicity. Until more data are available, bosentan should probably not be used in patients with more advanced liver dysfunction (Child class B/C).

It is also noteworthy that a trend towards a fall in systemic blood pressure was observed with bosentan in the present PPHTN patients, an observation that has not been made in other populations of PAH patients. Although the decline in systemic blood pressure was not associated with any clinical symptoms in the present patients, it is important to be careful regarding use of bosentan in patients with pre-existing hypotension. The appropriate dosage of bosentan in patients with liver dysfunction should be addressed in forthcoming studies.

Similar considerations apply to potential worsening of arterial oxygenation, since a mild-but-significant fall in P_{a,O_2} was observed in most of the present patients after 1 yr of bosentan treatment. The reason for this finding is unclear, but presumably, worsening of arterial oxygenation may have been caused by nonselective intrapulmonary vasodilation, resulting

in some degree of ventilation–perfusion mismatching. A fall in P_{a,O_2} was also reported with the use of epoprostenol in PPHTN [11], supporting the hypothesis that intrapulmonary vasodilation might be involved in this process.

The limitations of the present study are obvious. The number of patients investigated was small (11 patients treated at three university hospitals) and the study retrospective, patients and investigators were not blinded, and there was no control group. It needs to be emphasised that the presnt report describes all patients with PPHTN who were referred to the three participating centres over a 1-yr period, underscoring the fact that severe PPHTN is truly a rare condition. It is of note that there are also no controlled data on the use of epoprostenol in this condition, and most of the published case series with epoprostenol in PPHTN included even fewer patients [12, 14, 15], the largest published series consisting of 10 patients [11]. To date, no randomised double-blind controlled clinical trials have ever been performed in PPHTN, but, given the evolving cooperation between pulmonary hypertension centres, such trials might be feasible in the future.

In conclusion, bosentan treatment was found to be safe and effective in the present case series of patients with severe portopulmonary hypertension. If these findings can be confirmed in future trials, bosentan would be the first noninvasive treatment option for this life-threatening disease.

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