Bosentan for the treatment of pulmonary arterial hypertension (II)

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Evaluation of: Hoeper MM, Halank M, Marx C *et al.* Bosentan therapy for portopulmonary hypertension. *Eur. Respir. J.* 25(3), 502–508 (2005).

Portopulmonary hypertension is defined as pulmonary arterial hypertension occurring in the presence of portal hypertension. It is classified as a subset of pulmonary arterial hypertension and accordingly it is defined hemodynamically. Portopulmonary hypertension shares the main pathologic features as well as diagnostic approach with other forms of pulmonary arterial hypertension. Several nonpharmacologic and pharmacologic approaches are currently available. Among the pharmacologic approaches prostacycline and its derivatives, phosphodiesterase-5 inhibitors such as sildenafil and endothelin receptor antagonists such as bosentan, have been used in portopulmonary hypertension treatment. This is a case series report on the long-term efficacy of bosentan treatment for severe (New York Heart Association functional Class III and IV) portopulmonary hypertension.

Portopulmonary hypertension (PPHTN) is defined as pulmonary arterial hypertension (PAH) occurring in the presence of portal hypertension. Therefore, PPHTN is classified as a subset of PAH and defined in terms of cardiac hemodynamics accordingly [1]. Although PPHTN is the most frequently reported in hepatic cirrhosis patients it can occur along with portal hypertension even in the absence of liver disease [1].

PPHTN pathogenesis demonstrates similar features in small pulmonary arteries that are found in other forms of PAH, and the role of *in situ* thrombosis has been also postulated [1]. Pathophysiologic processes are triggered by portosystemic shunts that induce an inflammatory cascade followed by an imbalance between vasoconstrictive and vasodilatory substances in pulmonary circulation that subsequently produces PPHTN [1,2]. From a clinical point of view, PPHTN is suspected when symptoms and signs of right heart failure occur in patients with portal hypertension and screening for PPHTN is a mandatory step in patients referred for liver transplantation [3].

PPHTN diagnosis comprises the same noninvasive and invasive tests used in other forms of PAH – imagistic investigations (including echo Doppler), exercise capacity, electrocardiogram and cardiac catheterization. This approach allows for PPHTN detection and the quantification of its severity [1]. Treatment of PPHTN is based on pharmacologic and nonpharmacologic methods.

The nonpharmacologic approaches available include liver or liver–lung transplantation and portosystemic shunts.

Pharmacologic treatment of PAH comprises the classes belonging to so-called 'conventional therapy' (e.g., anticoagulants, diuretics, calcium-channel blockers and cardiac glycosides) as well as newer vasodilators (prostacyclin and derivatives, endothelin [ET]-receptor antagonists, phosphodiesterase [PDE]-5 inhibitors). Anticoagulants, diuretics and cardiac glycosides should either be avoided (anticoagulants) or prescribed cautiously (diuretics and glycosides) [1].

Unlike other forms of PAH such as primary pulmonary hypertension, calcium-channel blockers are not recommended in patients with PPHTN due to the unfavorable hemodynamic changes that it may produce [1,4].

Prostacyclin (intravenous epoprostenol, Flolan®) and prostacyclin derivatives have also been used in the PPHTN subset. Epoprostenol therapy was found to improve cardiac hemodynamics in the PPHTN patients and has been used as a therapeutic preoperative bridge for liver transplantation [5,6]. It also showed its efficacy in treating postoperatively progressing PPHTN after liver transplantation [7]. However, its short half-life, commonly observed side effects (flushing, headache, jaw pain, leg pain, diarrhea and nausea) along with complications related with delivery systems (central venous catheter) represent limiting factors for use in PAH patients.

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Prostacyclin derivatives have been used to treat PPHTN – subcutaneous treprostinil (Remodulin®) was found to improve exercise capacity [8], inhaled iloprost (Ventavis®) produced a reduction of pulmonary vascular resistance and mean pulmonary artery pressure in one patient [9], and oral beraprost (Dorner®) demonstrated efficacy in PAH patients (the sample included ~15% PPTHN patients) but no specific efficacy data on the PPHTN subset were reported [10].

Inhaled nitric oxide-use in PPHTN treatment is unclear as the efficacy data came from several case series demonstrating contradicting results regarding the hemodynamic improvement. The efficacy of its substrate L-arginine also requires further assessment in the context of PPTHN [11–13].

PDE-5 inhibitors such as sildenafil (Viagra®) are currently approved for the treatment of PAH. Sildenafil demonstrated its efficacy in PAH treatment [13], and two case reports suggest that it might be beneficial for PPHTN, in particular prior to liver or liver–lung transplantation [14,15].

ET-receptor antagonists represent another pharmacologic class used in PAH treatment. Bosentan (Tracleer®) is an oral dual (ET-A and -B) receptor antagonist that has been approved in Europe and North America for PAH treatment. Its short and long-term efficacy in improving exercise tolerance, hemodynamics, survival and functional class has been demonstrated in PAH secondary to connective disease and in primary pulmonary hypertension [16–18]. In terms of safety profile, a dose-dependent increase of hepatic aminotransferase levels was reported in PAH patients receiving at least 125 mg twice daily [16,18], probably precluding the use of bosentan in PPHTN patients.

The current study is the first clinical report on the long-term efficacy of bosentan 125 mg twice daily in severe PPHTN (New York Heart Association [NYHA] Class III and IV) patients with liver (child A) cirrhosis [19].

Methods & results
The study cohort consisted of 11 consecutive patients with PPHTN and stable liver cirrhosis (child A), that were started on 62.5 mg of bosentan twice daily for 4 to 8 weeks and then switched to 125 mg bosentan twice daily – if this approach was considered appropriate by the clinician. After a run-in period, five patients were receiving 62.5 mg twice daily and six patients were receiving 125 mg twice daily.

Liver aminotransferase and bilirubin levels were monitored throughout the observational period. Clinical assessment, functional class, exercise capacity (assessed by a 6 min walking distance and cardiopulmonary testing), pulmonary function, right heart catheterization and blood gas analysis data were available prior to bosentan initiation (baseline) and after 1 year of treatment. All of these variables were analyzed retrospectively at baseline and 1 year. Pulmonary function testing at baseline showed mild-to-moderate diffusion impairment and mild airflow obstruction, and remained virtually unchanged after 1 year.

There were no death, liver or liver–lung transplantations during the observation period. Functional severity improved in six patients by one class and there was a significant improvement in walk distance compared with baseline. Cardiopulmonary exercise testing showed significant improvements in peak oxygen uptake and oxygen pulse, and a nonsignificant increase in ventilatory efficiency at anaerobic threshold.

Although bosentan caused a nonsignificant decrease in mean pulmonary artery pressure, it produced an increase in cardiac output (cardiac index) and subsequently a significant decrease in pulmonary vascular resistance after 1 year of treatment. There were also nonsignificant reductions in right atrial pressure. Blood–gas analysis detected a significant decrease in arterial oxygen pressure. The study also found a decrease of mean systemic arterial blood pressure, but no symptoms or signs related to hypotension have been found. In terms of side effects, there was no drug-induced liver toxicity throughout the study period – liver transaminase and bilirubin levels remained virtually unchanged and there was no sign of impaired liver synthesis (international normalized ratio or albumin).

Discussion & significance
The current study reports on bosentan efficacy for the treatment of severe PPHTN patients. This study demonstrates that bosentan can even be safely administered to patients with underlying liver disease (cirrhosis child A), improving functional class, hemodynamics and exercise capacity in these patients.

Epoprostenol & PPHTN
The current study observed severe (NHYA Class III and IV) patients with PPHTN receiving bosentan, and reported a reduction of

functional severity of one class in six patients, as well as an improvement in exercise capacity, partial improvement in hemodynamics and a good safety and tolerability profile.

In a previous report, epoprostenol efficacy was assessed in a cohort of PAH patients. Subset analysis of PPHTN patients reported that long-term intravenous epoprostenol improved the cardiac output and reduced the mean pulmonary artery pressure significantly in severe PPHTN patients. There were also overall significant improvements in exercise capacity, functional class and pulmonary vascular resistance [5].

Another case series evaluated the acute and long-term effects of epoprostenol in moderate-to-severe PPHTN patients and found that acute improvements on hemodynamics translated to long-term significant changes. However, the same study reported a mortality rate of 60% throughout the study period without providing information on its predictors [20]. The current study reported no death, but disease severity in this cohort and different observational periods have to be taken into account when interpreting the results.

Safety profile of bosentan

In the specific setting of PPHTN there are two main concerns related with bosentan treatment – hepatotoxicity and hypotension. These were also reported along with other side effects in several studies assessing bosentan safety in other PAH subsets [18,21]. In the Bosentan: Randomized Trial of Endothelian-receptor Antagonist THErapy for pulmonary hypertension (BREATHE)-1 study, performed with patients showing PAH Class III and IV, a dose-dependent increase in liver aminotransferase levels was found in patients with PPH or with PAH associated with connective tissue disease. No significant reductions in systemic blood pressure were reported [18].

In the BREATHE-2 study, the combination between bosentan and epoprostenol in PAH treatment was investigated. Shortly, efficacy and safety of two dosages of bosentan added to epoprostenol were compared with those of placebo and epoprostenol. Elevated liver aminotransferases were reported more often in the placebo and epoprostenol group and the most frequently encountered adverse drug reactions were those associated with epoprostenol therapy (jaw pain, diarrhea, flushing and headache). Decreases in systemic blood pressure were more evident in placebo/epoprostenol group and hypotension was reported in the same group [21].

Expert commentary & outlook

The current case series shows that it is feasible to give bosentan, even when patients have PAH associated with PPHTN and liver disease. Bosentan can improve clinical severity, exercise tolerance and cardiac hemodynamics in severe PPHTN patients and can have also a favorable safety profile.

However, the data from this study have to be interpreted cautiously, taking into account several of its limitations – small study sample, absence of any comparison with placebo or historic controls and the safety profile of bosentan in patients with more severe liver disease. Provided that these results can be reproduced within a randomized, placebo-controlled setting, these results will bring more consistent efficacy data on bosentan in PPHTN patients. Moreover, survival and safety data will add to the current information available on the role of bosentan in PPHTN treatment.

It would also be interesting to assess bosentan efficacy in less severe PPHTN patients (lower functional classes) and the potential impact of the underlying liver disease on bosentan treatment duration in more severe cirrhotic patients. Specifically, an investigation into the efficacy and safety of long-term bosentan treatment in these patients is required.

Highlights

- Portopulmonary hypertension is a form of pulmonary arterial hypertension that occurs in the presence of portal hypertension.
- Bosentan can improve clinical severity, exercise tolerance and cardiac hemodynamics in patients with severe portopulmonary hypertension.
- Bosentan can also be safely given to patients with portopulmonary hypertension, despite hepatotoxicity concerns.
- However, the safety and efficacy of bosentan in portopulmonary hypertension have to be further documented on a long-term basis.

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