

Adult patients with pulmonary arterial hypertension due to congenital heart disease: a review on advanced medical treatment with bosentan

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Abstract: Pulmonary arterial hypertension (PAH) is a progressive disease with poor survival outcome. PAH is classified by the 2009 updated clinical classification of pulmonary hypertension and a major subgroup is PAH due to congenital heart disease (CHD) with systemic-to-pulmonary shunt. CHD-PAH is a result of systemic-to-pulmonary shunting and chronic increased flow that ultimately results in adaptations of pulmonary vasculature and endothelial dysfunction. The advanced stage is called Eisenmenger syndrome which forms a small percentage (1%) of all CHD patients. Therapies targeted on PAH symptoms are called primary therapy for PAH, but most CHD-PAH patients progress to advanced therapy which is directed at the PAH itself. In CHD-PAH, advanced therapies are extensively investigated for all three major pathways: endothelin-1 receptor antagonists such as bosentan, prostanoids such as epoprostenol and phosphodiesterase 5 inhibitors such as sildenafil. Endpoints in most trials were catheterization hemodynamics, World Health Organization functional class, six-minute walking distance and patient-focused outcomes, based on quality of life questionnaires and Borg dyspnea index. The BREATHE-5 and EARLY study were two important randomized controlled trials showing efficacy of bosentan at short follow-up. Moreover in patients with Eisenmenger syndrome, one recent survival retrospective study with majority of patients on bosentan showed strong survival benefit over conservative therapy. A diversity of prospective cohort and retrospective studies were performed but all with limited data, due to small numbers and heterogeneity of underlying CHD diagnoses. Further larger studies are needed to determine optimal treatment for adults with CHD-PAH. This review focuses on bosentan in CHD-PAH. In particular, we discuss outcome of various clinical trials and compare efficacy and safety of bosentan to other advanced therapies.

Keywords: pulmonary arterial hypertension, bosentan, endothelin-1 receptor antagonist, congenital heart disease

Introduction to the management of pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a syndrome characterized by symptoms of dyspnea, fatigue, chest pain, and syncope. Underlying mechanism is a progressive increase of pulmonary vascular resistance and a sustained elevation of pulmonary arterial pressure to more than 25 mmHg at rest.¹ It may lead to a decreased functional capacity, and right ventricular failure, and is often associated with early death.^{2,3} PAH can be classified into five main categories according to the updated clinical classification of PAH.¹ This updated clinical classification is a result of the expert conference at Dana Point in

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2008. This conference revised the Venice classification from 2003 and evaluated the five main groups. In this review we focus on pulmonary arterial hypertension due to congenital heart disease (CHD-PAH), which is part of group one. The CHD-PAH group is a well defined population which is investigated and compared to other groups thoroughly.⁴⁻⁶ New in the updated clinical classification of PAH is the subdivision of CHD-PAH in four main groups: 1) Eisenmenger syndrome; 2) PAH associated with systemic-to-pulmonary shunts; 3) PAH with small defects; and 4) PAH after corrective cardiac surgery. The pathophysiologic mechanism for all these four groups involves intracardiac shunting and increased flow, though in different stages. Longstanding increased flow leads to pulmonary vascular changes and increased pulmonary vascular resistance. Ultimately this can lead to a reversal of the systemic-to-pulmonary shunt and cyanosis, the so called Eisenmenger syndrome classified as group one within CHD-PAH. Eisenmenger syndrome is a multiorgan syndrome with symptoms of dyspnea, arrhythmia, congestive heart failure, endocarditis, cyanosis, increased blood viscosity, iron deficiency anemia, blood-clotting disturbances and early death.⁷ Patients with Eisenmenger syndrome form a small percentage (1%) of the CHD population.⁷ An important subgroup in this Eisenmenger population is patients with Down syndrome.⁸ Once developed Eisenmenger syndrome patients tend to remain stable for many years, although highly symptomatic, requiring major lifestyle adjustments due to limited functional capacity.⁹ Exercise capacity and quality of life (QoL) are diminished, pregnancy is strongly contraindicated in female patients¹⁰ and associated life-threatening complications are numerous.¹¹ Survival in patients with Eisenmenger syndrome is lower than in the general population (55% reach 50 years of age). Treatment of pulmonary arterial hypertension is based on the updated clinical classification of PAH. Therapies targeted on their symptoms are called primary therapy for PAH.¹² Unfortunately most primary therapies for category one in the updated classification of PAH are not effective to slow down progression. However, primary therapies remain applicable for treatment of complications as thrombosis, cardiac failure and rhythm disorders. Patients with CHD-PAH who progress to functional class II, III, or IV, irrespective of anticoagulation, diuretics, digoxin, oxygen or lifestyle advices, qualify for advanced therapy. Advanced therapy is directed at the underlying mechanism of PAH. For PAH treatments with advanced therapy three main pathways have been detected: prostacyclin, nitric oxide and endothelin-1.¹³ This resulted in therapies with prostanoids such as epoprostenol, phosphodiesterase-5 inhibitors such

as sildenafil and endothelin-1 receptor antagonists such as bosentan.¹²

Bosentan for treatment of patients with CHD-PAH

The mechanism of bosentan is a competitive dual inhibition of the endothelin-1 receptor.¹⁴ Endothelin-1 is a potent vasoconstrictor, which also mediates cell proliferation, fibrosis and inflammation.¹⁵ Experimental data also showed that endothelin-1 not only modulates vascular smooth muscle tone but also promotes cellular proliferation, initiates cardiac myocyte and nonmyocyte hypertrophy. Moreover, endothelin-1 regulates secretion of neurohormonal mediators of cardiac and vascular hypertrophy. It is mainly synthesized in endothelial cells and works locally.¹⁶ The plasma level of endothelin-1 in patients with PAH appeared to be elevated, inducing histopathological changes in the pulmonary vascular bed.^{17,18} Endothelin-1 acts on two receptor types, subtype A and subtype B. Endothelin-1 receptor subtype A (ETA) is predominantly found in smooth muscle cells and fibroblasts. Agents which selectively block the type A endothelin-1 receptor are ambrisentan and sitaxsentan. Endothelin-1 receptor subtype B (ETB) is expressed in smooth muscle and endothelial cells.¹⁹ Activation of endothelial ETB mediates clearance of endothelin-1 and vasodilatation by nitric oxide and prostacyclin release.¹⁶ Because of these effects ETB activation is theoretically desirable in PAH. Bosentan exhibits a relative ETA to ETB affinity of 20:1 *in vitro* assays and is therefore classed a dual endothelin-1 receptor blocker.²⁰ PAH is common in adult patients with congenital heart disease^{21,4} and treatment of CHD-PAH with bosentan is extensively investigated.

Efficacy and comparative studies

To determine the efficacy of bosentan for advanced treatment of PAH various endpoints have been investigated. The gold standard for diagnoses of PAH and evaluation of effect remains cardiac catheterization. Most clinical studies performed catheterization. However, alternative, less invasive endpoints as the World Health Organization functional class, the Borg scale of dyspnea and the total distance walked in six minutes (6MWD) were also used to examine treatment efficacy.²² The use of the World Health Organization modified functional classification (FC) scale allows for standardized grading, which is also incorporated into treatment guidelines.²³ The functional class ranges from class I representing PAH without limitation of physical activity to class IV meaning PAH with inability to carry out any physical activity without symptoms. The six-minute walking distance (6MWD) is an exercise test with outcome in meters. Benefit of the 6MWD is the simplicity, the ease of replication and the

possibility of measurements of oxygen saturations at peak exercise and its prognostic clinical correlation and prognostic significance.²⁴ The validity of the 6MWD is questionable in patients with an intellectual disability.^{25,26} The third noninvasive efficacy endpoint is the score on the Borg scale of dyspnea with 0 representing no dyspnea and 10 the maximal dyspnea.²⁷ An overview of efficacy studies in patients with CHD-PAH in which the effect of endothelin-1 receptor antagonist was investigated is shown in Table 1. The small number of patients included in all CHD-PAH studies is worth mentioning as well as the heterogeneity of underlying diagnosis.

Randomized controlled trials

In 2001, the first clinical randomized controlled trial on the effect of the dual endothelin-receptor antagonist bosentan was performed in PAH patients.²⁸ Only patients with idiopathic PAH and associated with collagen vascular disease were included. For patients with congenital heart disease in total two randomized controlled trials (RCT) were conducted. The first randomized controlled trial, the BREATHE-5 study described bosentan as endothelin-1 receptor antagonist therapy in patients with ES.²⁹ This trial also included children (patients > 12 years) and at baseline all patients were in functional class III. The study showed a statistically significant treatment effect for reduction of the pulmonary vascular resistance index and decrease of the mean pulmonary arterial pressure. Remarkable in this trial was the increased pulmonary vascular resistance

index (PVRi) observed in the placebo arm. This elevation in functional class III patients in a small period of time, 16 weeks, was not expected. The 6MWD resulted in a treatment effect of 53 m ($P = 0.008$). Directly after the end of this study, a subgroup was included in an extension prospective cohort study. This 6MWD data showed improvement in those patients who had initially received placebo (33 m) and maintenance of the effect in patients who were treated with bosentan (67 m).³⁰

The second randomized controlled trial investigating bosentan was the EARLY study by Galiè et al about bosentan treatment exclusively of PAH patients in functional class II.³¹ A subgroup ($n = 32$) were patients with CHD-PAH. Change in 6MWD was not statistically significant at 6 months from baseline, though the 6MWD was increased in the endothelin-1 receptor antagonist group and decreased in the placebo group. Bosentan treatment was associated with a lower incidence of decline in functional class compared to placebo ($P = 0.03$).

Long-term follow-up and survival

Since approval of the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for bosentan, four long-term trials have been conducted (follow-up 12–28 months). D'Alto et al described a 12 months safety and efficacy study in ES patients and showed a significant reduction of the pulmonary vascular resistance index (PVRi) and systemic vascular resistance index (SVRi) ratio.³² This

Table 1 PAH studies reporting effect of bosentan in patients with CHD-PAH

First author	Design	Year	n	F/U (months)	Endpoint	Adverse effect
Galiè (BREATHE-5)	RCT	2006	54	4	Functional class; catheterization	LE; headache; dizziness; palpitations
Apostolopoulou	Prospective cohort	2007	21	28	Treadmill	Dizziness; flushing; hemoptysis
D'Alto	Prospective cohort	2007	22	12	6MWD; catheterization	Leg edema, LFT > 3UNL
Diller	Retrospective cohort	2007	18	24	6MWD	Death
Galiè (EARLY)	RCT	2008	32	6.5	6MWD; catheterization	Anemia, cardiac failure
Gatzoulis	Prospective cohort	2008	37	10	6MWD	LE; diarrhea; headache; AP; abortion
Berger	Post-hoc	2009	54	4	Catheterization	Angina pectoris
Diaz (BREATHE-5)	Prospective cohort	2009	10	25	6MWD	None
Duffels	Retrospective cohort	2009	58	22	Laboratory tests; 6MWD; MRI	Throat pain; LFT > 3UNL; death
Dimopoulos	Retrospective cohort	2010	50	48	Survival	–
Jing	Multicenter open-label trial	2010	34	6	6MWD; catheterization	–

Abbreviations: F/U, follow-up; PAH, pulmonary arterial hypertension; RCT, randomized controlled trials; 6MWD, 6 minute walking distance; MRI, magnetic resonance imaging; GI, gastrointestinal; LE, leg edema; AP, angina pectoris; LFT, liver function test; UNL, upper normal limits.

suggests a greater effect of endothelin-1 receptor antagonists on pulmonary rather than on systemic circulation. Bosentan increased the pulmonary and systemic flow significantly. The pulmonary and systemic pressures decreased although not significantly. Bosentan treatment caused a greater reduction in right ventricular than in the left ventricular after-load after one-year follow-up, resulting in a reduction of right-to-left shunting, an improvement in pulmonary blood flow, and ultimately, in systemic oxygen delivery.

The second long-term study was performed by Diller et al looking at 18 (14 females) patients with median follow-up of 29 months.³³ In total 15 patients had Eisenmenger syndrome. At baseline all patients were in functional class III. Compared to baseline the arterial saturation increased within the first six months of treatment ($81.1 \pm 4.9\%$ vs $84.7 \pm 2.6\%$, $P = 0.014$). 6MWD improved significantly in 0–6 months, 6–12 months and 1–2 years of treatment ($P = 0.005$). Functional class also improved during follow-up ($P = 0.001$). Two long-term studies that showed a short-term efficacy followed by gradual return to baseline were performed by Apostolopoulou et al and Duffels et al.^{26,34} The first study showing stabilization was by Apostolopoulou et al with two year follow-up using treadmill exercise testing, using an exercise protocol described Northridge et al.³⁵ Most patients (68%) were cyanotic and all patients had severe right ventricular dilatation and hypertrophy on echocardiography. After the initial improvement at 16 weeks of treatment in maximal and submaximal exercise, all exercise parameters at two years seem to be slowly returning to baseline. Next study was by Duffels et al who have done a subgroup analysis after two years follow-up on bosentan efficacy in CHD-PAH, comparing patients with and without Down syndrome.²⁶ Although not significant, a trend towards improvement was seen in patients with Eisenmenger syndrome. This treatment effect in both studies is different from the observation by D'Alto et al and Diller et al.^{32,33} The discrepancy between the first two studies and the other two CHD-PAH trials may be due to a higher cardiac output with lower pulmonary vascular resistance of their population, possibly indicating less advanced disease stage or natural progression.

In contrast, a strong survival benefit was shown in one recent retrospective study performed in patients with Eisenmenger syndrome on various advanced therapies (AT) with majority of patients on bosentan (73.5%, $n = 50$).⁹ These patients were compared to 168 patients with Eisenmenger syndrome not on AT, showing a strong survival benefit for advanced therapies. In absolute numbers two (2.9%) patients on AT died versus 50 (29.8%) not on AT. In this survival study Eisenmenger syndrome patients who received advanced therapy were likely to be at the

worst end of the spectrum and therefore at a higher risk of death. In accordance with this, patients on advanced therapy in the study were significantly older, were more exercise impaired, and were more likely to receive anticoagulants and to have a history of syncopal episodes, indicating overall a more advanced disease stage. Furthermore, another recent meta-analysis demonstrated improved survival with targeted therapy resulting in a number of 20 needed treatment to prevent one death at 1 year.³⁶

Finally, one study investigated the short-term and long-term effect of bosentan on systemic-to-pulmonary shunts in adults compared to children.³⁷ This study showed short-term improvement in both adults and children with PAH but at long-term follow-up a progressive decline in beneficial bosentan effect was observed. The decline appeared most pronounced in the pediatric patients, who, in that study, tended to have more severe disease at baseline.

Retrospective and prospective cohort studies

Besides the randomized controlled trials and long-term studies, several prospective cohort, one post hoc analysis and multiple retrospective studies were performed. The post hoc subgroup analysis of the BREATHE-5 study by Berger et al compared atrial septal defects versus ventricular septal defects.¹¹ The group of ventricular septal defects included patients with an isolated ventricular septal defect and patients with an atrial septal defect combined with a ventricular septal defect. Interestingly, an increased pulmonary vascular resistance index (PVRi) appeared more in placebo-treated ASD patients and an opposite decrease in PVRi was more observed in the VSD bosentan-treated patients. The analysis showed that the effect of bosentan treatment was similar in ES patients with ASDs and patients with VSDs, indicating that the location of septal defect may have little bearing in relation to the tricuspid valve. Results of the BREATHE-5 prospective cohort extension study with two cohorts, ex-placebo patients and ex-bosentan patients, showed longer 6MWD and less deterioration of functional class for the ex-bosentan group.³⁰ The study by Jing et al performed cardiac catheterization after 12 weeks follow-up and included 34 (37%) patients with CHD-PAH.³⁸ For the total cohort, including CHD-PAH patients, the increase in cardiac output agrees with the results of two previous studies, whereas Duffels observed no change in cardiac output response to 6 months of treatment with bosentan.³⁹

Safety and tolerability

In addition to efficacy, the clinical studies mentioned above investigated the safety and tolerability of endothelin-1 receptor

antagonist treatment. An overview of adverse effects in those studies with CHD-PAH is shown in Table 1. Relative contraindications to initiate bosentan treatment are moderate to severe hepatic impairment because the metabolism of bosentan occurs by cytochrome P450 CYP2C9 and CYP3A4.²⁰

Severe adverse events

In the BREATHE-5 study, severe adverse events were more frequently seen in bosentan-treated patients than in the placebo group: palpitations (11% versus 0%) and chest pain (8% versus 0%). In the BREATHE-5 prospective cohort extension study, four patients (11%) experienced a total of seven serious adverse events (palpitations, viral gastroenteritis, increased liver function test (LFT), lethargy, nausea and chest pain (11%).³⁰ The report of spontaneous abortion in BREATHE-5 open-label extension (OLE) highlights the importance of the use of effective contraception. D'Alto et al reported one patient with nonsustained ventricular tachycardia. Debates about enhanced hypoxemia induced by endothelin-1 receptor antagonists in patients with PAH due to congenital heart disease have been rejected by the described studies. Initially, concerns were raised about the effect of endothelin-1 receptor antagonists on the potentially more reactive systemic circulation compared to the obstructed pulmonary vascular bed, which could hypothetically result in worsening of systemic hypoxemia (as a result of increased right-to-left shunting). However, no such effect occurred.

In the survival analysis of Eisenmenger syndrome patients by Dimopoulos et al, 52 patients died during a median follow-up of 4.0 years.⁹ Only two of them died while on advanced therapy but what is unclear is whether they were on bosentan or other advanced therapy.

Liver function test disturbances

A potential major complication is disturbance of the liver function tests (LFT). In the long-term trials, D'Alto et al reported three patients with a four times elevation of liver function tests at two months of follow-up. Bosentan was reduced from 125 mg twice a day to 62.5 mg twice a day with a complete normalization of the aminotransferase level.³² In the other two studies with a long-term follow-up no significant rises in liver transaminases were reported.^{33,34} Furthermore, the induction of hepatic enzymes can make hormonal contraception unreliable. To conclude, aminotransaminases levels of more than three times upper normal limits need further evaluation. Discontinuation of bosentan is recommended when levels are more than five times UNL, and reintroduction can only be considered if levels were less

than eight times upper normal limits. In all studies, liver function tests normalized after dose reduction. Other laboratory tests were often not described in the studies mentioned above. However, a decrease in hemoglobin (<10 g/dL) was seen in one patient (3%) in the study of D'Alto et al and in the BREATHE-5 study.³⁰ Monitoring of the international normalized ratio in the study of Apostolopoulou did not show interference.³⁴

Mild adverse effects

Various mild adverse events were reported eg, edema, hypersensitivity, rash and reversible thrombocytopenia.⁴⁰ Clinical studies (not focusing) on CHD-PAH showed incidences of leg edema between 10% reported by Channick et al⁴¹ and 27% in BREATHE-2.⁴² In the BREATHE-5 study, leg edema was more frequently reported in the bosentan-treated patients compared to the placebo group (19% vs 12%). Moreover, headache (14% versus 12%) and dizziness (8% versus 6%) were more common in bosentan-treated patients.²⁹ In the EARLY study the most commonly reported mild adverse event in the bosentan group was nasopharyngitis.³¹ The incidence of leg edema was similar in the two groups. BREATHE-5 OLE showed fatigue, dizziness, and headache (each 5%), leg edema (19%); nasopharyngitis (11%); diarrhea (8%).³⁰ The mechanism of edema is not entirely clear. Alternatively it may be the result of vasodilatation caused by bosentan, or dysfunction of renal tubular function.¹⁶ In the 28 months follow-up study of Apostolopoulou et al only flushing and dizziness were reported which resolved within two weeks without regimen changes.³⁴ In all but one study, hypotension or syncope did not appear. Only the BREATHE-5 reported one episode of vasovagal syncope.²⁹ Additionally, none of the studies reported an increase in cyanosis after long-term treatment with endothelin-1 receptor antagonist (28 months).³⁴

Patient-focused outcomes

Patient focused assessments in clinical CHD-PAH studies are important due to possible discrepancies between clinical performance and objective exercise capacity of patients. PAH patients are likely to adapt to decreased needs. In the literature, several scores are developed to measure perception of improvement in CHD-PAH.^{15,43} The quality of life (QoL) scores and the Borg dyspnea index are most frequently used. Unfortunately, the CHD-PAH trials did not consistently use one type of scoring system.¹⁵

The QoL evaluation was usually performed using the 36-item Short Form health survey (SF-36) or the Minnesota liv-

ing with PAH questionnaire.⁴³ The SF-36 is a well-documented, widely used and validated, self-administered QoL scoring system incorporating 36 questions.²⁶ The SF-36 includes eight independent scales (scored as 0–100) that assesses the general health concepts of Physical Functioning, limitations caused by physical health problems (Role – Physical), Body Pain, General Health Perceptions, Vitality, Social Functioning, limitations caused by emotional problems (Role – Emotional), and Mental Health. The SF-36 was used by Duffels et al in the description of exercise capacity and quality of life in adults with CHD-PAH with and without Down syndrome.²⁶ In EARLY study, the SF-36 scores showed that 57% of bosentan-treated patients and 38% of placebo-treated patients had experienced improved clinical performance ($P < 0.05$).³¹ The study reported significantly improvement of QoL in 2 of 8 SF-36 scales in patients without Down syndrome. The Minnesota living with PAH questionnaire measures patients' perceptions on physical, socioeconomic, and psychological aspects of daily life in relation with their CHD.²⁶ Scores for the total Minnesota questionnaire ranged from 0–105, with higher scores reflecting worse perceived QoL. Duffels et al reported no changes in mean questionnaire scores comparing patients with and without Down syndrome (33, range 6–67; and 38, range 0–67; $P = 0.7$).

The Borg dyspnea index was only used in a few trials.^{31,32,44} This scoring system is a visual analog score which attempts to quantify effort during the 6MWD.¹⁵ A fall in score means less exertional breathlessness. D'Alto et al described a reduction in the Borg index (5.3 vs 6.5; $P < 0.001$) after 12 months follow-up.³² Apostolopoulou et al reported a decline of Borg dyspnea index by 0.8 points, reaching baseline values at 2 years follow-up.³⁴

Combination of therapies

With multiple advanced therapies for PAH acting on three different pathways a logical step forward in treatment of PAH was to look at the combination agents.¹⁵ Most evidence was gained for the efficacy of bosentan as monotherapy and the combination of the endothelin-1 receptor antagonist with another oral advanced therapy is becoming increasingly commonplace.⁴⁵ For the combination of therapies the goal-oriented approach is a recommended strategy.⁴⁶ This goal-oriented approach in patients with severe PAH focuses on combinations of endothelin-1 receptor antagonists, sildenafil and inhaled iloprost to achieve acceptable long-term results. Moreover the goal-oriented therapy reduces the need for intravenous prostaglandin treatment and lung transplantation.⁴⁶ Safety investigation of combination therapy was performed in healthy subjects by Burgess et al.⁴⁷ This study reported interaction

for coadministration of bosentan 125 mg twice daily with sildenafil 80 mg three times daily; this resulted in a 50% rise in bosentan levels and fall in sildenafil by nearly two thirds. Moreover one report (not placebo-controlled) looking at the combination of bosentan and sildenafil showed no greater number of liver enzyme elevations compared to endothelin-1 receptor antagonist monotherapy.⁴⁶

Conclusions

The rationale for treatment is clear, given the progressive character of the disease. Clinical recommendations are found in several guidelines described by the European Society of Cardiology and the American College of Cardiology.^{48,49} Regarding effectiveness in the presented studies, bosentan treatment has shown to improve short-term exercise tolerance in patients with CHD-PAH in functional class II, III and IV.³¹ The data for long-term follow-up remains conflicting because two long-term trials showed beneficial effect and two trials reported initial efficacy followed by gradual return to baseline. Only limited data is available for specific diseases or subgroups in CHD-PAH. The BREATHE-5 study showed patients with functional class III Eisenmenger syndrome to deteriorate when they were placebo-treated in contrast to bosentan-treated patients who improved significantly.²⁹ Conclusion for Eisenmenger syndrome patients is that bosentan treatment could be considered irrespective of the nature of the septal defect.¹¹ Finally, larger studies are needed to determine optimum treatment strategy for adults with CHD-PAH due to systemic-to-pulmonary shunt. The application of endothelin-1 receptor antagonist like bosentan (and other advanced therapies) in Eisenmenger syndrome seems to be beneficial and treatment with bosentan is a proper consideration. Systematic cohort studies and ultimately new placebo-controlled trials are desired to assess the effects on survival to examine the effect of bosentan on long-term survival. In conclusion, bosentan seems to offer benefit to those patients with CHD-PAH in moderate to severe cases (Eisenmenger patients), but the incidence of adverse events require close monitoring by clinicians.

Disclosure

The authors report no conflict of interest in this work.

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