PULMONARY HYPERTENSION

Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease

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Objective: To examine long-term safety and efficacy of bosentan—an oral dual endothelin receptor antagonist—in patients with pulmonary hypertension associated with congenital heart disease or Eisenmenger's syndrome.
Design: Retrospective study.
Setting: Tertiary cardiology referral centre.
Patients: All adult patients with pulmonary arterial hypertension associated with congenital heart disease treated with bosentan at the Royal Brompton Adult Congenital Heart Centre were included.
Main outcome measures: Oxygen saturation, functional (WHO) class, 6-minute walk test distance and liver enzymes were analysed.
Results: Eighteen patients (14 female) with pulmonary arterial hypertension associated with congenital heart disease (15 patients with Eisenmenger's syndrome) with a mean (SD) age of 41 (9) years (range 23–69) were included. Median follow-up was 29 months (range 1–39). One patient died during follow-up. Patients tolerated bosentan well and no significant rise in liver transaminases was seen. Arterial oxygen saturation remained stable throughout follow-up. Mean (SD) functional class ($p=0.001$) and the 6-minute walk test distance improved compared with baseline (284 (144) vs 363 (124) m, 380 (91) m and 408 (114) m at baseline, 0–6 months, 6–12 months and 1–2 years of treatment, respectively; $p<0.05$ for each).
Conclusions: Bosentan appears to be safe and well tolerated in adults with pulmonary arterial hypertension associated with congenital heart disease or Eisenmenger's syndrome during mid- to long-term follow-up. In addition, functional class and the 6-minute walk test distance improved and this effect was maintained for up to 2 years of bosentan treatment.

Bosentan, a dual-receptor endothelin antagonist, has an established role in the management of patients with idiopathic pulmonary arterial hypertension (PAH).[1] Lately, preliminary results have also suggested that bosentan is safe and improves exercise capacity over the short term in patients with Eisenmenger's physiology.[2 3] Long-term experience with bosentan in these cohorts, however, is limited. We report our experience with bosentan in patients with PAH associated with congenital heart disease and examine the safety profile and clinical effects during a longer-term follow-up.

METHODS

All adult patients with significant PAH associated with congenital heart disease or Eisenmenger's syndrome who were treated with bosentan at our institution were included in this retrospective analysis. A subgroup of patients (n = 10) had been included in a previous prospective 16-week safety and tolerability study of bosentan and these patients were subsequently treated with bosentan on compassionate grounds. Treatment with bosentan as part of clinical studies was approved by the local ethics committee and all patients provided informed consent before the start of treatment. Our policy is to start treatment with 62.5 mg twice daily, increasing this to 125 mg twice daily after 4 weeks, as tolerated. Treatment was started in hospital with close monitoring of oxygen saturation and blood pressure. Medical records were reviewed for underlying demographic and clinical characteristics. Additional measures analysed included functional (WHO) class, oxygen saturation in room air, liver function tests, and 6-minute walk test distance (SMWTd). MedCalc version 8.1 (MedCalc, Mariakerke, Belgium) and R version 2.3.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. A p value <0.05 was considered significant.

RESULTS

Overall, 18 (14 female) patients with a mean (SD) age at the start of bosentan treatment of 41 (9) years (range 23–69) were included. All patients were in WHO class III at the onset of treatment. Median follow-up was 29 months (range 1–39). Underlying diagnoses were simple lesions in 12 (large atrial septal defect (n = 2), non-restrictive ventricular septal defect (VSD) (n = 7), persistent arterial duct (n = 2), aortopulmonary window (n = 1)), and complex lesions in six patients (atrioventricular septal defect (n = 2), ''single ventricle'' physiology (n = 3), double discordance with non-restrictive VSD (n = 1)). Fifteen patients did not undergo previous corrective surgery and constituted the Eisenmenger group; three patients had undergone corrective surgery late in infancy and subsequently developed PAH.

All but one patient received 125 mg bosentan twice a day after the initial uptitration period. One patient had noticed subjective improvement with the initial dose of 62.5 mg bosentan twice daily, but experienced light-headedness after uptitration to 125 mg and was therefore downtitrated to 62.5 mg bosentan twice daily. None of the patients needed to

Abbreviations: PAH, pulmonary arterial hypertension; SMWTd, 6-minute walk test distance; VSD, ventricular septal defect

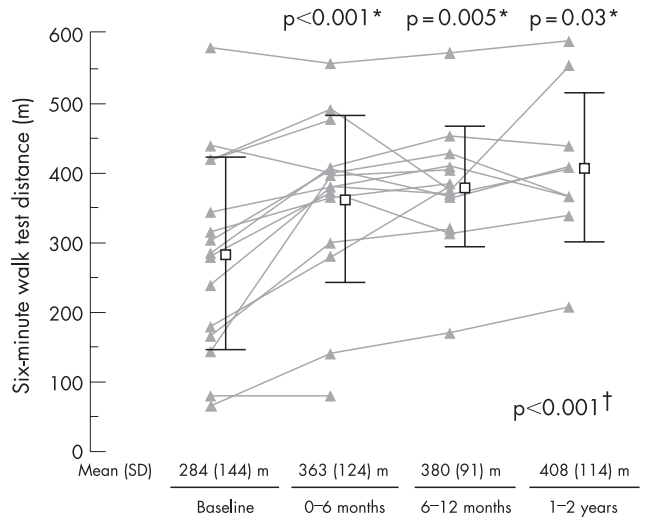

Figure 1 Six-minute walk test distance at baseline and during follow-up. *Individual comparisons with baseline values were made using a non-parametric test (Wilcoxon paired rank test); † analysis of covariance.

discontinue bosentan treatment owing to untoward effects. No significant rise in liver transaminases was seen during follow-up and none of the patients had raised transaminase values exceeding three times the upper limit of the reference range.

One patient died during follow-up. Treatment of this 69-year-old patient with ''single ventricle'' physiology and unprotected pulmonary circulation (situs solitus, double inlet left ventricle, rudimentary right ventricle, non-restrictive VSD and discordant ventriculoarterial connection) was started with bosentan on compassionate grounds after marked deterioration in functional class. The patient reported symptomatic improvement with the bosentan treatment, but died 11 months later owing to progressive heart failure.

There was no significant drop in oxygen saturation, either within the first 6 months of treatment or during longer-term follow up. Arterial saturation (mean (SD)) in patients with Eisenmenger's syndrome increased compared with baseline within the first 6 months of treatment (81.1 (4.9)% vs 84.7 (2.6)%, $p = 0.014$). There was a non-significant trend towards higher oxygen saturation at 1 and 2 years of follow-up (81.1 (4.9)% vs 84.5 (2.8)%, $p = 0.054$; and 81.1 (4.9)% vs 84.2 (4.8)%, $p = 0.078$, respectively).

The SMWTd improved significantly during bosentan treatment compared with baseline (mean (SD) 284 (144) m vs 363 (124) m, 380 (91) m and 408 (114) m at baseline, 0–6 months, 6–12 months and 1–2 years of treatment, respectively; $p<0.05$ for each). Consistent with this objective improvement in exercise capacity, patients' perceived functional class improved during follow-up ($p = 0.001$):11 patients had an improvement in their functional class during treatment, while the remaining seven remained stable. None of the patients felt subjectively worse during treatment.

DISCUSSION

In this study, bosentan was found to be safe and well tolerated in patients with PAH associated with congenital heart disease during medium- to long-term treatment. Oxygen saturation remained stable during treatment and indeed a modest but statistically significant increase in oxygen saturation was found early during follow-up. In addition, no evidence of a clinically relevant rise in serum levels of aspartate or alanine aminotransferase as markers of hepatic function during bosentan treatment was seen. In none of the patients studied did these measures exceed by threefold the upper reference value during treatment.

We found a significant increase in SMWTd early during treatment and this effect was maintained for up to 2 years of bosentan treatment (fig 1). Recently, improved SMWTd in adult patients with Eisenmenger's syndrome and PAH associated with congenital heart disease followed up at six different German centres was reported.[4] Our study confirms these results and expands these findings by providing a detailed overview over the time course of improvement in objective exercise capacity during long-term follow-up. In addition, our findings concur with studies in patients with idiopathic PAH, in which initial improvement in SMWTd was sustained during long-term bosentan treatment.[5 6] Moreover, in agreement with the observed improvement in objective exercise capacity, symptomatic status improved during treatment.

Clinical implications

Bosentan was found to be safe and was associated with improved subjective and objective exercise tolerance in highly symptomatic patients with PAH associated with congenital heart disease and Eisenmenger's syndrome. Bosentan can be considered safe and beneficial—at least during short-term follow-up. In addition, our current study provides evidence that the beneficial effects of endothelin antagonism are sustained over mid- to long-term follow-up.

Limitations

This was a retrospective study describing the experience of a single centre. Long-term placebo-controlled randomised trials are required to confirm the results of the current study. Nevertheless, previous studies in patients with PAH have not noted improvement in SMWTd beyond the first 12 weeks of placebo treatment,[4 5] suggesting that the objective functional improvement seen in our study after initiation of bosentan is genuine. The possibility of a learning or practice effect confounding the results of the SMWT cannot be excluded. Analysis of covariance with time as a covariate was used to account for such an effect, confirming the significant increase in SMWTd after initiation of bosentan.

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Conflicts of interests: None declared.

REFERENCES

1 **Galie N**, Torbicki A, Barst R, *et al*. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004;**25**:2243–78.
2 **Galie N**, Beghetti M, Gatzoulis MA, *et al*. Bosentan therapy in patients with Eisenmenger's syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006;**114**:48–54.

3 **Apostolopoulou SC**, Manginas A, Cokkinos DV, *et al*. Effect of the oral endothelin antagonist bosentan on the clinical, exercise, and haemodynamic status of patients with pulmonary arterial hypertension related to congenital heart disease. *Heart* 2005;**91**:1447–52.
4 **Schulze-Neick I**, Gilbert N, Ewert R, *et al*. Adult patients with congenital heart disease and pulmonary arterial hypertension: first open prospective multicenter study on bosentan therapy. *Am Heart J* 2005;**150**:716e7–12.
5 **Sitbon O**, Badesch DB, Channick RN, *et al*. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. *Chest* 2003;**124**: 247–54.
6 **Channick R**, Simonneau G, Sitbon O, *et al*. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo controlled study. *Lancet* 2001;**358**:1119–23.

IMAGES IN CARDIOLOGY

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Parallel stenting using two sirolimus-eluting stents in an ectatic coronary artery stenosis

With the introduction of the drug-eluting stent (DES), re-stenosis rates have been reduced. In saphenous vein graft or ectatic coronary artery disease due to large vessel diameter their use is precluded. We report a challenging case of implantation of two sirolimus-eluting stents (SES; Cypher; Cordis) parallel to each other in an ectatic vessel.

A coronary angiogram (CAG) and intravascular ultrasound (IVUS) examination carried out on a 57-year-old man with unstable angina showed severe eccentric stenosis in the ectatic proximal left anterior descending artery (panel A). The lesion was predilated by a ''parallel ballooning'' technique. Two 3.5×18 mm SES were simultaneously deployed (upper and lower SES; 22 atm each; panel B). Final angiography and IVUS showed two widely patent stents without underexpansion or malposition (panel D). At 1 month, the patient presented with rest angina, and subsequent CAG showed patent parallel stents, but the acetylcholine provocation test showed significant diffuse vasospasm distal to the ectatic portion with typical chest pain (panel E); a 200 μg intracoronary nitroglycerine injection reversed the vasospasm and the chest pain. The 6 month routine CAG showed a peculiar membrane in the new stent carina, which is a similar observation to that after the kissing stenting in the left main bifurcation lesion (panel F). This membrane does not seem to be related to clinical events.

In lesions which have a large reference diameter one can consider parallel stenting using DESs as a new intervention strategy. It also depicts the association of vasospastic angina with coronary ectasia.

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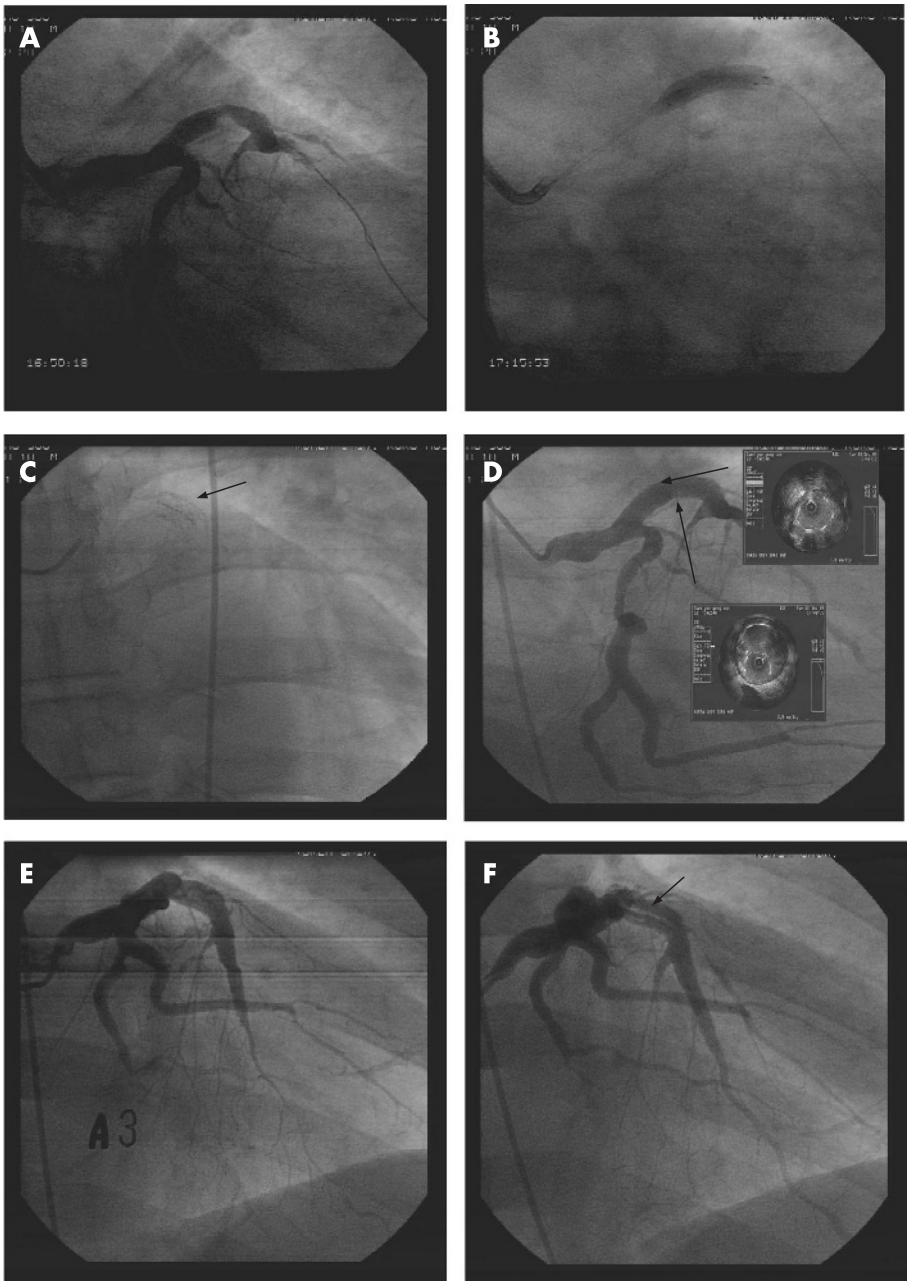

Coronary angiogram showing severe eccentric stenosis in the proximal left anterior descending artery at baseline (panel A), during parallel stenting (panel B). Fluoroscopic visualisation of two implanted parallel SESs (panel C). Post stenting angiogram with intravascular ultrasound delineation of superior and inferior stents (panel D). One month follow-up angiogram showing diffuse severe vasospasm with acetylcholine injection (panel E). Six month follow-up angiogram showing the new membrane between the two stents (arrow, panel F).