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Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist?

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ABSTRACT

Background
Data on long-term response to bosentan in adults and especially children with pulmonary arterial hypertension (PAH) associated with systemic-to-pulmonary shunt are scarce.

Methods
We studied bosentan efficacy in 30 patients (20 adults, 10 children) with the disease at short- (4 months), and long-term follow-up (through 2.7 years). World Health Organization functional class (WHO class), transcutaneous oxygen saturation and 6-minute walk distance (6MWD) were assessed at baseline, 4 months, 1 year, 1.5 years and at latest follow-up (median 2.7 years).

Results
At baseline, children tended to have more severe disease compared to adults with regard to WHO class and congenital heart defects. At 4 months’ follow-up, WHO class and 6MWD significantly improved in both adults and children. During long-term follow-up, this improvement persisted through 1 year, but declined thereafter in the total group. In the children, a progressive decline in exercise capacity was observed from 1-year follow-up, whereas in the adults, improvement lasted longer. No change from baseline was seen in transcutaneous oxygen saturation. Three (10%) patients died, 2 (7%) discontinued bosentan and 5 (17%) required additional PAH therapy (of whom 1 eventually died). One and 2-year persistence of beneficial bosentan effect was 68% and 43% (total group), 78% and 57% (adults), and 50% and 20% (children), respectively.

Conclusions
Our experience with bosentan suggests short-term improvement in both adults and children with PAH associated with systemic-to-pulmonary shunt. 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 this study, tended to have more severe disease at baseline.
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and ultimately lethal pulmonary vascular disease which can be idiopathic or associated with underlying conditions. Eisenmenger syndrome is the most advanced form of PAH associated with congenital heart disease due to systemic-to-pulmonary shunt. It develops as a result of chronically increased pulmonary blood flow and pressure which ultimately cause increased pulmonary vascular resistance, permanent reversal of the shunt and hypoxemia. Although survival estimates are reported to be better compared with patients with idiopathic PAH (iPAH), morbidity, including decreased exercise capacity, is high and, therefore, stresses the need for therapy.

Bosentan, a dual endothelin receptor antagonist, has been introduced as an important new oral PAH therapy targeting over-expression of endothelin-1. It currently is an accepted and effective short and long-term treatment for iPAH and PAH secondary to connective tissue disease. Due to the similarities in pulmonary vascular changes and increased endothelin-1 levels seen in different types of PAH, it could be expected that patients with PAH associated with systemic-to-pulmonary shunt will benefit from this medication as well.

Short-term improvements in functional class, exercise capacity and hemodynamics at 4 months’ follow-up were recently demonstrated in a placebo-controlled randomized trial with bosentan in adults with PAH associated with systemic-to-pulmonary shunt, without compromising systemic oxygen saturation (and thus not increasing right-to-left shunting). Long-term bosentan effects, however, are less well known. Four non-controlled studies have suggested persisting improvement at follow-up of 1 to 2 years, whereas a report by Apostolopoulou et al. suggested a decline in exercise capacity after 2 years’ follow-up.

The use of bosentan in pediatric patients with PAH associated with systemic-to-pulmonary shunt has yet to be evaluated. Most non-controlled studies reporting results with bosentan in patients with PAH associated with systemic-to-pulmonary shunt have included adult patients. Very few studies that report response to bosentan in pediatric PAH exist. Moreover, they include only small numbers of children with systemic-to-pulmonary shunt and mainly describe short-term follow-up.

The purpose of this study was to assess short (4 months) and long-term bosentan effects (through 2.7 years) on functional class and exercise capacity in both adults and children with PAH associated with systemic-to-pulmonary shunt. To assess differences between adults and children, we subsequently analyzed bosentan efficacy separately within both groups.
METHODS

Patients
Between November 2002 and February 2007, a cohort of 30 patients (20 adults, 10 children) with PAH associated with congenital or surgically created systemic-to-pulmonary shunt and treated with bosentan (Tracleer, Actelion Pharmaceuticals, Alschwill, Switzerland), had standardized follow-up at two Dutch tertiary medical referral centers for pulmonary hypertension. Eight patients included in the series, initially received bosentan as part of a clinical trial. All patients or patients’ parents/caregivers gave informed consent and institutional review board approval was obtained for the study.

Patients with Eisenmenger syndrome or PAH after corrected systemic-to-pulmonary shunt who were clinically stable in World Health Organization functional class (WHO class) II or worse, were selected for treatment. Eisenmenger syndrome was diagnosed echocardiographically as right-to-left shunting through the shunt-defect. In cases with corrected shunts, mean pulmonary arterial pressure (mPAP) of more than 25 mmHg (measured invasively by cardiac catheterization), established the diagnosis of PAH. Patients with severe left ventricular dysfunction and/or pulmonary venous congestion (measured invasively or assessed echocardiographically) were excluded.

In 1 child, bosentan was started with the aim of ending epoprostenol therapy, because of recurrent problems with central venous lines for epoprostenol delivery. In 1 adult, it was started in addition to previously initiated epoprostenol, because of failure to improve from WHO class IV. In the total cohort, supportive medication present at start of bosentan therapy, including diuretics, ACE-inhibitors, digoxin and/or antithrombotic agents, was continued unchanged during follow-up.

Treatment regimen
In the adult patient group, bosentan target dose was 125 mg twice daily. Pediatric patients received bosentan according to body weight: 31.25 mg (10-20 kg weight), 62.5 mg (20-40 kg) or 125 mg (>40 kg) twice daily. During the first 4 weeks of treatment, patients received half the target dose once daily. After 4 weeks, this was increased to the target dose, if bosentan was well tolerated.

Study assessments
Patients were followed within routine clinical practice, using a standardized protocol for assessments at baseline and during follow-up. Data were collected at baseline, 4 months, 1 year, 1.5 years and at most recent follow-up (median 2.7 years, range 2.0-3.4 years).

Assessments included WHO class, transcutaneous oxygen saturation at rest (TcSO2), heart rate, blood pressure and 6-minute walk distance (6MWD). Additional outcome parameters included survival and persistence of beneficial bosentan effect, as previously defined by Rosenzweig et al (freedom from death, lung or heart lung transplant, atrial septostomy, discontinuation of treatment or requirement of additional PAH therapy: epoprostenol, treprostinil, sildenafil). Because criteria for the introduction of
add-on therapy are not clearly defined for patients with PAH associated with systemic-to-pulmonary shunt, not all patients in this series in whom initial improvement in 6MWD disappeared during follow-up, received such additional therapy. Therefore, we subsequently extended the definition by including decline in 6MWD during follow-up to below baseline value. Liver function tests, hemoglobin and hematocrit were tested monthly to screen for adverse effects.

**Statistical analysis**

Data are presented as mean±SD or median and range, where appropriate. Change in 6MWD from baseline is expressed as mean±SEM. To compare changes from baseline to each of the follow-up visits, paired Student t tests (6MWD, TcSO2, blood pressure, heart rate and hematocrit) and Wilcoxon rank sum tests (WHO class) were used. Kaplan-Meier curves were applied to depict survival and persistence of beneficial bosentan effect.

To analyze differences between measurements in adults and children, independent-samples t tests (continuous variables) and Mann-Whitney U tests (WHO class, type of heart defect) were used. The log-rank test was used to assess differences in survival and persistence of beneficial bosentan effect between adults and children.

The association between age group (adults versus children) and indicators of disease severity at baseline (type of heart defect, WHO class, 6MWD, invasive hemodynamics) and persistence of beneficial bosentan effect was assessed by means of the log-rank test. Subsequently, a multivariate Cox regression analysis was performed to assess variables found to be predictive in the univariate analysis. All P-values were two-tailed and those <0.05 were considered significant.

**RESULTS**

**Patients**

Baseline characteristics are summarized in Table 1. Ventricular septal defect (VSD) was the most common heart defect (53%), and frequently associated with additional shunt-defects, such as atrial septal defect (ASD) and persistent ductus arteriosus (PDA). An isolated ASD was seen in 19% of all patients, all of whom were adults. Twenty-six patients (87%) had classical Eisenmenger syndrome, 6 of these with a shunt before and 20 after the level of the tricuspid valve. The remaining 4 patients had persistent PAH despite closure of their systemic-to-pulmonary shunts years earlier. One child with VSD and PDA had undergone corrective surgery in the past. Because of clinical deterioration 1 year after corrective surgery, an ASD had to be created (9 years prior to study enrolment). This patient was categorized as having a pre-tricuspid shunt. More post-tricuspid shunt defects were present in the children than in the adults (80% and 60%, respectively).

At baseline, all children and 90% of the adults were in WHO class III or IV (Table 1, Figure 1).
Table 1. Patient demographics and baseline exercise capacity

<table>
<thead>
<tr>
<th></th>
<th>All patients n=30</th>
<th>Adults n=20</th>
<th>Children n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>20 (67)</td>
<td>12 (60)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Age at start bosentan (years)</td>
<td>30.2 ± 16.0</td>
<td>39.3 ± 10.2 *</td>
<td>11.8 ± 4.8 *</td>
</tr>
<tr>
<td></td>
<td>31.2 (4.7; 59.3)</td>
<td>39.0 (26.7; 59.3) *</td>
<td>12.8 (4.7; 17.3) *</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASD isolated</td>
<td>5 (16)</td>
<td>5 (25)</td>
<td>0</td>
</tr>
<tr>
<td>VSD isolated</td>
<td>9 (30)</td>
<td>7 (35)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>VSD ± ASD ± PDA</td>
<td>7 (23)</td>
<td>3 (15)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>PDA</td>
<td>2 (7)</td>
<td>0</td>
<td>2 (20)</td>
</tr>
<tr>
<td>cAVSD</td>
<td>3 (10)</td>
<td>2 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>DORV</td>
<td>2 (7)</td>
<td>2 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Complex</td>
<td>2 (7)</td>
<td>1 (5)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Shunt patency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>26 (87)</td>
<td>17 (85)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Pre-tricuspid shunt</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Post-tricuspid shunt</td>
<td>20</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Closed †</td>
<td>4 (13)</td>
<td>3 (15)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>WHO class *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (7)</td>
<td>2 (10)</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>22 (73)</td>
<td>16 (80)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>IV</td>
<td>6 (20)</td>
<td>2 (10)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>TcSO2 (%)</td>
<td>87 ± 7</td>
<td>89 ± 6</td>
<td>83 ± 9</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>367 ± 101</td>
<td>388 ± 99</td>
<td>326 ± 95</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.51 ± 0.10</td>
<td>0.48 ± 0.08 *</td>
<td>0.56 ± 0.10 *</td>
</tr>
</tbody>
</table>

Data are presented as n (%), mean ± SD, median (range), as appropriate.

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; cAVSD, complete atrio-ventricular septal defect; DORV, double outlet right ventricle; Complex, truncus arteriosus (n=1), tetralogy of Fallot with Potts anastomosis (n=1).

Pre-tricuspid shunt: ASD. Post-tricuspid shunt: VSD, PDA, cAVSD, DORV, complex.

TcSO2, transcutaneous oxygen saturation at rest, 6MWD, 6-minute walk distance.

* Significant difference between adults and children: age, P=0.00; WHO class, P=0.04; hematocrit, P=0.05.

† Shunt closed: VSD+ASD (n=1), truncus arteriosus (n=1), DORV (n=1), tetralogy of Fallot and Potts anastomosis (n=1).

Children had a worse WHO class (P=0.04) and higher hematocrit level (P=0.05) compared to the adults. Baseline 6MWD and TcSO2 tended to be lower in the children, although not reaching statistical significance.

Baseline cardiac catheterization was performed in 27 of 30 patients (Table 2). Children tended to have worse baseline hemodynamics compared to adults: the ratio of mPAP to mean systemic arterial pressure (mPAP/mSAP) was significantly higher in the children (P=0.03). Cardiac index and pulmonary-to-systemic blood flow ratio tended to be lower in the children, although not reaching statistical significance.
Figure 1. World Health Organization functional class during follow-up for total group

![Graph showing functional class distribution](Image)

Number of patients in each class is indicated in the bars.
† Follow-up visits at 1.5 and 2.7 years: after addition of sildenafil in 3 and 4 patients, respectively.
* significant change from baseline.

Table 2. Baseline hemodynamic characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP (mmHg)</td>
<td>64 ± 21</td>
<td>64 ± 24</td>
<td>62 ± 8</td>
</tr>
<tr>
<td>mPAP/mSAP</td>
<td>0.87 ± 0.19</td>
<td>0.80 ± 0.18 *</td>
<td>0.98 ± 0.13 *</td>
</tr>
<tr>
<td>mPCWP (mmHg)</td>
<td>7 ± 3</td>
<td>7 ± 2</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>5 ± 2</td>
<td>5 ± 2</td>
<td>6 ± 3</td>
</tr>
<tr>
<td>CI (l/min/m2)</td>
<td>2.8 ± 1.1</td>
<td>2.9 ± 1.2</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>Qp/Qs</td>
<td>0.91 ± 0.35</td>
<td>0.98 ± 0.37</td>
<td>0.79 ± 0.28</td>
</tr>
<tr>
<td>PVRix (WU.m2)</td>
<td>32.9 ± 15.9</td>
<td>33.3 ± 18.2</td>
<td>32.3 ± 11.7</td>
</tr>
<tr>
<td>SVRix (WU.m2)</td>
<td>34.9 ± 15.8</td>
<td>39.3 ± 16.7</td>
<td>26.8 ± 10.8</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>1.07 ± 0.64</td>
<td>0.92 ± 0.57</td>
<td>1.3 ± 0.70</td>
</tr>
</tbody>
</table>

mPAP, mean pulmonary artery pressure; mPAP/mSAP, ratio between mean pulmonary and systemic arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; CI, cardiac index; Qp/Qs, pulmonary-to-systemic blood flow ratio; PVRix, pulmonary vascular resistance index; WU, Woods units; PVR/SVR, pulmonary-to-systemic vascular resistance ratio.

* Significant difference between adults and children: mPAP/mSAP, P=0.03.

Follow-up assessments

Median duration of bosentan treatment was 2.2 years (range 0.04-3.4 years) in the total group, 2.1 years (range 0.4-3.1) in the adults and 2.4 years (range 0.04-3.4) in the children. Twenty-six (87%) patients received long-term treatment (median 2.4 years, range 1.0-3.4 years). Four (13%) patients had a follow-up of less than 1 year (median 0.5 years, range 0.04-0.7 years) due to death (n=2) or discontinuation of treatment (n=2).
Figure 2. Mean (SEM) change from baseline of 6MWD in total group

† 1.5 years and 2.7 years follow-up: 2 and 3 patients, respectively, underwent a 6-minute walk test after addition of sildenafil.
* Significant change from baseline.

Short-term follow-up
At 4 months after bosentan initiation, 1 child had died (after 2 weeks). Cause of death was hemoptysis associated with acute circulatory failure. In the remaining 29 patients clinical condition and exercise capacity improved significantly from baseline (Figures 1 and 2). When analyzed separately, significant improvement in WHO class and 6MWD was present in both the adults and children (Figures 3 and 4).

Figure 3. World Health Organization functional class during follow-up for adults (A) and children (B)

Number of patients in each class is indicated in the bars.
† Follow-up visit at 1.5 years after addition of sildenafil in 3 adults and at 2.7 years in 3 adults and 1 child.
* Significant change from baseline.
Significant difference between adults and children at baseline (P=0.04) and a tendency to difference at 2.7 years (P=0.07)
Figure 4. Mean (SEM) change from baseline of 6MWD in adults and children

<table>
<thead>
<tr>
<th>6-minute walk distance (m)</th>
<th>6-minute walk distance (m) after addition of sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>12†</td>
<td>8</td>
</tr>
<tr>
<td>9†</td>
<td>7</td>
</tr>
</tbody>
</table>

† 1.5 and 2.7 years’ follow-up: 2 adults, and 2 adults and 1 child, respectively, underwent a 6-minute walk test after addition of sildenafil.
* Significant change from baseline.
Significant difference between adults and children at 1 year (P=0.01) and 2.7 years follow-up (P=0.04)

**Long-term follow-up**

During longer follow-up, 2 more children died: after 8.4 months and 3.1 years. Causes of death were, respectively, progressive right ventricular failure and infection of the epoprostenol delivery system leading to sepsis.

Overall, the initial WHO class improvement persisted during long-term follow-up at 1 and 1.5 years. However, at the latest follow-up visit, improvement could no longer be demonstrated in the remaining total cohort (Figure 1). When analyzed separately, a similar pattern was seen mainly in the children (Figure 3).

The initial increase in 6MWD persisted in the total cohort during 1-year follow-up, but declined after longer treatment duration (Figure 2). The decline in 6MWD particularly appeared to be the case in the children. A significant difference between adults and children was observed at 1 and 1.5 years (p=0.01 and p=0.04 respectively) (Figure 4).

During follow-up, additional sildenafil was started in 5 patients (17%, 4 adults, 1 child) after a median bosentan treatment duration of 1.3 years (range 1.0-2.4 years). Based on the physician’s discretion, reasons for starting additional therapy were decreased 6MWD and/or decline or failure to improve in clinical condition (decline to WHO class IV, remaining in WHO class III). After addition of sildenafil, 1 patient improved, 1 remained stable and 3 patients worsened, of whom 1 adult required addition of intravenous epoprostenol.

TcSO2, heart rate, blood pressure and hematocrit level did not change from baseline through last follow-up.
Survival is illustrated in Figure 5. The difference in survival between children and adults was not statistically significant. Using criteria as defined by Rosenzweig et al for persistence of beneficial bosentan effect, three events occurred in the children (3 deaths, of which 1 death occurred 9 months after additional sildenafil) and 6 events in the adults (2 patients discontinued bosentan, and 4 patients required additional sildenafil). One- and 2-year persistence of beneficial bosentan effect according to criteria as defined by Rosenzweig et al was, respectively, 79% and 71% (total group), 78% and 65% (adults), and 80% and 80% (children). Persistence of beneficial bosentan effect, including decline in 6MWD, revealed lower 1- and 2-year event-free estimates and was significantly different between adults and children (P=0.04) (Figure 6).

Figure 5. Survival from baseline stratified for adults and children

Figure 6. Persistence of beneficial bosentan effect including decline in 6MWD, stratified for adults and children
Difference, adults vs children, P=0.04
In contrast, baseline indicators of disease severity (type of heart defect, WHO class, 6MWD and hemodynamics) could not be demonstrated to be predictive for persistence of beneficial bosentan effect. Furthermore, the predictive value of age group remained unchanged after adjustment for different indicators of disease severity in a multivariate Cox regression analysis.

All but 1 patient tolerated bosentan treatment. This adult patient discontinued treatment after half a year because of side effects consisting of nasopharyngeal complaints. A second adult discontinued treatment because he experienced lack of improvement with bosentan therapy.

**DISCUSSION**

This study, to our knowledge, is the first to report long-term response to bosentan through 2.7 years of follow-up in both adults and children with PAH associated with systemic-to-pulmonary shunt. Our results demonstrate short-term improvement in functional class and exercise capacity in both patient groups, which is in congruence with previous reports.\(^{11,20}\) During longer follow-up, improvement in 6MWD, the major outcome parameter in PAH studies, persisted up to 1 year, but declined thereafter. Separate analyses within the adult and pediatric group indicated that the decline was most pronounced in the children. One and 2-year persistence of beneficial bosentan effect was 68% and 43% (total group), 78% and 57% (adults) and 50% and 20% (children), respectively.

The improvement in 6MWD for up to 1 year corresponds with the 1-year follow-up reports of bosentan efficacy in adults with PAH associated with systemic-to-pulmonary shunt.\(^{12-14}\) From 1.5 years’ follow-up, however, we observed a decline in exercise capacity in our total group. In the only other study evaluating a minimum of 2 years’ follow-up, Apostolopoulou et al\(^{16}\) reported a similar observation, noticing a decline in 6MWD and peak oxygen consumption to baseline value in 19 patients with PAH associated with congenital heart disease.

Reports of long-term bosentan efficacy in iPAH have used event-free estimates, including addition of therapy as event, to assess persistence of bosentan effect.\(^{6,7}\) In these series, additional prostanoid and/or sildenafil therapy, suggesting insufficient effect of bosentan, was given in up to 44% of patients during 2 years of follow-up.\(^{6,7}\) In our study, additional therapy was given less frequently (17% of patients). This can be explained by the lack of data on the use of add-on therapy for PAH associated with systemic-to-pulmonary shunt, which is in contrast to the presence of aggressive guidelines for iPAH.\(^{24}\) In order to make more appropriate comparisons, we studied persistence of beneficial bosentan effect, an outcome parameter which integrated addition of other PAH therapy and decline in 6MWD. Using this outcome measure, we found 1 and 2-year event-free estimates in our adult group (78% and 57%, respectively) which are in line with those reported by Provencher et al (63% and 45%) and McLauglin et al (85% and 70%) for
adults with iPAH treated with bosentan. In contrast, our pediatric 1- and 2-year event-free estimates were markedly lower (50% and 20%, respectively).

One may speculate that the worse outcome in the children was caused by more severe disease. This is supported by our observation of worse baseline hemodynamics in this group. The greater percentage of post-tricuspid shunts may also have played a role in their less favorable outcome. Advanced pulmonary vascular disease appears to develop more frequently and more rapidly in patients with uncorrected post-tricuspid than pre-tricuspid shunt-defects. Although our analyses suggested that the predictive value of age was independent of underlying cardiac pathology and disease severity, our study may not have been powered sufficiently to conclude this.

The three deaths out of 10 children may be another reflection of more end-stage disease in this age group. Survival rates in Eisenmenger syndrome are reported to be favorable compared to iPAH (30-40 vs 2.8 years respectively). However, they are mainly derived from cohorts of adult patients. This obviously will have lead to a selection bias, excluding patients who died before reaching adulthood due to more severe disease.

In the assessment of patients with PAH, 6MWD is considered to be the most important outcome parameter. In evaluating children, the 6-minute walk test has been suggested to be reliable in children >7 years of age. In our experience with pediatric patients, we noticed that previous training resulted in reproducible 6-minute walk tests.

The present study is limited by the relatively small number of patients and the lack of a control group. Therefore, this study cannot ascertain whether bosentan may have long-term effect on the natural decline of these patients. Data collection within routine clinical practice and recent start of therapy resulted in some unavailable follow-up measurements in the adults. However, in PAH associated with systemic-to-pulmonary shunt, studies with larger numbers of patients hardly are available.

In conclusion, this study depicts long-term experience in daily clinical practice with bosentan in patients with PAH associated with systemic-to-pulmonary shunt. It raises important questions about persistence of beneficial effects with bosentan monotherapy. Short-term improvements ultimately declined during long-term follow-up and persistence of beneficial bosentan effect decreased progressively over time. The decline in treatment effect was most pronounced in the children. The difference in treatment effect between adults and children may have been confounded by differences in cardiac pathology and disease severity. Our analyses, however, could not demonstrate this, possibly due to a lack of power. In our adult patient group, beneficial effects lasted longer and treatment effect was comparable with reports in patients with iPAH. However, the clinical importance of a 1- to 2-year treatment effect in iPAH compared to patients with Eisenmenger syndrome is greatly affected by the large difference in survival between these two groups (2.8 vs 30-40 years, respectively). Larger prospective studies, including children, are warranted in order to confirm these preliminary long-term results and to assess the use of add-on therapy.
REFERENCES


