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Abstract

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Bosentan in Pediatric Patients with Pulmonary Arterial Hypertension

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CONCLUSION: Recent experience, although uncontrolled, suggests that bosentan is a well-tolerated and effective therapy for pediatric PAH.

Keywords: Bosentan, endothelin, endothelin receptors, pulmonary arterial hypertension, pediatrics.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a complex disease characterized by vasoconstriction and progressive remodeling of the pulmonary arterial wall leading to right ventricular failure and death. The pathologic features are similar in children and adults but the spectrum of associated conditions, clinical presentation, and factors influencing survival differ [1]. The most common etiologies in children after the immediate neonatal period are idiopathic (IPAH), familial, or PAH related to congenital heart disease [1].

Historically, PAH carried a dismal prognosis in children less than 16 years with a median survival of 0.8 years compared with 2.8 years in adults [2], mainly as the result of right heart failure. This outcome dramatically improved with the development of chronic vasodilator therapy including calcium channel blockers for acute responders to vasodilator testing and continuous intravenous (i.v.) epoprostenol for non-responders, and some children now survive more than 10 years after diagnosis [3]. Recently, new pharmacologic approaches have demonstrated significant efficacy in the management of adults with PAH; these include prostacyclin analogues delivered subcutaneously (treprostinil [4]) or by inhalation (iloprost [5]), endothelin receptor antagonists (bosentan [6, 7], sitaxentan [8], and ambrisentan [9]) and phosphodiesterase type 5 inhibitors (sildenafil [10]).

Bosentan is an antagonist of the ETₐ/ET₆ endothelin receptors, which exerts its pharmacologic effects by inhibiting the vasoconstrictor, mitogenic, and remodeling activities of endothelin-1 on the pulmonary arteries [11]. Bosentan improves exercise capacity, hemodynamics and time to clinical worsening in adult patients with PAH [6, 7], and also improves survival in adult patients with IPAH compared with historical controls [12]. However, no randomized placebo controlled trials have been conducted in pediatric PAH due to the dismal survival in the absence of therapy and the efficacy of new therapies in adults. Thus, this systematic review of published data may provide useful information on effectiveness and safety of bosentan in children. Bosentan is one of three endothelin receptor antagonists available to clinicians. However, although the specific ETₐ receptor antagonists sitaxentan and ambrisentan are used to treat PAH in adults there are no data available on their use in pediatric patients and further pediatric studies are expected in the future with these substances. To date there appears to be no clear evidence that receptor selectivity is clinically relevant [13].

DATA SOURCE AND STUDY SELECTION

A database search including MEDLINE, EMBASE and BIOSIS was performed for the period January 2000 – October 2007 using the key words ‘pulmonary arterial hypertension’, ‘bosentan’, and ‘pediatric patients/children’. All clinical
studies using bosentan in pediatric PAH were identified and references from the identified articles were reviewed.

Overall 165 publications were identified. Excluded from this list were publications focusing on adult patients, on drugs other than bosentan, or on indications other than PAH. Hence, 21 clinical studies are included in the present review: 1 interventional prospective [14], 6 observational prospective [15–20], 5 observational retrospective [21–26], and 9 case reports/case series [27–35] (Table 1). Studies were included irrespective of sample size, geography, study design and quality. Additionally, the search results included 2 comments [36, 37] and 11 reviews [1, 38–47] on the pediatric use of bosentan.

CLINICAL STUDIES

One Interventional Prospective Study

In a two-center, open-label study, Barst et al. [14] describe 19 children (aged 3 to 15 years) with IPAH or PAH related to congenital heart disease (New York Heart Association functional class (NYHA FC) II–III). Patients weighing 10–20 kg, 20–40 kg, and over 40 kg received 31.25 mg bosentan once daily, 31.25 mg twice daily (bid), and 62.5 mg bid, respectively, for 1 month, then 31.25 mg bid, 62.5 mg bid and 125 mg bid, respectively, for the remainder of the study. After 12 weeks of treatment, 5 children improved by one NYHA FC and 1 child worsened. Changes in exercise test parameters assessed in children over 8 years of age were variable and not significant. Hemodynamic parameters improved; mean pulmonary artery pressure decreased by 8.0 mmHg (95% confidence interval: [−12.2; −3.7]) and pulmonary vascular resistance index decreased by 300 dyne.s.m⁻².cm⁻⁵ (95% confidence interval: [−576; −24]). Bosentan showed a similar pharmacokinetic profile as in healthy adults and was well tolerated; the most frequent adverse events were flushing (21%), headache, edema and increased liver aminotransferase activity (16%) each. No deaths were reported. In the patients concomitantly treated with epoprostenol, there was no evidence of drug interactions. This study is the current reference for dosing bosentan in children and most studies reviewed hereafter used this regimen, unless otherwise indicated.

Six Observational Prospective Studies

Gilbert et al. [15] report their experience with bosentan in 7 young children (mean age 3.8 years) with congenital heart defects who presented with PAH (NYHA FC II–III) a) preoperatively representing a contraindication to corrective surgery, or b) persisting after corrective surgery. The children received 1.5 mg/kg/day bosentan for 4 weeks, then the dose was doubled. After a mean follow-up of 8.6 months, bosentan had stabilized or improved NYHA FC in all patients (from 2.6 ± 0.6 to 1.7 ± 0.6, p < 0.05) and had significantly reduced right ventricular systolic pressure (from 96 ± 11 to 72 ± 26 mmHg, p < 0.05). One patient showed an increase of liver enzymes to almost 3 times the upper limit of normal (ULN); otherwise, bosentan was well tolerated. Two patients died of cardiac decompensation, 1 due to severe pneumonia and the other following an epileptic seizure.

In another study, Brun et al. [16] followed 14 children (mean age 10 years) with Eisenmenger’s syndrome (NYHA FC II–III). The patients received a dose of 2 mg/kg/day bosentan for 4 weeks, then the dose was doubled. These authors observed a lasting symptomatic benefit over 12 months: the pulmonary hypertension symptom score increased by 2.7 ± 3.3 (p = 0.009). Flat walking and tiredness subscores significantly improved, and a positive trend was seen for climbing stairs. However, there was no improvement in mean saturation of oxygen and exercise capacity for the 6 patients able to perform a treadmill test. The authors suggest that these conflicting results could be explained by improved cardiac output following reduced systemic vascular resistance at submaximal exercise, while lower saturation becomes limiting at higher exercise levels. No significant increases in liver enzymes were seen. One patient developed obstructive sleep apnea but the symptoms disappeared after cessation of treatment. No other serious side effects were seen.

Ivy et al. [17] assessed the effect of bosentan in 8 children (mean age 12.8 years) with IPAH in NYHA FC II–III already treated with epoprostenol. After bosentan addition, epoprostenol doses were decreased weekly, depending on stable or decreasing right ventricular peak systolic pressure. Epoprostenol could be reduced in 7 children without clinical or hemodynamic deterioration, or decrease in aerobic capacity; it was even discontinued in 3 patients with stabilization of hemodynamics for up to 1 year. Peak workload and peak oxygen pulse increased (p < 0.05), suggesting an improvement in cardiac output. Four patients experienced a liver enzyme elevation and 1 had to discontinue bosentan. This small study indicates that in selected patients, bosentan facilitates the reduction of epoprostenol dose and its associated side effects, without adversely affecting hemodynamic parameters.

Lunze et al. [18] report on 11 patients (median age 12.9 years, 3 adults, 8 children ≤ 18 years) with PAH (NYHA FC II–III) identified as IPAH or PAH related to congenital heart disease, associated with chronic pulmonary thromboembolism or radiotherapy. Patients received combination treatment with bosentan (0.75 mg/kg bid for 4 weeks, then 1.5 mg/kg bid) and sildenafil. After a mean follow-up of 1.1 years, clinical benefit was demonstrated by improvements in NYHA FC (from 2.8 ± 0.4 to 1.6 ± 0.8, p = 0.001), in transcutaneous oxygen saturation (from 89.9 ± 9.9 to 92.3 ± 7.1%, p = 0.037), in maximum oxygen uptake (from 18.1 ± 6.8 to 22.8 ± 10.4 mL.min⁻¹.kg⁻¹, p = 0.043), and in 6-min walk distance (6MWD) (from 351 ± 58 to 451 ± 119 m, p = 0.039). Mean pulmonary arterial pressure decreased (from 62 ± 12 to 46 ± 18 mmHg, p = 0.041). No major side effects regarding liver function and blood pressure regulation were noted but one 6-year old child with IPAH, died of sudden death. Overall, in this patient group including 8 children and 3 adults, a combination of bosentan and sildenafil was well tolerated and effective.

Recently, an observational, disease-based registry was initiated in Switzerland to collect real-world disease management experience on pediatric patients with PAH [19], 23 patients (median age 3 years) with PAH (IPAH (35%), PAH related to congenital heart disease (52%) or associated with...
### Table 1. Clinical Studies on Bosentan in Pediatric PAH.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Reference</th>
<th>Patients (n)</th>
<th>Age (year)</th>
<th>NYHA Functional Class</th>
<th>Additional PAH Treatment</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional prospective</td>
<td>Barst et al. [14]</td>
<td>19</td>
<td>3-15</td>
<td>II-III</td>
<td>epoprostenol</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td>Gilbert et al. [15]</td>
<td>7</td>
<td>1.5-6.4</td>
<td>II-III</td>
<td>-</td>
<td>8.6 months (mean)</td>
</tr>
<tr>
<td></td>
<td>Brun et al. [16]</td>
<td>14</td>
<td>3-18</td>
<td>II-III</td>
<td>iloprost</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>Ivy et al. [17]</td>
<td>8</td>
<td>6.6-16.2</td>
<td>II-III</td>
<td>epoprostenol</td>
<td>up to 1 year</td>
</tr>
<tr>
<td></td>
<td>Lunze et al. [18]</td>
<td>8 (+3 adults)</td>
<td>5.5-54.7</td>
<td>II-III</td>
<td>sildenafil</td>
<td>1.1 years (mean)</td>
</tr>
<tr>
<td></td>
<td>Fasnacht et al. [19]</td>
<td>23</td>
<td>0-18</td>
<td>II-IV</td>
<td>iloprost sildenafil</td>
<td>3.5 years (median)</td>
</tr>
<tr>
<td></td>
<td>Beghetti et al. [20]</td>
<td>146</td>
<td>2-11</td>
<td>I-IV</td>
<td>sildenafil prostanoid</td>
<td>29.1 weeks (median)</td>
</tr>
<tr>
<td>Observational prospective</td>
<td>Maiya et al. [21]</td>
<td>40</td>
<td>0.6-17</td>
<td>III-IV (1 patient in I)</td>
<td>epoprostenol sildenafil</td>
<td>12.7 months (mean)</td>
</tr>
<tr>
<td></td>
<td>Rosenzweig et al. [22]</td>
<td>86</td>
<td>0.7-18</td>
<td>I-IV</td>
<td>epoprostenol sildenafil</td>
<td>14 months (median)</td>
</tr>
<tr>
<td></td>
<td>Simpson et al. [24]</td>
<td>7</td>
<td>7 (mean)</td>
<td>(2.4)</td>
<td>sildenafil epoprostenol beraprost</td>
<td>35.6 months (median)</td>
</tr>
<tr>
<td></td>
<td>Van Loon et al. [25]</td>
<td>10 (+20 adults)</td>
<td>-</td>
<td>II-IV</td>
<td>Sildenafil treprostinil epoprostenol</td>
<td>2.7 years (median)</td>
</tr>
<tr>
<td></td>
<td>Penny et al. [26]</td>
<td>7</td>
<td>2.1-14.7</td>
<td>(2.8)</td>
<td>epoprostenol</td>
<td>8 months</td>
</tr>
<tr>
<td>Observational retrospective</td>
<td>Hsu et al. [27]</td>
<td>1</td>
<td>1.3</td>
<td>IV</td>
<td>-</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>Dulac et al. [33]</td>
<td>1</td>
<td>1.3</td>
<td>-</td>
<td>-</td>
<td>36 months</td>
</tr>
<tr>
<td></td>
<td>Rugolotto et al. [28]</td>
<td>1</td>
<td>0.7</td>
<td>-</td>
<td>epoprostenol sildenafil</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>Brancaccio et al. [29]</td>
<td>1</td>
<td>7</td>
<td>III</td>
<td>epoprostenol sildenafil</td>
<td>4 years</td>
</tr>
<tr>
<td></td>
<td>Beghetti et al. [30]</td>
<td>1</td>
<td>8</td>
<td>-</td>
<td>iloprost</td>
<td>3 months</td>
</tr>
<tr>
<td>Single case / Case series</td>
<td>Das et al. [31]</td>
<td>1 (+9 on other treatment)</td>
<td>9</td>
<td>-</td>
<td>sildenafil</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>Goissen et al. [32]</td>
<td>2</td>
<td>newborns</td>
<td>-</td>
<td>iNO epoprostenol sildenafil</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Nemoto et al. [34]</td>
<td>2</td>
<td>0.4, 0.75</td>
<td>-</td>
<td>-</td>
<td>11, 22 days</td>
</tr>
<tr>
<td></td>
<td>Fraisse et al. [35]</td>
<td>3</td>
<td>4.5, 8 and 14</td>
<td>-</td>
<td>-</td>
<td>40, 12, and 6 months</td>
</tr>
</tbody>
</table>

Pulmonary diseases (13%) in NYHA FC II–IV were included in this registry. One patient died before treatment start and 22 patients were followed for a median of 3.5 years. At that time, 19 patients were receiving bosentan (9 as monotherapy and 10 in combination with iloprost and/or sildenafil; 3 patients were treated with other medications). Over a 2-year period, NYHA FC remained stable (19 patients) or improved from III to II (3 patients). An initial improvement in 6MWD was observed in 6 of 13 evaluated patients, which was sustained in 4 patients. As most patients were receiving bosentan, these data suggest that the disease is stabilized in bosentan-treated pediatric patients.

Beghetti et al. [20] have published data from a prospective internet-based post-marketing surveillance system focused on collecting real-world safety experience with bosentan. Registry results in the pediatric population (2–11 years) were compared with those in the population ≥ 12 years. Over 30 months, 4,994 patients were entered into the surveillance
program, including 146 bosentan-naïve children aged 2–11 years. The majority of children were in NYHA FC II (28.1%) or III (50.7%) and predominant etiologies were IPAH (40.4%) and PAH related to congenital heart disease (45.2%). The median exposure to bosentan was 29.1 weeks in children 2–11 years and 29.7 weeks in patients ≥ 12 years. Cases of elevated liver aminotransferases and discontinuations were fewer in children 2–11 years (2.7% vs. 7.8% and 14.4% vs. 28.1%, respectively). These data provide ‘real world’ evidence on the safety profile of bosentan in young children with PAH.

Five Observational Retrospective Studies

Maiya et al. [21] report on their institution’s experience with bosentan in 40 children, 20 with IPAH (mean age 8.0 years) and 20 with PAH associated with other conditions (mean age 8.3 years). Thirty-nine patients were in NYHA FC III–IV, 1 was in FC I. Bosentan was given as first line therapy in 25 children, whereas 9 children were already treated with epoprostenol and 6 with sildenafil. Mean follow-up was 12.7 months. In the IPAH group, 19 children stabilized with bosentan: no significant changes were observed in NYHA FC, 6MWD, and weight gain, although 12 patients required combined treatment with epoprostenol. In contrast, in patients with PAH associated with other conditions, significant improvements were reported for NYHA FC (p = 0.001), 6MWD (+128 m, p = 0.002), and weight gain (+17.5%, p = 0.01). At study end, 39 patients (97%) were still treated with bosentan and 1 patient (3%) had died. All 15 patients initially treated with epoprostenol or sildenafil improved with the addition of bosentan. In 1 patient, aspartate aminotransferase activity increased to less than 2 times the ULN. The adverse effects often reported in adults receiving bosentan, including headache, dizziness, cough, dyspnea, and flushing [7], were not observed. None of the 4 patients with Eisenmenger’s syndrome experienced a significant fall in systemic arterial oxygen saturation. The authors conclude that bosentan stabilizes children with IPAH whereas it improves the clinical status of children with PAH associated with other diseases.

From a retrospective study across 2 centers, Rosenzweig et al. [22] report on the long-term effects of bosentan with or without concomitant prostanooid therapy in a cohort of 86 children (mean age at bosentan initiation 11 years) with IPAH, PAH related to congenital heart disease, or PAH associated with connective tissue disease (NYHA FC I-IV). Out of 78 patients with NYHA FC assessments at bosentan initiation and at one follow-up, 36 (46%) improved by at least one NYHA FC (p < 0.001) and 8 patients (10%) worsened by 1 class. The median follow-up of these patients was 12 months. In 49 children who had hemodynamic assessments within a 3 month period preceding bosentan initiation, modest but significant hemodynamic improvements were demonstrated at cardiac catheterization with a median follow-up of 9 months. Mean pulmonary artery pressure and pulmonary vascular resistance decreased (64 ± 3 to 57 ± 3 mmHg, p = 0.005, and 20 ± 2 to 15 ± 2 U·m², p = 0.01, respectively). At the end of the observation period, 68 patients (79%) still received bosentan, 13 (15%) had discontinued, and 5 (6%) had died (median exposure to bosentan 14 months). At 2 years, the survival was 91% (88% for IPAH and 96% for secondary PAH). Asymptomatic increases in liver aminotransferases were reported in 10 patients (12%), leading to discontinuation in 3. The most frequent adverse events were peripheral edema (8%) and systemic hypotension (3%). Two patients (2%) with unrepaired congenital heart disease discontinued bosentan due to systemic arterial oxygen desaturation. Three patients died in the subgroup starting bosentan with concomitant prostanoid therapy: two from hemoptysis and acute respiratory distress syndrome, and 1 from worsening right heart failure. Two patients died from right heart failure in the subgroup starting bosentan without prostanoid therapy. All deaths were considered to be due to the clinical progression of PAH. This study was subsequently extended to a median follow-up of 30 months [23], at which time 25 (29%) patients were continuing bosentan. Five (6%) patients discontinued bosentan due to liver function test abnormalities. Disease had progressed in 53% at 3 years (n = 20 patients at risk). Survival in patients on bosentan at 1, 2, 3 and 4 years was 98% (n = 69 patients at risk), 88% (n = 42), 82% (n = 27) and 82% (n = 16), respectively.

Simpson et al. [24] report on 7 children (mean age 7.4 years) with IPAH treated with bosentan as first line therapy (adding, when necessary, first sildenafil, then epoprostenol). Survival and clinical status in these patients were compared with a group of 12 historical control patients (mean age 6.9 years) who were diagnosed prior to the availability of epoprostenol, bosentan, and sildenafil, and who received only conventional therapy including anticoagulants and calcium channel blockers. The median bosentan treatment duration was 13.6 months (5.2 to 21 months) for monotherapy and 35.6 months (7.7 to 40.7 months) for combination with sildenafil. Freedom from initiation of epoprostenol was 100% at 12 months, 83% at 34 months and 41.7% at 45 months. There were no adverse effects attributed to bosentan or sildenafil, including no increase in hepatic transaminase activity. One patient died of a pulmonary hypertensive crisis 37 months after presentation, during an anesthetic insertion of a central venous catheter for intravenous epoprostenol. Survival in the bosentan-treated group was 100% at 36 months and 75% at 60 months, compared with 33% at both time-points in the historic control group (p = 0.044 by log-rank test). The authors conclude that treatment with bosentan delays IPAH disease progression and, in combination with other therapies, improves survival.

Van Loon et al. [25] describe the effectiveness of bosentan in 30 patients (20 adults, 10 children) with PAH related to congenital heart disease (NYHA FC II-IV) for a median follow-up period of 2.7 years. In the whole group, initial (4 months) improvements in NYHA FC and 6MWD were maintained throughout the first year but were followed by a decline at 2.7 years. The decline in walk distance occurred earlier in children (after 1 year). The persistence of the beneficial effect of bosentan at 1 and 2 years was 78% and 57% in adults, and 50% and 20% in children, respectively. Three deaths occurred during the study at 0.5 month (hemoptysis associated with acute circulatory failure), 8.4 months (progressive right ventricular failure) and 37.2 months (infection of the epoprostenol delivery system). In this study, the worse outcome observed in children could have been caused by a more severe disease at baseline.
Bosentan in Pediatric PAH

In an abstract, Penny et al. [26] report their experience with bosentan in 7 children with IPAH (median age 9.5 years) treated for 8 months. In the majority of children, bosentan was associated with an improvement in symptomatic status (mean NYHA FC decreased from 2.8 to 2.1) and a decrease in pulmonary vascular resistance index (3 out of 4 evaluated patients had a decrease from 18.4 U·m⁻² to 10.1 U·m⁻²). There was no adverse effect and no deterioration of liver function.

Nine Case Reports/Case Series

The treatment of pediatric PAH with bosentan as monotherapy or combined therapy is further documented in 9 single case reports/case series [27–35].

In 2 separate studies, Hsu et al. [27] and Dulac et al. [33] reported on the use of bosentan in two 16 month-old children with IPAH. In both cases, the patient’s parents refused epoprostenol treatment and bosentan was administered at a dosage of 15.6 mg twice daily (Hsu et al. [27] initiated bosentan at a dosage of 15.6 mg once daily in the first month). After 6 months of treatment, improvements were reported for the functional status and quality of life [27, 33], as well as in stabilization of echocardiographic parameters that was maintained after 36 months of therapy [33]. Regular biological exams showed good hepatic and hematological tolerance.

Rugolotto et al. [28] describe the use of bosentan (10 mg bid, doubled 1 month later) and concomitant epoprostenol, followed by the addition of sildenafil, in an 8 month-old infant suffering from severe bronchopulmonary dysplasia and PAH. Four months after treatment initiation, systolic right ventricular pressure measured by echocardiography had decreased from 68% to 40% of the systemic level. The combination therapy was well tolerated. Epoprostenol and subsequently bosentan were discontinued while sildenafil treatment was pursued at a lower dose. The patient subsequently died from septic shock and refractory hypoxia.

Brancaccio et al. [29] and Beghetti et al. [30] report the cases of a 7 year-old and an 8 year-old child, respectively, with severe IPAH treated with combination therapy of epoprostenol, bosentan, and sildenafil [29] or iloprost and bosentan [30]. In the first case [29], functional status improved from class III to class II, which allowed a gradual weaning and discontinuation from prostacyclin. After 4 years of combined treatment, the child had satisfactorily grown in height and weight; the latest echocardiogram showed right atrial and ventricular enlargement with half systemic pressure in the right ventricle; the 6MWD was 430 m and the patient was in NYHA FC I. The combination of bosentan and sildenafil was well tolerated. In the second case [30], after 3 months of combined treatment, the 6MWD had increased from 295 m to 400 m. There was a significant reduction in right ventricular size and normalization in interventricular septal curvature. The patient’s quality of life improved and lung transplantation could be postponed. This case shows that combined bosentan and iloprost therapy can be associated with remarkable improvements in children with PAH.

Das et al. [31] describe 10 children that underwent cardiac catheterization after recovery from high altitude pulmonary edema, and were found to have chronic pulmonary hypertension. In one 9 year-old boy who developed persistent pulmonary hypertension despite calcium channel blockers and moving to a lower altitude, oral bosentan and sildenafil were added to the treatment regimen. After 2 years, the patient had improved exercise tolerance with an estimated systolic pulmonary arterial pressure of 50 mmHg.

Use of bosentan in newborns is reported for the first time by Goissen et al. [32]. These authors describe 2 cases of persistent pulmonary hypertension of the newborn (PPHN) complicating a transposition of the great arteries with intact ventricular septum (TGA/IVS). Both infants had failed to respond to usual management (correction of hypotension, inhaled nitric oxide, epoprostenol infusion) and to oral sildenafil, and they could not have repair surgery. In both cases, PPHN resolved within 3 days after starting bosentan (1 mg/kg bid). The arterial switch surgical procedure could subsequently be performed. No adverse effect was associated with the use of bosentan. This favorable response to treatment suggests a possible role for bosentan in the treatment of newborn infants with PPHN complicating TGA/IVS.

Nemoto et al. [34] report their experience with bosentan in 2 children (aged 5 and 9 months) with sustained pulmonary hypertension in the acute phase after surgical correction of a complete atroventricular septal defect and closure of a ventricular septal defect. As symptoms did not improve following the administration of sildenafil, bosentan (1.5 mg/kg/day) was added. Symptoms of sustained pulmonary hypertension alleviated in both patients and sildenafil was gradually reduced and stopped. When signs of pulmonary hypertension had resolved, bosentan therapy was also stopped after 11 and 22 days. Bosentan caused a transient increase in liver aminotransferase in the 5-month-old child that resolved upon discontinuation.

In a case series, Fraisse et al. [35] describe 3 children (aged 4.5, 8 and 14 years) with end-stage PAH and recurrent syncope treated by atrial septostomy along with combined epoprostenol and bosentan (31.25, 62.5, and 125 mg bid). Within a few weeks, the NYHA FC improved from III to II in all 3 patients. No syncope occurred and the children remained in NYHA FC II during follow-up (6–40 months). This small case series demonstrates that children with end-stage PAH may benefit from atrial septostomy associated with combined epoprostenol - bosentan therapy.

DISCUSSION

In the last decade, therapeutic advances have considerably improved the outcome of patients with various forms of PAH. Despite increasing knowledge regarding treatment of PAH in adult patients, there are limited data describing the response to treatment and survival in children. In general, children with PAH are treated with the clinical strategies used in adults. In current treatment algorithms for adults [48] and children [49], bosentan treatment is considered for NYHA FC III patients with a negative response to acute vasoreactivity testing and for patients who do not have a sustained response to calcium channel blockers (Fig. (1)). Bosentan therapy may also be an oral alternative to prostanooid infusion in severe PAH, especially for patients refusing invasive therapy. In children, the efficacy and safety of
bosentan is supported by a number of prospective and retrospective studies of varied size and design but no controlled trials. Most of these studies are observational and do not follow the methodologic rules associated with randomized controlled trials but they do have inherent strengths [50]: taken together, they provide typical routine care data from a large number of children with PAH (n = 388) who are treated with bosentan therapy for 1 day up to over 12 years. Thus, they provide a fairly extensive ‘real world’ experience on the effectiveness and safety of bosentan. Although bosentan is only commercially available in tablets of 62.5 mg and 125 mg, which can be difficult to administer to children, a pediatric formulation, in the form of a dispersible tablet with an adjustable dosing of 8 to 32 mg, is currently undergoing clinical evaluation in children in Europe and in the USA.

**Effectiveness**

Functional and hemodynamic improvements have been demonstrated in placebo-controlled clinical trials of bosentan in adult patients with PAH [6, 7] but no controlled trials have been performed in children.

In real-world clinical settings, for children with PAH, the change in NYHA FC is often used to measure disease progression. As reported for adults [6, 7], most children treated with bosentan (including the youngest under 6 years of age) improve or stabilize their NYHA FC for treatment durations of up to 2 years [14, 15, 22, 26 and unpublished results]. This benefit is also reported in single cases or case series [27, 29, 35]. The improvements may be more pronounced in PAH related to another condition than in IPAH [21].

The 6MWD is a useful tool to detect changes in exercise tolerance and endurance. However, in clinical trials and clinical practice, exercise capacity measurements are limited by concerns of feasibility and reliability, especially in the very young [14, 51, 52]. In pediatric patients with PAH related to congenital heart disease, van Loon et al. [25] observe an improvement in 6MWD after 4 months but a decline after 1 year. Brun et al. [16] also report a decrease in exercise capacity after 1 year of treatment in children with Eisenmenger’s syndrome who could perform a treadmill test. Maiya et al. [21] find that the improvement at 1 year in 6MWD is significant in patients with PAH related to a secondary condition but not in those with IPAH. Thus, in children, the

![Fig. (1). Pediatric pulmonary arterial hypertension treatment guidelines (a 'Responder' is defined as a patient who has a significant response to acute pulmonary vasodilator testing with a reduction in mean pulmonary artery pressure of at least 20%, with no change or an increase in cardiac output (reproduced with permission from reference [49]).]
long-term benefit of bosentan could not be established via the measurement of exercise capacity, perhaps confounded by methodological issues.

Pulmonary hemodynamic measurements are widely used in randomized controlled trials in adults to evaluate the response to treatment [53] even though they are not always strongly correlated to functional status and exercise capacity [54]. In several pediatric observational studies [14, 15, 22, 26], serial cardiac catheterization or echocardiography was performed and suggested modest but significant hemodynamic improvements after up to 9 months of bosentan treatment.

In 2 separate pediatric studies [21, 22, 55], 97% and 79% patients continued bosentan treatment after a median follow-up of 12.7 and 14 months, respectively, and 29% continued after 30 months [55]. Survival has only been assessed in 1 retrospective study [22] and its longer-term extension [55]; Rosenzweig et al. report high survival rates after 2 years especially for patients with PAH related to congenital heart disease (96%) compared with IPAH (88%). After 4 years, the survival was still 82% [55]. Although most children stabilize or improve with bosentan treatment, some quickly deteriorate [21, 22, 55]. The occurrence of sudden death is not unexpected in this population, since children with PAH are prone to develop syncope resulting in sudden death [18, 21, 24, 56]. However, most deaths are associated with clinical worsening due to PAH progression [22, 24] presenting as a decrease in exercise capacity or the development of right ventricular failure [15].

Safety Profile

The pediatric studies did not reveal any unexpected safety signals beside the known safety profile of bosentan established in the clinical trials in adults [7, 12]. The primary elimination of bosentan is via hepatic metabolism, which could result in hepatocellular injury in some patients, especially in children with an immature hepatic metabolism. However, no safety concern was apparent in children treated according to the dosing recommendation of Barst et al. [14], i.e., for children weighing 10–20 kg, 20–40 kg, and over 40 kg, 31.25 mg once daily, 31.25 mg bid, and 62.5 mg bid for 1 month, then 31.25 bid, 62.5 bid and 125 mg bid, respectively. In most studies, liver function tests remained within normal limits [16, 18, 24, 26, 27, 33]. When hepatic function abnormalities were present, they were transient or resolved following dose reduction [15, 17, 21] or discontinuation (3% of all patients [22 and unpublished results]). These results are in line with the findings from the bosentan post-marketing surveillance program, which shows a lower rate of elevated liver enzymes in children 2–11 years than in patients ≥ 12 years [20, 57].

Other adverse effects previously noted in adult patients receiving bosentan, including headache, dizziness, cough, dyspnea, and flushing [7, 12], are not consistently reported in children [14, 15, 21, 22]. In the largest pediatric study to date, Rosenzweig et al. [22] report peripheral edema (8%), systemic hypotension (3%), and systemic arterial oxygen desaturation leading to discontinuation in patients with unpaired congenital heart disease (2%). On the other hand, in a study including 4 patients with Eisenmenger’s syndrome, none experienced a significant fall in systemic arterial oxygen saturation [21].

Combination Therapy

The combination of drugs with different mechanisms of action and different metabolic pathways is an attractive therapeutic option to address the multiple pathophysiologic mechanisms present in PAH [58] while reducing dosing and side effects. Although only uncontrolled and limited supportive data are available, combination therapy is frequently used in clinical practice [14]. Epoprostenol and sildenafil use was not allowed in the 2 phase III trials of bosentan [6, 7] but in some of the pediatric studies reported here, many patients were already receiving epoprostenol or sildenafil, prior to bosentan initiation [14, 21, 22, 32 and unpublished results]. Two studies report further improvements in functional status and/or hemodynamics following the addition of bosentan [14, 21]. However, in a third study [22], the improvement was less pronounced possibly because the patients receiving epoprostenol at baseline tended to have more severe disease.

The latest international recommendations [59] suggest that combination therapy is an option for adult patients not responding sufficiently to endothelin receptor antagonists or non-parenteral prostanoids. This approach may provide a substantial treatment advantage for children with PAH by delaying the initiation of intravenous epoprostenol. Two small studies document the benefits of adding sildenafil to bosentan: NYHA FC, hemodynamics, exercise capacity [18] and survival [24] improved and the need to commence intravenous epoprostenol was delayed [24]. These studies are limited by their retrospective design without control, a small number of patients, and the comparison of data from different treatment eras. The combination of bosentan and iloprost also led to a dramatic improvement in exercise capacity and echocardiography parameters in a case of severe IPAH [30]. Although these results are promising, long-term prospective studies are required to establish the impact of bosentan combined with other agents on functional status and survival in childhood PAH.

Until recently, continuous i.v. epoprostenol was the only treatment for severe unreactive pulmonary hypertension. It is a very challenging therapy for the family and the child, with painful side effects and serious complications [60]. Therefore, in a number of studies, the epoprostenol dose was decreased after adding less invasive PAH treatments in an attempt to decrease epoprostenol-related side effects. This approach is supported by the work of Ivy et al. [17] who report that, in selected patients, bosentan facilitates the reduction of epoprostenol dosage without adversely affecting hemodynamic parameters. In line with these results, Brancaccio et al. [29] used a combination of bosentan and sildenafil to wean a 7-year-old girl with severe PAH from epoprostenol.

The above studies do not reveal any safety concern related to the use of bosentan in combination with epoprostenol or sildenafil. Combination therapy is generally well tolerated [14, 18, 21–24, 29 and unpublished results]. Pharmacokinetic interaction between bosentan and epoprostenol is unlikely since the drugs have different metabolic and excretory pathways and the pharmacokinetics of bosentan are
not affected by concomitant treatment with epoprostenol [14, 61, 62]. On the other hand, sildenafil inhibits CYP3A4 activity and thus leads to an increase in bosentan plasma concentrations [63]. It is unknown whether this increases the potential of bosentan to cause liver damage but, in the bosentan post-marketing surveillance of about 5000 patients, the combination of bosentan and sildenafil (n = 119) was not associated with an increased rate of aminotransferase elevations [57]. Conversely, bosentan reduces the plasma concentration of sildenafil in patients with PAH [63] and increasing the sildenafil dose might be justified in patients treated with chronic bosentan.

Clearly more data are needed to provide efficacy and safety evidence for future combination treatment strategies. Although current guidelines suggest that combination therapy is a possible option for patients with NYHA FC III PAH who respond poorly to monotherapy, the criteria for instituting combination therapy have not been defined.

CONCLUSIONS
In children, evidence for the effectiveness and safety of bosentan is supported by a number of prospective and retrospective studies of varied sample size and design. This suggests that the results obtained in adult patients may be extrapolated to children, thus offering a well-tolerated and effective therapy that is easy to administer. However, additional long-term prospective studies may be required to establish the impact of bosentan alone, and in combination with other agents, on survival and functional status in pediatric PAH.

ACKNOWLEDGEMENTS
The author thanks Sylvie I. Ertel, PhD, who provided medical writing services on behalf of Actelion Pharmaceuticals Ltd.

CONFLICT OF INTEREST
Maurice Beghetti is a consultant, advisory board member, and investigator for Actelion, advisory board member for Mondo Biotech, Pfizer, Encysive, GlaxoSmithKline, EliLilly and Bayer Schering, he has received consultant grant from INO Therapeutics.

ABBREVIATION
6MWD = 6-Minute walk distance
bid = Twice daily
CCB = Calcium channel blocker
ERA = Endothelin receptor antagonist
FC = Functional class
iNO = Inhaled nitric oxide
IPAH = Idiopathic pulmonary arterial hypertension
i.v. = Intravenous
NYHA = New York Heart Association
PAH = Pulmonary arterial hypertension
PDE-5 = Phosphodiesterase type 5
PGI2 = Prostacyclin
PPHN = Persistent pulmonary hypertension of the newborn
TGA/IVS = Transposition of the great arteries with intact ventricular septum
ULN = Upper limit of normal

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Bosentan in Pediatric PAH  

Current Vascular Pharmacology, 2009; Vol. 7, No. 2 9


