The heart in Down syndrome
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Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down’s syndrome

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ABSTRACT

Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) due to systemic-to-pulmonary shunting is associated with a high risk of morbidity and mortality. In this retrospective study, we evaluated longer-term treatment effect of bosentan on exercise capacity and quality of life in 58 adult patients (>18 years) with PAH associated with CHD, including patients with Down syndrome. All patients were evaluated at baseline and during follow-up with laboratory tests, 6-minute walk test, quality of life questionnaires, and Doppler echocardiography. We analyzed treatment efficacy separately within patients without (n=30) and patients with Down syndrome (n=28). Median follow-up of all patients treated with bosentan was 22 months (range 3-36 months). In patients without Down syndrome, mean 6-minute walk distance (6-MWD) increased from 427 ± 97 m to 461 ± 104 m (p<0.01) after 6 months of treatment, followed by a gradual return to baseline and disease stabilization. Quality of life improved significantly during treatment and maintained during 18 months follow-up (p<0.05). In the patients with Down syndrome, 6-MWD and quality of life remained stable during treatment. In conclusion, our findings suggest that in patients without Down syndrome longer-term bosentan treatment resulted in a persistent improvement of quality of life and a stabilization of exercise capacity.
INTRODUCTION

Until recently, treatment options for patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) were limited to the avoidance and treatment of complications. A major breakthrough in the treatment of patients with PAH has been the introduction of oral endothelin receptor antagonists. Short-term treatment with bosentan has shown to improve morbidity of patients with PAH, including those with Eisenmenger syndrome. However, results on longer-term treatment response are equivocal and data on quality of life (QoL) is limited despite the importance of QoL assessment. Although several studies reported a persistent beneficial effect of bosentan on exercise capacity, other studies reported a gradual decline of exercise capacity to baseline values after 2 years of bosentan treatment. In patients with Down syndrome, the treatment effect of bosentan is largely unknown. The aim of our study was to evaluate the short- and longer-term treatment effect of bosentan in adult patients with PAH associated with CHD with and without the Down syndrome, by assessing exercise capacity and QoL.

METHODS

The study population consisted of adult patients with PAH associated with CHD, including patients with Eisenmenger syndrome. Patients were divided into 2 groups: patients without Down syndrome (the “non-Down” patients) and patients with Down syndrome. Enrolled patients were diagnosed with any of the following congenital heart defects: univentricular heart, patent ductus arteriosus and septal defects such as ventricular septal defect, atrial septal defect, or atrioventricular septal defect. Patients with persistent PAH after previous closure of their CHD were also enrolled. Patients with obstruction of the right ventricular outflow tract, pulmonary valve or pulmonary arteries or patients on prostacyclin, glibenclamide or cyclosporine treatments were excluded.

We performed a retrospective study. After baseline examinations, adult patients with PAH associated with CHD were treated with bosentan according to a standardized treatment protocol (as described in more detail below). At baseline, patients’ clinical and functional status were evaluated using laboratory tests (including haemoglobin, creatinine, uric acid and NT-pro-BNP levels), 6-minute walk
distance (6-MWD), QoL questionnaires, and Doppler echocardiography. To exclude other causes of PAH, lung function tests (spirometry, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC)) were obtained. Additionally, in non-Down patients, maximal exercise capacity (peak VO2)\textsuperscript{15} and Cardiovascular Magnetic Resonance Imaging were performed at baseline and during follow-up.

Submaximal exercise capacity was assessed using the 6-MWD, according to the guidelines of the American Thoracic Society with continuous pulse oximetry monitoring.\textsuperscript{16} To exclude the effect of a learning curve, the 6-MWD at baseline was performed twice, using the second test as baseline value. The 6-MWD was used as primary endpoint and the test was repeated every 3 months during bosentan treatment.

QoL was evaluated by means of the SF-36\textsuperscript{5} and by means of the Minnesota Living with Pulmonary Hypertension Questionnaire. The SF-36 is a well-documented, widely used and validated, self-administered QoL scoring system incorporating 36 questions. It includes 8 independent scales (scored as a number between 0 and 100) that assess the following general health concepts: physical functioning, limitations because of physical health problems (role physical), bodily pain, general health perceptions, vitality, social functioning, limitations because of emotional problems (role emotional), and mental health.\textsuperscript{5} The Minnesota Living with Pulmonary Hypertension Questionnaire rates patients’ perceptions of how much their disease affects the physical, socio-economic, and psychological aspects of daily life. Scores on the total questionnaire range from 0 to 105, with higher scores reflecting a worse perceived QoL. Both QoL questionnaires were filled in by the patient or, in case of Down syndrome, by the parent or guardian of the patient, at baseline and with regular intervals of 6 months during follow-up.

Doppler echocardiography (VIVID 7 General Electric, USA) was performed to define the heart defect and confirm the Eisenmenger syndrome, which was defined as a right-to-left shunt through the defect. Moreover, we evaluated left and right ventricular function during bosentan treatment every 6 months in both patient groups. Right ventricular function was measured by tricuspid annular plane systolic excursion and the systolic pulmonary arterial pressure was estimated by the peak velocity of the tricuspid regurgitation jet using continuous-wave Doppler.\textsuperscript{17} Tricuspid annular peak systolic velocity (TDS)\textsuperscript{18}, TEI-index and contraction duration of the right ventricle were assessed using tissue Doppler imaging. Right ventricular contraction
duration, corrected for heart rate, was measured from the onset of the QRS complex to the onset of early diastolic filling of the right ventricle (E).19 All echocardiographic images were acquired and recorded digitally, and analyzed offline by a single observer (HdB).

Additionally, in non-Down patients, Cardiovascular Magnetic Resonance Imaging was used to assess ventricular volumes, ejection fraction, and stroke volume of both ventricles. At baseline and after 1 or 2 years follow-up, end-diastolic and end-systolic volumes of both ventricles were calculated by the sums of the traced contours in end-diastole and end-systole. End-diastolic volume and end-systolic volume were used to calculate stroke volume and ejection fraction.

After performing baseline evaluation, oral bosentan was administered at an initial dose of 62.5 mg twice daily. Four weeks after treatment initiation, the initial dose was increased to the target dose of 125 mg twice daily. Liver function, serum haemoglobin levels, and serum haematocrit levels were tested monthly to screen for adverse effects.

Descriptive data are presented as mean with standard deviation if normally distributed or as median with range, as appropriate. Changes from baseline to each of the follow-up visits were assessed by paired student t tests. Data for the SF-36 and Minnesota Living with Heart Failure Questionnaire were summarized by mean change from baseline to each time-point for the patients observed. A value of p<0.05 was considered to be significant.

RESULTS

Between January 2005 and June 2008, 58 adult patients with PAH associated with CHD started oral bosentan treatment. The median follow-up duration was 22 months (range 3 to 36 months). Forty-eight percent (n=28) of enrolled patients had Down syndrome. Table 1 summarizes patients’ baseline characteristics. Of the 6 non-Down patients without Eisenmenger syndrome, 3 patients had persistent PAH after previous closure of their CHD, 2 patients had refused operation and in 1 patient operative risk was deemed too high due to co-morbidity.
Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Total (n=58)</th>
<th>Non Down (n=30)</th>
<th>Down syndrome (n=28)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range, yrs)</td>
<td>42 (20-75)</td>
<td>47 (20-75)</td>
<td>38 (20-75)</td>
<td>0.050</td>
</tr>
<tr>
<td>Gender, male</td>
<td>29 (50%)</td>
<td>10 (33%)</td>
<td>19 (68%)</td>
<td></td>
</tr>
<tr>
<td>Eisenmenger syndrome</td>
<td>49 (86%)</td>
<td>24 (80%)</td>
<td>25 (100%)</td>
<td></td>
</tr>
<tr>
<td>Median Follow up (months)</td>
<td>20 (3-36)</td>
<td>22 (3-36)</td>
<td>18 (3-36)</td>
<td>0.9</td>
</tr>
<tr>
<td>Follow up &gt; 6 months</td>
<td>53 (91%)</td>
<td>27 (85%)</td>
<td>26 (92%)</td>
<td></td>
</tr>
<tr>
<td>Underlying congenital heart defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect primum</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect secundum</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect sinus venosus</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect (= patient ductus arteriosus)</td>
<td>21 (41%)</td>
<td>14 (47%)</td>
<td>7 (25%)</td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>3 (6%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Univentricular Heart</td>
<td>4 (8%)</td>
<td>4 (13%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Atrioventricular septal defect (= patient ductus arteriosus)</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Transposition of the great arteries</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>85 (6%)</td>
<td>86 (6%)</td>
<td>84 (6%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Six-minute walk distance at baseline (m)</td>
<td>371 (115)</td>
<td>427 (97)</td>
<td>308 (102)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3 (5%)</td>
<td>3 (10%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>55 (95%)</td>
<td>27 (90%)</td>
<td>28 (100%)</td>
<td></td>
</tr>
<tr>
<td>Systolic pulmonary arterial pressure (mmHg)</td>
<td>88 (17)</td>
<td>83 (22)</td>
<td>92 (11)</td>
<td>0.2</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>75 ± 28</td>
<td>75 ± 28</td>
<td>66 ± 30</td>
<td>0.6</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5 ± 2</td>
<td>6 ± 2</td>
<td>5 ± 3</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean NT-pro-BNP (ng/L)</td>
<td>904 ± 1335</td>
<td>1036 ± 1634</td>
<td>791 ± 874</td>
<td>0.5</td>
</tr>
<tr>
<td>Creatinine (mmol/L)</td>
<td>81 ± 22</td>
<td>72 ± 16</td>
<td>94 ± 32</td>
<td>0.004</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Haemoglobin (mmol/L)</td>
<td>13 ± 2</td>
<td>11 ± 2</td>
<td>13 ± 2</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Induction of oral bosentan therapy was well tolerated in both patient groups, without signs of decreasing oxygen saturation. During follow-up, 2 patients died. One non-Down patient died suddenly 4 months after treatment initiation, probably due to cardiac arrhythmia and 1 patient with Down syndrome died from a brain abscess when 14 months bosentan treatment. One non-Down patient experienced severe throat pain and in 1 non-Down patient an asymptomatic increase in liver transaminases (>3 times upper limit of normal) was observed. Both resolved within 2 weeks after dose reduction, whereupon the 125 mg twice daily dose was resumed without reoccurrence of the problems.

The individual changes in 6-MWD in non-Down patients are shown in figure 1a. In the whole group of non-Down patients, the 6-MWD increased significantly from 427 ± 97 m at baseline to 461 ± 104 m (p<0.01) after 6 months of bosentan treatment. After this initial improvement, however, 6-MWD gradually returned to baseline values in the following 6 months (p=0.1). After this first year of treatment, 6-MWD appeared to remain stable for the following 12 months (p=0.4). Subgroup analysis revealed that treatment effect persisted after 2 years in the Eisenmenger population (n=24), compared to the non-Eisenmenger population (n=6), while mean baseline 6-MWD was similar in patients with and without Eisenmenger syndrome. In the Eisenmenger patients, after 1 and 2 years of bosentan treatment, 6-MWD
improved with a mean of respectively 19 ± 41 m (p=0.06) and 24 ± 35 m (p=0.07), respectively, compared to baseline.

Figure 1a. Six-minute walk test in non-Down patients with PAH associated with CHD at baseline and during follow-up. After the first year of treatment, 6-minute walk distance stabilized.

In addition to the 6-MWD, 11 non-Down patients performed a maximal exercise capacity test (peak VO2) at baseline and after 1 year bosentan treatment. Maximal exercise capacity test remained unchanged (15 ± 5 ml/min/kg to 17 ± 5 ml/min/kg; p=0.2) after 1 year follow-up compared to baseline.

Figure 1b depicts the individual 6-MWD of patients with Down syndrome during treatment. In these patients, exercise capacity remained unchanged during bosentan treatment.
Figure 1b. Six-minute walk test in patients with Down syndrome with PAH associated with CHD at baseline and during follow-up. During treatment with bosentan, exercise capacity remained unchanged compared to baseline.

Thirteen non-Down patients and 14 patients with the Down syndrome completed the SF-36 and the Minnesota Living with Pulmonary Hypertension Questionnaire. In non-Down patients, QoL improved significantly in 2 of the 8 scales assessed by the SF-36, as shown in figure 2a and b. Daily life limitations caused by physical health problems (role physical) improved significantly compared to baseline and the improvement seemed to persist during longer-term follow-up (figure 2a). In addition, vitality improved significantly after 6 months and the improvement remained until 18 months of bosentan treatment (figure 2b). In patients with Down syndrome, all 8 scales of the SF-36 remained stable. The mean Minnesota Living with Pulmonary Hypertension Questionnaire scores remained unchanged in both patient groups (33, range 6-67 and 38, range 0-67, p=0.7).
Figure 2a and b. Quality of life scores of the two SF-36 areas: role physical and vitality during treatment with bosentan in both non-Down patients and patients with Down syndrome. Data shown represent the mean score of the SF-36 quality of life questionnaire.

Echocardiographic parameters at baseline and during treatment are shown in table 2. In general, most echocardiographic parameters remained unchanged in both groups of patients during follow-up. However, analyses of the left ventricle in non-Down patients showed that stroke volume tended to increase after 1 year bosentan treatment. Analyses of the right ventricle demonstrated an average decrease in right ventricular contraction duration after 1 year bosentan treatment in those non-Down patients whose 6-MWD improved compared to baseline (n=11). In patients with Down syndrome, 1 year treatment resulted in a significant increase in tricuspid annular peak systolic velocity (TDS).
In 9 non-Down patients we performed Cardiovascular Magnetic Resonance Imaging at baseline and after a mean follow-up of 21 ± 8 months. Of these patients, 3 patients had a previously closed CHD with persistent PAH, 1 patient had a patent ductus arteriosus and 5 patients had a ventricular septal defect. On average, exercise capacity remained stable in these patients during 6 and 12 months follow-up. Both mean end diastolic volume, and end systolic volume, as well as mean stroke volume and mean ejection fraction of the left and right ventricle remained stable during bosentan treatment, as shown in table 3.
NT-pro-BNP levels remained unchanged during bosentan treatment (table 2) in both patient groups. As did haemoglobin, creatinine and uric acid levels. No associations could be found between changes in 6-MWD during bosentan treatment and mean NT-pro-BNP at baseline or NT-pro-BNP changes. In addition, no relations were found between changes in 6-MWD and haemoglobin, creatinine or uric acid levels.

**DISCUSSION**

This is the first study reporting on the effect of almost 2 years of bosentan treatment on exercise capacity and QoL in adult patients with PAH associated with CHD, including patients with the Down syndrome. In non-Down patients, we demonstrated a significant increase in exercise capacity after the first 6 months of treatment and an improvement in QoL. After the initial improvement, mean exercise tolerance declined to baseline values and finally stabilized during longer term follow-up. Improvement of QoL persisted throughout the follow-up period. In contrast, exercise tolerance and QoL remained unchanged in patients with the Down syndrome during treatment. Overall, we found no changes in cardiac function as determined by echocardiography, cardiovascular magnetic resonance and serum NT-pro-BNP levels in both groups during treatment.

The observed treatment effect of bosentan on exercise capacity in non-Down patients compares well with the observations of Apostolopoulou et al., who reported a decline in 6-MWD to baseline values in patients with PAH associated with CHD after 2 years of therapy. Additionally, van Loon et al. demonstrated similar findings in both adults and children with PAH associated with CHD at long-term follow-up. The decline in 6-MWD during treatment might be due to the development of tolerance for bosentan, as previously observed in some patients receiving epoprostenol. On the other hand, natural disease progression may also play a role. The Breathe-V study, a placebo-controlled randomized trial on 54 patients with Eisenmenger syndrome, showed a steady decrease in exercise capacity in patients with PAH associated with CHD when treated with placebo for 4 months. As a consequence, stabilization of exercise capacity can be considered an important gain in the treatment of PAH, also in patients with PAH associated with CHD.

Additionally, we demonstrated that stabilization of exercise capacity was accompanied by a statistically significant and sustained improvement of QoL. The 8
domains of the SF-36 were evaluated separately. Although some QoL domains remained stable during treatment, others improved significantly. Role physical increased significantly during bosentan treatment, indicating that patients experienced less problems at work and during daily activities after 18 months of treatment. Vitality improved as well during follow-up, indicating an increased sensation of energy. In accordance with our results, Keogh et al showed similar results in patients with idiopathic PAH or PAH associated with connective tissue diseases during bosentan treatment. In patients with PAH, health related QoL is significantly impaired and the evaluation of QoL is of great importance. Moreover, from the patients’ perspective, QoL is one of the most important measures of treatment effect. Therefore, it is important to assess QoL as a major outcome parameter of treatment effect in patients with PAH.

We also evaluated treatment effect in patients with Down syndrome. Little is known about the benefit of bosentan in patients with Down syndrome and PAH associated with CHD, while PAH is particularly common in these patients. In a previous small study, we reported a short-term increase in 6-MWD during bosentan treatment. Presently, in our larger population, this short-term improvement could not be confirmed. This could be due to the disputable validity of the 6-MWD in patients with Down syndrome, who have reduced mental capacity. Nonetheless, we chose to evaluate 6-MWD in these patients, as a more validated test to evaluate exercise capacity is presently lacking. Similarly, QoL questionnaires have not been properly validated in patients with Down syndrome, making their use for the evaluation of treatment effect questionable. To increase their validity, QoL questionnaires were filled in by the patients’ parents or guardians. In accordance with the 6-MWD, QoL scores remained unchanged during treatment, as did NT-pro-BNP levels. The present study is limited by the lack of a placebo group and the heterogeneity of underlying diagnoses e.g. patients with and without the Down syndrome, patients with and without Eisenmenger syndrome, patients with and without closed defects and the variety of defects. Moreover, the 6-MWD is frequently used to evaluate treatment effect in PAH patients although the validity of this endpoint to reflect treatment effect is questionable. Other end points should be validated for the adequate evaluation of treatment effect. In the absence of an ideal endpoint, data on QoL, imaging of the right ventricle and the pulmonary vessels, and chemical markers of PAH should be used in parallel and compared with the 6-MWD.
in patients with and without Down syndrome. Therefore, definite conclusions on long-term treatment effects of bosentan cannot yet be made. In conclusion, our findings suggest that in patients without the Down syndrome longer-term bosentan treatment resulted in a persistent improvement of QoL and a stabilization of exercise capacity.

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