Down patients with Eisenmenger syndrome: Is bosentan treatment an option?

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Abstract

Background: Favorable results of treatment with bosentan in patients with Eisenmenger syndrome are available. However, data in Down patients are lacking. In this study, we evaluate the therapeutic role of bosentan treatment in Down patients with Eisenmenger syndrome.
Methods: In this open-label study, 24 Down patients (>18 years) with Eisenmenger syndrome (17 males) were treated with bosentan. Their mean age was 38 years (range 19–55 years). All Down patients were evaluated at baseline and during follow-up with laboratory tests, six-minute walk test (6-MWT), Doppler echocardiography, and quality of life questionnaires.
Results: The median follow-up of Down patients treated with bosentan was 11.5 months (range 3–23 months). Induction of oral bosentan therapy was well tolerated among all 24 Down patients. Bosentan treatment was generally well tolerated. No serious adverse drug reactions were noted. Median 6-MWT increased from 296 m (range 40–424 m) to 325 m (range 84–459 m, $p < 0.05$) after 12 weeks. After 26 and 52 weeks of treatment with bosentan, median 6-MWT distance was 276 m (range 140–462 m, $n = 15$, $p = 0.6$) and 287 m (range 131–409 m, $n = 7$, $p = 0.3$), respectively. Quality of life questionnaire scores remained stable during treatment.
Conclusion: Also patients with Down syndrome may benefit from bosentan treatment when they have Eisenmenger syndrome. Medical treatment appears to be safe and the treatment effects do not deviate from those observed in Eisenmenger patients without Down syndrome.
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Keywords: Down syndrome; Congenital heart disease; Eisenmenger syndrome; Pulmonary arterial hypertension; Bosentan treatment

1. Introduction

Trisomy 21 is the most common single chromosome abnormality at birth, occurring in about 1 in 800 births [1,2]. The frequency of congenital heart disease in patients with Down's syndrome is very high with a prevalence between 40% and 60% [3,4]. Atrioventricular septal defect is the most common congenital heart disease among patients with Down's syndrome followed by ventricular septal defect [4]. In the context of congenital heart disease, pulmonary arterial hypertension (PAH) may develop as a consequence of a systemic-to-pulmonary shunt. Increased pulmonary vascular resistance may ultimately lead to a reversal of the systemic-to-pulmonary shunt leading to cyanosis, the so called Eisenmenger syndrome. In patients with Down's syndrome, PAH has been suggested to develop earlier and to have a more violent course [5,6].

Eisenmenger syndrome carries a high risk of morbidity in a relatively young patient population and has limited therapeutic options [7,8]. Once the Eisenmenger syndrome

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has occurred, repair of the underlying defect is contra-indicated. The right ventricle will be unable to cope with the progressively increased afterload due to the high pulmonary vascular resistance and will fail [9]. Dyspnoea, arrhythmia and premature death are common features of PAH [10,11]. Exercise tolerance and quality of life in patients with PAH related to congenital heart disease has been shown to be low [12,13].

New medical treatment strategies, such as prostacyclin, endothelin receptor antagonists (bosentan) and phosphodies-terase-5-inhibitors have substantially improved the clinical status and life expectancy of patients with PAH [14–17]. The BREATHE-V study showed that bosentan is safe and well tolerated in patients with Eisenmenger syndrome without any worsening of pulmonary-to-systemic shunting [18]. However, in Down patients with Eisenmenger syndrome, the therapeutic role of bosentan is not known, as patients with Down syndrome were generally not included in these studies. It is important to establish the applicability of bosentan in this group specifically, as Down patients born in the seventies frequently have uncorrected congenital heart disease.

The aim of this study was to evaluate the safety and tolerability of oral bosentan therapy in Down patients with Eisenmenger syndrome by assessing its effects on clinical status and functional capacity.

2. Methods

2.1. Patients

In January 2005, the Interuniversity Cardiology Institute of the Netherlands (ICIN) initiated a treatment protocol for adult patients with PAH associated with congenital heart disease, including patients with Down's syndrome. The diagnosis Eisenmenger syndrome was based on clinical findings and echocardiographic features. Patients could have any of the following congenital heart disease: univentricular heart, patent ductus arteriosus and septal defects such as ventricular septal defect, atrial septal defect, or atrioventricular septal defect. Patients with obstruction of the right ventricular outflow tract, pulmonary valve or pulmonary arteries or patients receiving prostacyclin, glibenclamide or cyclosporin treatments were excluded from the protocol.

2.2. Study protocol

This was an uncontrolled open-label study. All Down patients were evaluated at baseline, WHO functional class, laboratory tests, six-minute walk test (6-MWT), Doppler echocardiography, and quality of life questionnaires were assessed. The 6-MWT, commonly used as measure for treatment effect in PAH, was performed according to the guidelines of the American Thoracic Society with continuous pulse oximetry monitoring [19]. The 6-MWT is easy to administer, well tolerated and reflects activities of daily living [20]. In this study, in analogy with paediatric PAH patients, we selected Down patients who were capable of performing an adequate and reproducible 6-MWT. To consider the effect of a learning-curve, the 6-MWT at baseline was performed twice, the second 6-MWT was used as baseline value. Doppler echocardiography was used to establish the Eisenmenger syndrome and to estimate the systolic right ventricular and pulmonary arterial pressure (sPAP) by means of the tricuspid regurgitation jet velocity. Quality of life was assessed by means of the Minnesota Living with Heart Failure Questionnaire and by means of the SF-36 [21]. The Minnesota Living with Heart Failure Questionnaire rates patients' perceptions of how much their disease affects the physical, socio-economic, and psychological aspects of daily life. For the present study, the term "heart failure" was replaced by "pulmonary arterial hypertension" as reported in other studies [22,23]. The SF-36 is a generic multi-item questionnaire comprising 36 questions addressing 8 areas representing physical functioning, role functioning physical, bodily pain, general health perceptions, vitality, social functioning, role functioning emotional, and mental health. Both quality of life questionnaires were filled in by the parents or guardians of the patient.

After performing baseline evaluation, oral bosentan was administered at an initial dose of 62.5 mg twice daily. Four weeks later, after measurement of oxygen saturation and liver function tests, bosentan was increased to a maximum dose of 125 mg twice daily, if well tolerated. At 12 weeks of treatment 6-MWT, and at 26 and 52 weeks 6-MWT and Doppler echocardiography were repeated.

Safety was evaluated at 12, 26 and 52 weeks of treatment by monitoring adverse events such as flushing and nasal congestion, vital signs, pulse oximetry, and premature treatment discontinuations. Resting systemic arterial oxygen saturation was measured transcutaneously by non-invasive finger pulse oximetry after 5 min of absolute rest in the sitting position. Liver function tests and haemoglobin levels were checked every two weeks during the first two months and monthly thereafter. According to the bosentan summary of product characteristics, the standard threshold for liver function abnormality of >3 times the upper limit of normal was applied.

2.3. Statistical analysis

The descriptive data are presented as median with range. Changes from baseline to 12, 24, 52 and 76 weeks were evaluated with a paired t test for continuous variables (and with Wilcoxon's rank sum test for categorical variables). A value of $p < 0.05$ was considered to be significant.

3. Results

3.1. Patients

Between January 2005 and May 2007, 28 Down patients with Eisenmenger syndrome, were enrolled in the standardised treatment protocol. All patients were able to perform an

Table 1
Baseline characteristics of Down patients with Eisenmenger syndrome
($n=24$).

Mean age (years)	38 (19–55)
Men, n (%)	17 (71)
Underlying diagnosis, (n)	
– Ventricular septal defect	7
– Ventricular septal defect, patent ductus arteriosus	2
– Atrioventricular septal defect	14
– Atrioventricular septal defect, patent ductus arteriosus	1
Median pulmonary arterial pressure (mmHg)	89 (76–110)
Median oxygen saturation (%)	84 (63–94)
Median six minute walk distance (m)	296 (40–424)
Median NT-pro-BNP (ng/L)	339 (35–4414)

adequate and reproducible 6-MWT. None of these patients had undergone previous repair of their congenital heart defect.

Subsequently, 24 Down patients, 17 (71%) males and 7 (29%) females, aged 19–55 years (mean 38 years), started bosentan treatment. Four patients were excluded from the standardized treatment protocol. One patient could not swallow the tablet, in one patient hypothyroidism was diagnosed at the time of initiation of bosentan and in two patients, the health insurance company refused to reimburse the medication. These four patients were not considered in the analysis.

3.2. Baseline characteristics

Table 1 summarizes the patients' baseline characteristics. Fifteen patients had an atrioventricular septal defect of whom one patient had a concurrent patent ductus arteriosus, nine patients had a ventricular septal defect of whom two patients had a concurrent patent ductus arteriosus. All patients experienced dyspnea, impairment of exercise tolerance, and were in functional class III or IV as assessed by the WHO

functional class. All patients were cyanotic with a median transcutaneous oxygen saturation of 84% (63–94%) at rest. Baseline median systolic pulmonary arterial pressure (sPAP) was 89 mmHg (range 76–110 mmHg). Baseline median 6-MWT was 296 m (40–424 m).

3.3. Safety and tolerability

All 24 Down patients tolerated induction of oral bosentan therapy without any signs of decreased oxygen saturation. Median transcutaneous oxygen saturation remained virtually unchanged compared to baseline (84%, range 63–94%, $n=24$) after 12, 26 and 52 weeks of bosentan treatment (84%, range 67–92%, $n=22$; 81%, range 73–92%, $n=15$ and 85%, range 75–87%, $n=7$, respectively). Patients started bosentan 125 mg twice daily after receiving bosentan 62.5 mg twice daily for four weeks. Bosentan treatment was generally well tolerated. No serious adverse drug reactions were noted. No liver function abnormalities ($>3 \cdot$ upper limit of normal) were observed. Flushing was reported occasionally but resolved within two weeks without regimen changes. Headache was reported once and resolved within two weeks after dose reduction; whereupon the 125 mg twice daily dose was resumed without reoccurrence of the problems. No patient required additional therapy because of progression of disease. One patient died of a brain abscess after 14 months of treatment.

3.4. Treatment effect

The median follow-up of Down patients treated with bosentan was 11.5 months (range 3–23 months). Fig. 1 depicts the changes in 6-MWT of all 24 patients during bosentan treatment. During the first 12 weeks, 17 of 24 (71%) patients showed an increase of 6-MWT. Median 6-MWT increased
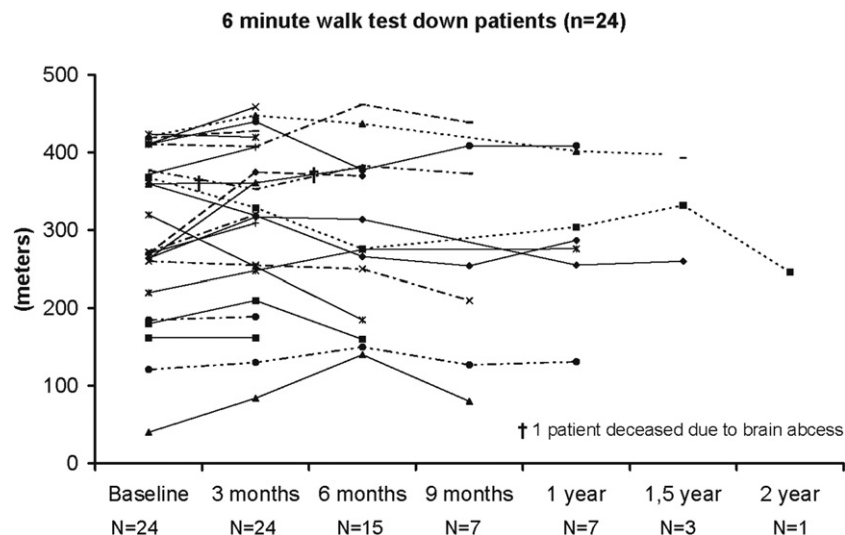

Fig. 1. Six-minute walk test in individual Down patients with Eisenmenger syndrome ($n=24$) during treatment with a median follow-up of 11.5 months (range 3–23 months). †: 1 patient deceased due to a brain abscess.
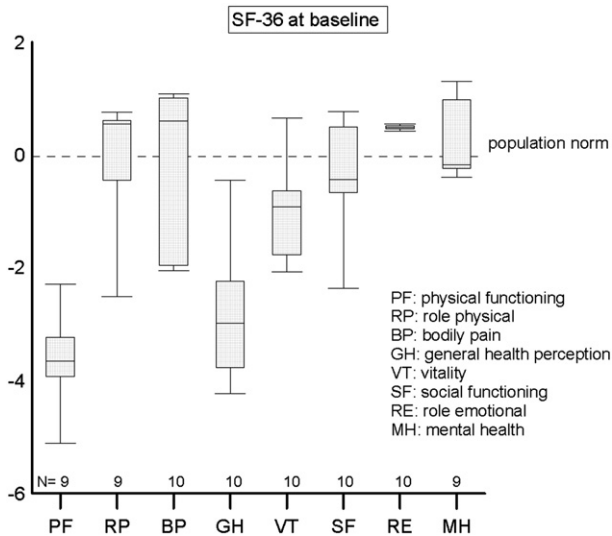
Fig. 2. Down patients with Eisenmenger syndrome show a significantly worse quality of life for the areas: physical functioning, general health and vitality of the SF-36 (all<p<0.05) compared to the general population (population norm). Data shown represent the percentage impairment of the SF-36 quality of life questionnaire.

from 296 m (range 40–424 m, n=24) at baseline to 325 m (range 84–459 m, n=24, p<0.05) after 12 weeks. After 26 and 52 weeks of treatment with bosentan, median 6-MWT distance was 276 m (range 140–462 m, n=15, p=0.6) and 287 m (range 131–409 m, n=7, p=0.3). After 1 year, 2 of 7 (29%) patients still showed an increased 6-MWT compared to baseline. Median NT-pro-BNP remained stable (339 ng/L, range 35–4414 ng/L, n=23) after 12, 26 and 52 weeks of bosentan treatment (respectively 415 ng/L, range 43–5714 ng/L, n=18; 670 ng/L, range 50–3148 ng/L, n=12 and 276 ng/L, range 28–728 ng/L, n=7).

3.5. Quality of life

Ten patients completed the SF-36 and the Minnesota Living with PAH questionnaire at baseline and 7 patients after 1 year of follow-up. Down patients with Eisenmenger syndrome had a significantly worse quality of life compared to the general Dutch population in 3 of the 8 areas assessed by the SF-36: physical functioning, general health and vitality (all p<0.05) (Fig. 2). The only area of quality of life in which patients with Down syndrome and Eisenmenger syndrome did have better outcome than the general population was role limitations caused by emotional problems (p<0.01). In Fig. 3, the follow-up of 3 areas: physical functioning, general health and vitality of the SF-36 are shown. Quality of life of these 3 areas remained stable during treatment.

In Fig. 4 the median total Minnesota Living with PAH Questionnaire is shown. The response of therapy on quality of life could be evaluated in 7 patients after 1 year follow-up. Scores on the total questionnaire range from 0 to 105, with higher scores reflecting a worse perceived quality of life. As shown in this figure, the mean Minnesota Living with
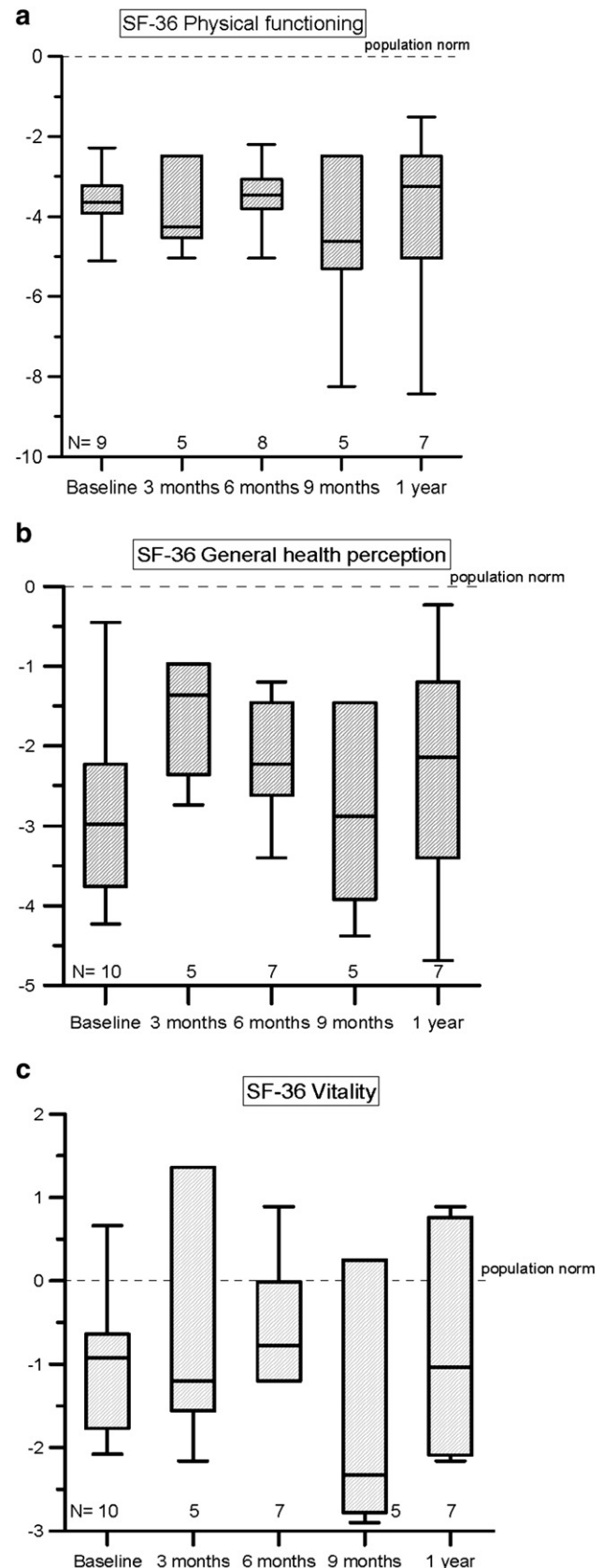

Fig. 3. a, b and c show the follow-up of the three SF-36 areas: physical functioning, general health and vitality during bosentan treatment. Data shown represent the percentage impairment of the SF-36 quality of life questionnaire.
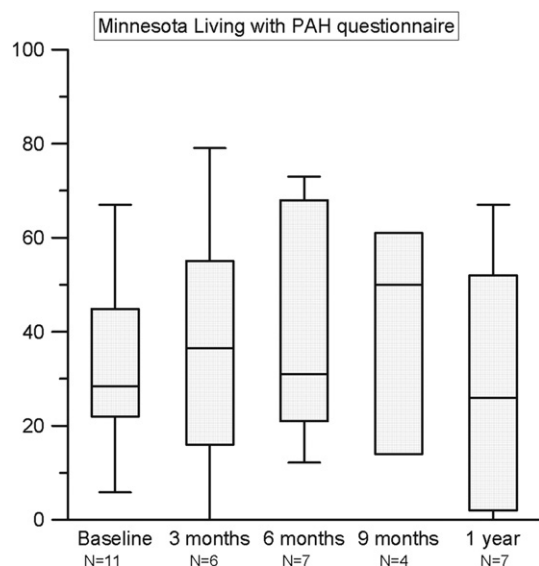
Fig. 4. Shows the median total Minnesota Living with pulmonary arterial hypertension questionnaire. Scores on the total questionnaire range from 0 to 105, with higher scores reflect a worse perceived quality of life. The Minnesota Living questionnaire scores remained stable during treatment.

PAH Questionnaire scores remained stable during treatment (28, range 6–67 and 26, range 0–67, $p = 0.7$).

4. Discussion

To our knowledge, this is the first study on the effect of bosentan in Down patients with Eisenmenger syndrome. Therapy with bosentan proved to be safe and well tolerated. Our results suggest that exercise tolerance improved during the first 3 months of bosentan treatment, after which 6-MWT slowly returned to baseline value.

Congenital heart defects in Down patients born in the seventies, often remained surgically uncorrected. Therefore, Eisenmenger syndrome is more common among these patients compared to non-Down patients with congenital heart disease. To prevent the exclusion of Down patients from evolving treatment, it is important to establish the applicability of new medical therapy in this group specifically. In non-Down patients, the 6-MWT is a generally accepted outcome parameter to assess the treatment effect in PAH. Its value in Down patients has not been validated and its applicability in this group is questionable due to a lack of understanding or cooperation. However, it can reliably be used in paediatric patients from seven years of age [24]. Therefore, we selected Down patients who were capable of performing an adequate and reproducible 6-MWT. In order to correct for a learning curve, the second of two baseline tests was used.

Similarly, quality of life questionnaires have not been validated in Down patients. In order to collect as much information as possible on the effect of bosentan treatment, we evaluated quality of life questionnaires recruited from the parents or guardians.

Therefore, outcome data were available from the 6-MWT and quality of life questionnaires. In spite of their shortcomings, we used the 6-MWT and quality of life questionnaires as outcome parameters in Down patients with Eisenmenger syndrome.

Our results showed that bosentan administration was safe and well tolerated in Down patients with Eisenmenger syndrome without increasing cyanosis or serious side effects. No patient required additional therapy for PAH. The general safety observations in this subgroup of patients with Down syndrome were in accordance with the recent studies with bosentan in non-Down patients with Eisenmenger syndrome [14–18,25].

Exercise tolerance assessed by the 6-MWT improved during the first 3 months of bosentan treatment. The magnitude of the observed positive treatment effect during the first 3 months in our study compared well with the observations on the 6-MWT in the other studies among patients with Eisenmenger syndrome without Down syndrome [14,15,17,18]. After this initial improvement, the 6-MWT appeared to return slowly to baseline. This is consistent with other studies on longer-term follow-up [16]. Although patient numbers at 1 year follow-up in our study were low, the treatment effects do not deviate from those observed in Eisenmenger patients without Down syndrome.

4.1. Study limitations

Limitations of this study include the lack of a placebo group and the relatively small sample size. However, our observations are in line with other recent studies. An increase of our study sample size with longer-term follow-up is needed to better assess the duration of the therapeutic effects of bosentan.

4.2. Conclusion

In conclusion, also patients with Down syndrome may benefit from bosentan treatment when they have Eisenmenger syndrome. Medical treatment appears to be safe and the treatment effects do not deviate from those observed in Eisenmenger patients without Down syndrome.

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