Effect of Bosentan on Exercise Capacity and Clinical Worsening in Patients With Dual Down and Eisenmenger Syndrome

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Abstract: This single-center, retrospective analysis evaluated long-term bosentan treatment in adult patients (n = 7) with both Down and Eisenmenger syndromes (DS-ES). Laboratory tests, 6-minute walk distance (6MWD), functional class, and Doppler echocardiography were assessed at baseline and during 2 years’ follow-up. Improvements or maintenance of 6MWD were observed (68 m improvement from baseline at month 12) after bosentan initiation. 6MWD was maintained up to year 2. Overall, 6 patients experienced a significant improvement in functional class during 2 years’ therapy (P = 0.01). There were no significant changes in parameters measured by Doppler echocardiography. None of the patients required either hospitalization or additional pulmonary arterial hypertension (PAH) therapy because of PAH progression. Bosentan treatment was generally well tolerated; no liver function abnormalities or serious adverse drug reactions were noted. In this DS-ES cohort, bosentan seemed to be well tolerated and clinically effective.

Keywords: pulmonary arterial hypertension, Eisenmenger syndrome, Down syndrome, congenital heart disease, bosentan, endothelin receptor antagonist
Introduction
Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by remodeling of the pulmonary vasculature leading to a progressive increase in pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure.\(^1\) PAH is commonly associated with congenital heart disease (CHD) and can develop earlier or later in life depending on size and location of the underlying defect. Recent data from a US registry reported that PAH-CHD was the second most prevalent etiology within the associated PAH patient subgroup.\(^2\)

Patients with PAH-CHD are at risk of developing right-to-left cardiac shunting, that is, Eisenmenger syndrome (ES). ES patients must make certain lifestyle adjustments due to limited functional capacity. Exercise capacity and quality of life (QOL) are also diminished.\(^3\) Moreover, there are a number of associated life-threatening complications and life expectancy is poorer than in the general population.\(^4\)

Congenital heart defects are highly prevalent (40%–58%) in patients with Down syndrome (DS).\(^5,6\) Patients with DS and CHD are considered to be at higher risk for PAH\(^1,3\) and ES\(^7\) (Defined within the Pulmonary Hypertension World Health Organisation (WHO) clinical classification system (Dana Point 2008) as Group 1), probably due to different pathogenetic factors.\(^7-12\)

According to European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines,\(^13\) ES represents the most advanced form of PAH-CHD and is characterized by a reversed pulmonary-to-systemic (right-to-left) shunt and central cyanosis. Several studies in adult patients with ES have reported a persistent beneficial effect of bosentan (an oral dual endothelin receptor antagonist) on exercise capacity and clinical status without any worsening of pulmonary-to-systemic shunt.\(^14-17\) In an open-label study, 24 patients with DS-ES were treated with bosentan with a median follow-up period of 11.5 months.\(^18\) The authors concluded that medical treatment was well tolerated in DS-ES patients and that results in patients with DS did not deviate from those observed in ES alone.\(^18\) The same authors in a retrospective study reported on the effect of almost 2 years of bosentan treatment on exercise capacity and QOL in 58 adult patients with PAH-CHD with and without DS.\(^19\) The results showed that in DS, patient’s 6-minute walk distance (6MWD) and QOL were stable during treatment. The aim of our retrospective study was to evaluate the effect of long-term treatment with bosentan in adult patients with DS-ES.

Methods
This was a retrospective analysis of data collected prospectively from all patients with DS-ES treated and undergoing active follow-up at our center (Department of Internal and Vascular Medicine IRCCS, Policlinico, San Donato Milano, Italy) between September 2008 and December 2010. Permission to prospectively collect patient data was obtained from the parents or the patients’ legal guardians. The authors of this manuscript have certified that they comply with the ethical standards of the responsible committee and with the Helsinki Declaration.\(^20\)

Eisenmenger syndrome was diagnosed prior to, or following, referral to our center, based on clinical and echocardiographic features and confirmed by right heart catheterization. It was required that patients included in this analysis had stable PAH for at least 1 month prior to the study, that is, had no sign of acute heart failure. Patients with concomitant causes of pulmonary hypertension, such as lung, liver, or connective tissue disease, were excluded from this analysis.

All patients received bosentan (Tracleer, \(^\text{\textregistered}\) Actelion Pharmaceuticals Ltd., Allschwil, Switzerland) treatment, which was started at an oral dose of 62.5 mg twice a day and increased to the target dose of 125 mg twice a day after 4 weeks. Patients started on bosentan therapy following a diagnosis of ES and subsequent assessment by our center confirming that they were suitable candidates for this treatment, that is, they were in New York Heart Association (NYHA) functional class (FC) above II. Bosentan is the first-line treatment of choice for ES-DS patients at our center.

Submaximal exercise capacity was assessed using 6MWD according to the guidelines of the American Thoracic Society (ATS), and transcutaneous arterial oxygen saturation was measured by continuous pulse oximetry monitoring (ATS guidelines) before and after 6MWD testing.\(^21\) Functional capacity was assessed using the NYHA FC system, by the same representative parent or guardian on behalf of the patient at each assessment point. Right ventricular function was measured using tricuspid annular plane systolic excursion (TAPSE), and systolic pulmonary arterial pressure (PAPs) was estimated using peak velocity of the tricuspid regurgitation jet with continuous wave
Bosentan patients with Down and Eisenmenger syndromes

Doppler. These parameters were evaluated at baseline and every 6 months during bosentan therapy. Parameters such as mortality, hospitalization, additional PAH therapy, and cardiac surgery that collectively signify clinical worsening were also recorded and assessed. Laboratory tests (including hemoglobin, liver function, and uric acid) were evaluated every 2 weeks during the first 2 months and every 2 months thereafter. All patients were subjected to a baseline electrocardiogram and a chest X-ray.

Statistical analysis
Statistical analysis was performed applying the Shapiro-Wilk W test. Measured variables (6MWD, oxygen saturation, NYHA FC, PAPs, and TAPSE) were statistically analyzed at baseline, 12 months, and at the end of the study period (24 months). Clinical and instrumental parameter changes from baseline were controlled and a $P$ value $< 0.05$ was considered as a level of statistical significance.

Results
Seven adult patients with DS-ES, five male (72%) and two female (28%) with a mean age 31.7 years (range 20–50 years), were included in this analysis. The majority of patients (5/7) had ventricular septal defect (VSD) (Table 1). Patients had not received corrective cardiac surgery. As these patients were referred to our center in adulthood, the reasons why they were not operated on in infancy were unknown. No patient received anticoagulant therapy or sildenafil therapy; concomitant medications for each patient are provided on Table 2.

In the first 6 and 12 months of bosentan therapy, patients showed an increase in 6MWD compared with baseline values (Figs. 1 and 2). Median 6MWD increased from 252 m at baseline to 320 m at 12 months ($P = 0.10$) and after 24 months 6MWD was maintained compared with the 12 month value (median 310 m, $P = 0.20$). Mean $±$ standard deviation 6MWD was $261 ± 64$ m at baseline, $306 ± 62$ m at 12 months, and $298 ± 60$ m at 24 months. There was no significant variation of oxygen saturation before and after 6MWD testing over the 2-year course of follow-up (Fig. 3). Overall, patients experienced a statistically significant improvement in NYHA FC (Fig. 4; $P = 0.01$). After 24 months of therapy, two patients improved from their baseline NYHA FC from IV to III, and four patients, from NYHA FC III to II. One 50 year-old male patient with perimembranous VSD and aortic valve insufficiency who initially remained in NYHC FC III worsened into NYHA FC IV after 24 months’ treatment. There was no significant change in Doppler echocardiography data (TAPSE, PAPs, and absence of pericardial effusion) observed. No patients required hospitalization for PAH or additional PAH therapy because of progression of disease in the 2-year observation period, and no patients required cardiac surgery.

Bosentan treatment was generally well tolerated and no serious adverse drug reactions were recorded. All seven patients with DS-ES tolerated induction of oral bosentan therapy and there was no indication of decreased arterial oxygen saturation over the treatment period studied. No liver function abnormalities ($> 3 ×$ upper limit of normal) were noted and uric acid, hemoglobin, white blood cells, and platelet count were unchanged during bosentan treatment.

Discussion
Overall, the DS-ES patients treated with bosentan in our study showed initial improvement in exercise

Table 1. Individual patient characteristics at baseline.

| Patient | Gender | Age, years | Weight, kg | Body mass index, kg/m² | CHD | NYHA FC | 6MWD, m |
|---------|--------|------------|------------|------------------------|-----|---------|---------|
| 1       | Male   | 34         | 47         | 17                     | AVC | IV      | 220     |
| 2       | Male   | 24         | 108        | 42                     | VSD | III     | 310     |
| 3       | Female | 20         | 55         | 20                     | VSD | IV      | 180     |
| 4       | Male   | 21         | 64         | 22                     | VSD | III     | 360     |
| 5       | Male   | 41         | 74         | 27                     | VSD | III     | 200     |
| 6       | Male   | 50         | 65         | 24                     | VSD | III     | 300     |
| 7       | Female | 32         | 60         | 24                     | AVC | III     | 200     |

Abbreviations: AVC, atrioventricular canal; VSD, ventricular septal defect.
capacity, as shown by the median and mean increases from baseline at 12 months, which was subsequently maintained up to 2 years. Although the changes from baseline in 6MWD at 12 and 24 months were not statistically significant, they are clinically meaningful. Given the progressive nature of ES, the fact that three patients showed an increase in 6MWD and the other four remained stable over the course of 2 years (even in one patient who was overweight) is encouraging (see Fig. 2 for individual patient data). Furthermore, NYHA FC improved in six patients over the course of the study providing strong supportive evidence that most of these patients derived a benefit from bosentan treatment over the long term. In addition, patients in our study did not exhibit any of the clinical parameters associated with clinical worsening, that is, death, hospitalization due to PAH, or a requirement for additional PAH therapy or cardiac surgery, although one patient did worsen to NYHA FC IV after 24 months’ treatment. We have shown long-term benefits in exercise capacity (6MWD) and NYHA FC in DS-ES patients treated with bosentan combined with a favorable safety profile in accordance with previously published literature.15,18,19,22–25

In our center, bosentan is selected as the first-line treatment for patients with DS-ES, based on the recommendations given in guidelines for the treatment of ES patients13 and the fact that sildenafil may have sexual side effects in men. Sildenafil may be initiated in combination with bosentan if a patient’s 6MWD decreases by at least 10% compared with the previous value and there are other indicators consistent with deterioration and no ethical impediments. None of the patients received targeted PAH combination therapy during the study period.

The BREATHE-5 study was the first to demonstrate improvements in hemodynamics and exercise capacity after treatment with bosentan in patients with ES.16 The study’s open-label extension confirms the early results over a longer treatment period of 40 weeks.26 A subgroup analysis of the BREATHE-5 patient population showed that the location of septal defect was a key determinant of treatment response.27

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**Table 2. Individual baseline medications.**

| Patient | Medication                                      |
|---------|------------------------------------------------|
| 1       | Digoxin + diuretics + allopurinol + iron       |
| 2       | Diuretics + aspirin + iron                     |
| 3       | Iron                                           |
| 4       | Diuretics + allopurinol                        |
| 5       | Diuretics + iron                               |
| 6       | Digoxin + diuretics + allopurinol              |
| 7       | Iron                                           |

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**Figure 1.** Changes in 6MWD at baseline, after 12 months ($P = 0.1$), and after 24 months ($P = 0.2$) of bosentan therapy in 7 patients with dual DS-ES.

**Figure 2.** Individual change in 6MWD over 24 months of bosentan therapy in 7 patients with dual DS-ES.

**Figure 3.** Arterial oxygen saturation before and after 6MWD testing in 7 patients with dual DS-ES.
Study strengths and limitations
The present study adds valuable evidence to the limited information reported in the literature regarding patients with DS-ES treated with the dual endothelin receptor antagonist, bosentan. This study demonstrated a significant and stable long-term clinical improvement with a favorable safety profile in accordance with previous reports. However, this study is subject to a number of limitations. These include the lack of a control group and the small sample size, but this is not surprising considering the low prevalence of this dual syndrome. Nevertheless, our observations are in line with other recent studies.18,19,22–25

Conclusions
In conclusion, in our experience and in accordance with latest literature, bosentan has been shown to be well tolerated and clinically effective in patients with DS-ES, and the clinical benefit is maintained over a long-term treatment period.

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Author Contributions
Planned and designed the study: GS, MCh, and MC. Treated patients and performed evaluations: MG, AM, DN, CL, and RD. Collected and statistically analyzed data: MG. Wrote the first draft of the manuscript: GS. All authors agree with manuscript results and conclusions, made critical revisions, and approved final version. All authors reviewed and approved of the final manuscript.

Competing Interests
Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics
As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and
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