ORIGINAL ARTICLE

Long-term Outcomes of Treatment With Bosentan in Pulmonary Hypertension

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OBJECTIVE: Treatment with bosentan improves exercise capacity in patients with pulmonary hypertension. Few studies have assessed treatment with this drug over long periods. The aim was therefore to assess long-term treatment with bosentan.

PATIENTS AND METHODS: A group of 22 functional class III patients—18 women and 4 men, mean age, 45.5 years (range, 19-77 years)—with pulmonary hypertension were treated with bosentan between April 2002 and June 2005. Pulmonary hypertension was idiopathic in 10 patients. In the remaining patients, etiologies were associated with compensated heart failure (n=4), scleroderma (n=4), peripheral embolism (n=3), and portal hypertension (n=1). Clinical and hemodynamic variables and their changes between baseline and the end of study were analyzed.

RESULTS: The mean duration of follow-up of the patients was 15.7 months (range, 12.6-31.8 months). Functional class improved or stabilized after 3 months of treatment in 21 (95%) and after 1 year in 14 (64%). At 3 months, the distance covered in the 6-minute walk test increased by a mean of 64.5 m, an improvement that was maintained at 6, 12, and 18 months. Treatment was interrupted in 4 patients (18%). Reasons for discontinuation were death in 2 patients, deterioration in 1 patient, and intolerance of the medication in 1 patient. Treatment was ineffective for 4 patients (18%). No patient experienced notable liver toxicity.

CONCLUSIONS: The results of this study suggest that treatment with bosentan is associated with long-term improvement in clinical variables and exercise capacity in approximately two thirds of the patients with pulmonary hypertension.

Key words: *Bosentan. Endothelin receptors. Pulmonary hypertension.*

Resultados a largo plazo del tratamiento con bosentán en la hipertensión arterial pulmonar

OBJETIVO: El tratamiento con bosentán mejora la capacidad de ejercicio de los pacientes con hipertensión pulmonar. Son muy escasos los estudios que evalúan este tratamiento a largo plazo, que es el objetivo propuesto en el presente trabajo.

PACIENTES Y MÉTODOS: Un grupo de 22 pacientes –18 mujeres y 4 varones, con una edad media de 45,5 años (rango: 19-77 años)– con hipertensión pulmonar en clase funcional III recibieron tratamiento con bosentán entre abril de 2002 y junio de 2005. La hipertensión pulmonar era idiopática en 10 casos y estaba asociada a cardiopatía corregida (n = 4), esclerodermia (n = 4), embolia periférica (n = 3) e hipertensión portal (n = 1) en los restantes. Se estudiaron los datos clínicos y hemodinámicos y los cambios que habían experimentado desde el inicio del tratamiento hasta el fin del estudio.

RESULTADOS: El seguimiento medio de los pacientes fue de 15,7 meses (rango: 12,6-31,8). La clase funcional mejoró o se estabilizó a los 3 meses de tratamiento en 21 (95%) y al año en 14 (64%). La distancia recorrida en la prueba de la marcha de 6 min se incrementó a los 3 meses de tratamiento una media de 64,5 m, mejoría que se mantuvo a los 6, 12 y 18 meses. El tratamiento se interrumpió en 4 pacientes (18%): por muerte en 2 casos, por empeoramiento en uno y por intolerancia a la medicación en otro. En otros 4 pacientes (18%) se objetivó falta de eficacia. Ningún paciente presentó hepatotoxicidad remarcable.

CONCLUSIONES: Los resultados del presente estudio apoyan la idea de que el tratamiento con bosentán se asocia a una mejoría clínica y de la capacidad de ejercicio a largo plazo en aproximadamente dos terceras partes de los pacientes con hipertensión pulmonar.

Palabras clave: *Bosentán. Receptores de la endotelina. Endotelina. Hipertensión arterial pulmonar.*

Introduction

Pulmonary hypertension (PHT) is a serious progressive disease. The idiopathic form is associated with 50% mortality at 3 years after diagnosis.[1] The term PHT, as proposed in the latest consensus meeting in Venice, Italy, in 2003, includes idiopathic and familial forms as well as forms associated with connective tissue disorders, liver diseases, congenital heart disease, intake of toxic substances (for example, toxic oil), or drugs. The definition also includes patients who develop the disease due to stimuli such as infection with the human immunodeficiency virus. The anatomical abnormalities in pulmonary vasculature are very similar in all forms

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of the disease, and conventional treatment generally includes administration of vasodilators and anticoagulants. In patients with the most severe forms of the disease, aggressive treatment in the form of continuous intravenous infusion of epoprostenol has been shown to improve survival. This success with epoprostenol has encouraged the development of new drugs that have a similar mechanism of action but that are more stable and do not require intravenous administration.

According to experimental data, endothelin-1 plays an important role in the pathogenesis of PHT. In fact, this molecule is an important mediator in a wide range of cell and tissue processes, particularly vasoconstriction, hypertrophy, fibrosis, inflammation, and neurohormonal activation. Concentrations of endothelin-1 in peripheral blood and pulmonary tissue are known to correlate with severity.[2] The pathological effects are mediated by 2 receptors denoted endothelin A receptor and endothelin B receptor. In patients with PHT, higher levels of endothelin 1 receptor are found in the medial layer of small pulmonary arteries, with a predominance of endothelin B receptor.[3] Although activation of endothelin B receptor in endothelial cells promotes the production of nitric oxide, leading to vasodilation, its activation in the medial layer of the small pulmonary arteries, where their levels are elevated in these patients, has a vasoconstrictive effect.

In recent years, endothelin receptor antagonists, in particular bosentan, have opened up new options in the treatment of patients with PHT. Bosentan is the first in class of oral drugs that act by blocking the A and B receptors of endothelin-1. Clinical trials have shown that treatment with this drug increases exercise capacity and improves dyspnea and pulmonary hemodynamics; moreover, these benefits persist after 7 months.[4-6] Little information is available on the long-term follow-up of patients treated with bosentan,[7] and less still on the effects of this drug in patients with PHT associated with other diseases such as corrected congenital heart defects, chronic forms of peripheral embolism, or portal hypertension.

We describe the experience in our hospital of long-term bosentan treatment outside a clinical trial setting in patients with idiopathic PHT and PHT associated with other conditions.

Patients and Methods

Patients

After publication in 2002 of initial evidence for the efficacy of bosentan in the treatment of PHT, we decided to adapt our treatment protocol for these patients and use this drug as the first choice treatment in functional class III patients. In this study, we analyzed clinical and hemodynamic data from 22 consecutive patients with PHT for whom treatment with bosentan was indicated between June 2002 and June 2004. The study was completed in June 2005 with a follow-up of at least 1 year. Prior to inclusion, patients were screened for PHT documented by right heart catheterization and follow-up of at least 1 year on bosentan treatment was required. The prior use of calcium channel blockers by 5 patients was not considered grounds for exclusion, but patients who were already receiving bosentan when referred to our hospital were excluded. The study population comprised 18 women and 4 men with a mean age of 45.4 years (range, 19-77 years) on starting treatment. PHT was idiopathic in 10 patients, associated with diffuse scleroderma in 4, associated with corrected congenital heart disease in 4 (transposition of the great vessels in 2 patients, ventricular shunt in 1, endocardial cushion defect in 1), due to chronic peripheral embolism in 3, and related to portal hypertension in 1 patient. The mean time between diagnosis of PHT and initiation of treatment with bosentan was 27.2 months (range, 0.2-120 months). All patients were in functional class III according to the New York Heart Association (NYHA) classification when they began treatment. In all cases, PHT was diagnosed by right heart catheterization. In 16 patients, right heart catheterization was also done on starting treatment with bosentan. The catheterized patients also underwent an acute vasodilatory test with intravenous infusion of epoprostenol. In these 16 patients, systolic/diastolic/mean pulmonary artery pressure was 83/31/48 mm Hg and the mean cardiac index was 2.3 L/min/m^2. Seventeen of the 22 patients had received no specific treatment for the PHT, whereas the five remaining ones had been previously treated with calcium channel blockers.

Methods

Treatment with bosentan was started at a dose of 62.5 mg every 12 hours during the first month, then increased to 125 mg every 12 hours provided it was well tolerated. Liver function, blood count, kidney function, and uric acid were determined before starting treatment, then every month for the first 6 months, and finally every 3 months. The NYHA functional class was assessed before treatment was started and then every 3 months while the patient was receiving bosentan as monotherapy. Before starting treatment and then every 3 months, patients did the 6-minute walk test according to a specific protocol. The distance covered in meters was recorded and theoretical values were not used.[8] Other variables measured were survival, need for lung transplant, and use of other drugs specifically for PHT. Therapeutic failure was recorded if a patient died or required a lung transplant or another drug specifically for PHT, or if his or her clinical condition worsened.

Quantitative variables were expressed as mean (SD) and range. The study was reviewed and approved by the ethics committee of the Hospital Universitario Vall d'Hebron.

Results

Mean follow-up lasted 15.7 months (range, 12.6-31.8 months). Two patients died, 1 after 3 months of treatment because of extensive accidental burns (unrelated death) and the other after 6 months; the case was reported as sudden death. The 18-month survival rate was 91%. Treatment was discontinued in 4 patients (18%) after a mean of 134 days (range, 30-255 days). The reasons for discontinuation were as follows: death (2 patients), worsening clinical condition (1 patient), and flu-like syndrome (1 patient). Four other patients (18%) were classed as treatment failures, treatment failure being defined as the need for another drug to treat PHT. Inhaled iloprost was added after 5 to 6 months of bosentan treatment in 3 patients; in the remaining patient with

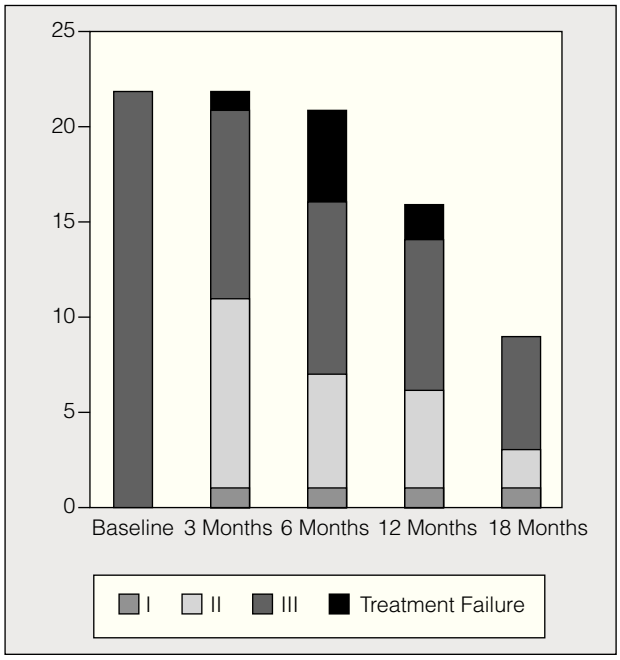

Figure 1. Changes in the New York Heart Association functional class of 22 patients treated with bosentan. At 3 months: 22 patients; 1 discontinued treatment on day 30. At 6 months: 21 patients; 2 died and 3 worsened. At 12 months: 16 patients; 2 worsened. At 18 months: 9 patients.

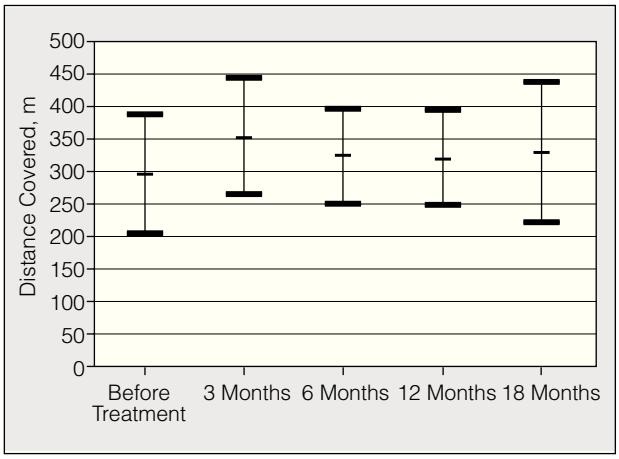

Figure 2. Changes in the distance covered in the 6-minute walk test in 22 patients (mean [SD]).

treatment failure, subcutaneous treprostinil was initiated 8 months after starting bosentan treatment (Table).

After 3 months of treatment with bosentan, improvement or stabilization was observed in the functional class of 21 patients (95%). The remaining patient had discontinued treatment early after developing flu-like syndrome that was reported as an adverse drug reaction. The improvement or stabilization of the functional class persisted in 16 patients after 6 months, in 14 patients after 12 months, and in 9 patients after 18 months (Figure 1). Before starting treatment with bosentan, the patients covered a mean (SD) of 296 (90) m (range, 180-471 m) in the 6-minute walk test. The distance covered in the same test was greater at 3 months (351 [81] m, corresponding to a mean increase of 64.5 m with respect to baseline) and the improvement was maintained at 6 months (323 [73] m, corresponding to a mean increase of 39.6 m), 12 months (319 [72] m, corresponding to a mean increase of 76 m), and 18 months (330 [106] m, corresponding to a mean increase of 118 m), as represented graphically in Figure 2.

TABLE
Demographic and Diagnostic Data and Disease Course in 22 Patients With Pulmonary Artery Hypertension Treated With Bosentan

Sex	Age, y	Diagnosis	Follow-Up, d	Clinical Course From Initiation of Treatment With Bosentan Until the End of Treatment
Female	24	Corrected ventricular shunt	564	Improvement
Female	59	Chronic peripheral embolism	715	Improvement
Female	50	Idiopathic	956	Improvement
Female	44	Corrected complex congenital heart defect	535	Improvement
Female	46	Idiopathic	30*	Flu-like syndrome
Female	67	Idiopathic	705	Stable
Male	26	Chronic peripheral embolism	835	Improvement
Female	19	Corrected transposition of the great vessels	98*	Sudden death
Male	44	Idiopathic	118*	Improvement. Death due to accidental burns
Female	77	Chronic peripheral embolism	726	Stable
Female	41	Scleroderma	248*	Deterioration. Subcutaneous treprostinol is added
Female	69	Idiopathic	255*	Bosentan is discontinued due to worsening
Male	55	Portal hypertension	537	Improvement
Female	55	Idiopathic	139*	Deterioration. Inhaled iloprost is added
Female	61	Scleroderma	685	Stable
Female	67	Scleroderma	820	Stable
Female	31	Idiopathic	501	Improvement
Female	31	Idiopathic	135*	Deterioration. Inhaled iloprost is added
Female	19	Corrected transposition of the great vessels	613	Stable
Female	27	Idiopathic	380	Stable
Male	46	Idiopathic	420	Stable
Female	64	Scleroderma	180*	Deterioration. Inhaled iloprost is added

*Day on which bosentan treatment was discontinued or therapeutic failure was documented.

Of the 22 patients treated, transient increases in liver enzymes were detected in 2 (9%) (at 1 month and 3 months after starting treatment with bosentan). Neither of these patients discontinued because of these abnormal values.

Discussion

The most important finding of the present study was that long-term treatment with bosentan in patients with PHT improved or stabilized exercise capacity in 2 out of every 3 patients treated. This finding was applicable regardless of whether the NHYA functional class or exercise capacity in the 6-minute walk test was used as the outcome measure. Furthermore, this improvement was maintained over the long term for many of these patients. In the 2 phase III clinical trials of the bosentan development program, improvements in functional class and the 6-minute walk test were observed, with lengthening of the progression-free period and improved hemodynamic variables, although the study period was limited to 12 weeks.[5,6] In the most important of these 2 studies, the distance covered by the group of patients treated with placebo decreased by 7.8 m but increased by 36.4 m in the group of patients treated with bosentan for 12 weeks. The treatment effect was therefore 44.2 m. The results of the present study, with an improvement of 64 m after 3 months, were similar to those observed in these clinical trials.

Much less information is available on the long-term outcome (after more than 3 months) of treatment with bosentan in patients with PHT. The follow-up data of 29 patients who participated in the first clinical trials were published after a mean treatment duration with bosentan of 15 months.[7] According to the investigators, the NHYA functional class had improved in 41% of these patients after 3 months of treatment. Furthermore, the distance covered in the 6-minute walk test increased, and this improvement was maintained after 9 months of treatment. Based on the findings of the study, the investigators concluded that the efficacy of bosentan treatment is maintained for 1 year. More recently, Provencher et al[9] reported the results from a study of 103 patients treated with bosentan in a single center for a mean of 24 months. The study was retrospective, and the investigators concluded that, after 4 months, 49% of the patients had an improved NYHA functional class and 42% remained stable. The mean increase in the distance covered in the 6-minute walk test was 42 m after the same 4-month period. This distance did not increase the following year. During follow-up, 43% of the patients required a prostanoid to be added to treatment because bosentan was not considered to be sufficiently effective. Our results are clearly consistent with this large series: after 3 months of treatment, 50% of the patients had an improved functional class and 45% had remained stable. Moreover, the mean increase in the distance covered in the 6-minute walk test after 3 months was 64 m, an increase that was maintained in patients who completed 18 months of follow-up. During follow-up, 8 patients (36%) had to discontinue treatment or combine bosentan with other drugs. In short, bosentan is effective in two thirds of the patients treated outside the special setting of clinical trials. This observation is essential for assessing the efficacy of the drug in PHT.

The impact of bosentan treatment on the survival of patients with PHT has not been fully established. Preliminary findings suggest that bosentan, administered as the first-line treatment, is associated with a lower mortality than in historical controls. In the main clinical trials, no differences in mortality were reported between the placebo group and the treatment group.[6] Very recently, mortality data at 1, 2, and 3 years were published for patients participating in the clinical trials.[10] The authors reported a clear improvement in survival at 3 years in the group of patients treated with bosentan compared to a historical cohort of North American patients from the 1980s.[1] Unfortunately, more recent cohorts are not available for comparison. In a series of patients in Paris, France, Provencher et al[9] reported survival of 93% at 1 year, 90% at 2 years, and 85% at 3 years. The findings from our series agree with existing data, as 91% of the patients in our study were still alive after 1.5 years.

Treatment with bosentan at a dose of 125 mg every 12 hours was well tolerated. Only 1 patient had an adverse drug reaction. It was necessary to discontinue treatment in 4 patients (18%), and a further 4 patients (18%) required another PHT drug to be added during the study period. Even accounting for the patient who discontinued treatment because of death due to causes other than PHT, the number who stopped treatment seemed greater than in previous reports.[11] A possible explanation for this discrepancy is that, in our hospital, we generally do not increase the dose of bosentan above 125 mg every 12 hours in patients who do not improve or who deteriorate. In a previous clinical trial, exercise capacity appeared to be dose dependent although the incidence of liver toxicity was also greater in the subgroup of patients who received the highest doses.[6] In the follow-up study, 3 of the 4 patients with an increased dose showed an improved exercise capacity. In accordance with these results, we decided not to systematically use high doses of bosentan because of the risk of liver toxicity and because the option of a combination treatment or an alternative treatment is available. Finally, 1 patient suffered from flu-like syndrome which required discontinuation of the drug. Although this syndrome has been clearly described as an adverse drug reaction,[11] it does not normally require discontinuation of treatment.

Liver toxicity was a cause for concern during the introduction of this drug. An evaluation of liver function is therefore advisable before starting treatment and then every month thereafter. This recommendation is based on previous studies in which asymptomatic increases in liver enzymes were reported. These increases were more clinically significant and more frequent in patients who took the highest doses of bosentan.[6] In the present study, such increases were reported in 2 patients (9%) who received a dose of 125 mg every 12 hours. A similar incidence of elevated liver enzymes has been

reported in other clinical trials[6] and series with longer-term follow-up.[11] This complication was managed by reducing the dose to 62.5 mg every 12 hours; the liver enzymes then returned to normal.

In summary, the findings of the present study support the beneficial effect of bosentan in these patients in the long term, although the study is subject to certain limitations in its design and sample size. Nevertheless, we should consider that the most important finding is the positive effect of the drug, in full agreement with previous clinical trials, even though our study was conducted outside the rigid setting of a clinical trial. Studies such as ours allow the effectiveness of a drug to be studied in a real clinical setting. In view of our findings, treatment with bosentan is beneficial in the long term in approximately two thirds of patients treated. Larger series of patients are needed with longer follow-up to definitively establish the value of this treatment.

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