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Survival in patients with pulmonary arterial hypertension treated with first-line bosentan

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Abstract

Background Pulmonary arterial hypertension (PAH) is a devastating disease of the small pulmonary arteries and arterioles, characterized by intimal fibrosis, medial hypertrophy and plexiform lesions. When untreated both the idiopathic form (IPAH, formerly termed primary pulmonary hypertension, PPH) and PAH related to various other conditions such as scleroderma (SSc) often take a progressive course with high mortality. There is ongoing search for disease-specific treatments that are able to improve survival in these patients. The oral dual endothelin (ET_A/ET_B) antagonist bosentan has been shown to improve exercise capacity, time to clinical worsening, haemodynamics and quality of life in short-term studies.

Materials and methods To determine the long-term effects of bosentan on survival, patients from the two double-blind, randomized trials and their open-label extensions, treated with first-line bosentan, were followed for up to 3 years. Data on survival were collected between September 1999 (first patient included in the placebo-controlled trials) and December 2002. Vital status was verified in each patient. The survival cohorts of these patients were compared with either the predicted survival for each patient based on an equation from the National Institutes of Health (NIH) PPH registry or with historical controls.

Results Observed survival up to 36 months was reported as a Kaplan-Meier estimate in three cohorts: (1) In 169 PPH patients treated with first-line bosentan, 1- and 2-year survival was 96% and 89%, respectively, vs. predicted untreated survival at 1 and 2 years of 69% and 57%, respectively; (2) in 50 patients with PAH associated with SSc (PAH-SSc), 1-, 2- and 3-year survival was 82%, 67% and 64%, respectively, vs. ~45%, ~35% and ~28%, respectively, from registry data of untreated PAH-SSc patients; and (3) in 139 PPH patients in WHO functional class III, 1- and 2-year survival was 97% and 91%, respectively, vs. 91% and 84% in a historical cohort of 346 patients treated with epoprostenol in five major referral centres.

Conclusions The present analyses suggest that first-line bosentan therapy, followed by the addition of other disease-specific therapies as required, improves survival in patients with advanced PAH.

Keywords Bosentan, endothelin receptor antagonism, epoprostenol, hypertension, pulmonary, survival.
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Introduction

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterized by a progressive increase of pulmonary vascular resistance, which is debilitating and ultimately leads to right ventricular failure and premature death [1]. Usually PAH has a poor outcome, but the natural history of the disease is heterogeneous, with some patients dying within months of diagnosis and others living for decades [2]. The underlying diagnosis is associated with the prognosis: for example, patients with PAH related to congenital heart disease have a substantially higher life expectancy than patients with the idiopathic form (IPAH, formerly

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Table 1 Survival in PAH with various underlying diagnoses (natural history)

Diagnosis	Year 1	Year 2	Year 3	Year 4	Year 5
CHD	0·92 (2)	0·885 (2)	0·77 (1)		0·77 (1)
Connective tissue disease	0·67 (3)	0·405 (2)	0·37 (2)		
HIV	0·58 (1)	0·39 (2)	0·21 (1)		
PPH	0·79 (21)	0·66 (12)	0·59 (14)	0·28 (3)	0·48 (14)
Portopulmonary hypertension			0·64 (1)		

*Data (number of studies) are presented as unweighted and unadjusted averages of entire data set.
CHD, congenital heart disease; HIV, human immunodeficiency virus; PPH, primary pulmonary hypertension.
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termed primary, PPH) or with PAH related to connective tissue disease (Table 1).

According to a recent review published as part of the ACCP evidence-based clinical practice guidelines for PAH, apart from the underlying disease, certain parameters, assessed at baseline, predict a worse prognosis. Parameters with high-quality evidence include advanced World Health Organisation (WHO) functional class (FC), low 6-min walk distance and presence of pericardial effusion, while for haemodynamic, electrocardiographic and laboratory findings the existing evidence is fair or even low and the net predictive value consequently limited [2].

Need for long-term observations to assess prognosis

While there is no cure for PAH, medical treatment has made great progress over the past decade. Usually, placebo-controlled clinical studies are limited to short observation periods of approximately 3–4 months, which is regarded to be appropriate for registration purposes by the relevant authorities. However, the results of short-term treated cannot be generally extrapolated to long-term use, as exemplified by the results of a trial with beraprost, an oral prostacyclin analogue. In a 12-month double-blind, randomized, placebo-controlled study of 116 patients with WHO functional class II or III PAH related to either connective tissue diseases or congenital systemic to pulmonary shunts, beraprost increased time to disease progression at 6 months, and improved exercise endurance compared with placebo at 3 and 6 months [3]. These effects dissipated at 9 and 12 months of therapy and were not associated with a detectable benefit in symptomatic status or quality of life as measured by standardized instruments, nor with haemodynamic improvement. In addition, disappointing results on long-term inhaled iloprost treatment have recently been reported [4].

These examples show that long-term observations are necessary to determine the impact of treatment on prognosis of the patients.

However, in view of the rapid progression of PAH in many cases, long-term placebo-controlled therapy is ethically not acceptable; treatment must not be delayed in these patients [5]. Larger head-to-head studies of drugs are not available, and there is a trend in PAH therapy to combine treatments early or as an add-on strategy [6].

Endothelin antagonism in PAH

Three different pathways are known to be involved in the pathophysiology in PAH (prostacyclin, nitric oxide, and endothelin (ET) pathways). Substantial evidence shows that ET plays a key role. The effects of ET include proliferation, vascular hypertrophy, inflammation, fibrosis and vasoconstriction [7]. ET levels correlate with PAH disease severity and outcome [8]. In the pathology of PAH, both ET receptors (ET_A/ET_B) mediate these deleterious effects and preclinical data have demonstrated that dual blockade is superior compared with single ET_A blockade in terms of haemodynamic effects and survival [9].

Short-term studies

Two studies have provided the basis for approval of the oral dual ET_A/ET_B receptor antagonist bosentan in the treatment of PAH patients in WHO (World Health Organisation) functional class III or IV (III in the European Union) [10,11]. In the pilot 12-week trial (study 351), treatment with bosentan at a dose of 62·5 mg twice daily for 4 weeks, and at 125 mg twice daily thereafter, improved the primary endpoint exercise capacity measured by the 6-min walk test (mean placebo-corrected treatment effect of +76 meters, $P = 0·02$). In addition, improvements in pulmonary vascular resistance were observed, and patients also experienced a reduced Borg dyspnea index and an improved functional capacity.

These preliminary results were confirmed by the pivotal 16-week Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 [11], in which 213 PAH patients in functional class III or IV (IPAH, PAH-SSc, PAH associated with systemic lupus erythematosus) were randomly assigned to receive placebo or bosentan (at a dose of 62·5 mg twice daily for 4 weeks; thereafter either 125 mg or 250 mg twice daily for at least 12 weeks). The mean effect of treatment on the 6-min walk test was a placebo-corrected improvement of 44 m in the combined bosentan groups ($P < 0·001$). Patients receiving bosentan also had improvement in the time to clinical worsening (death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation of treatment, a need for epoprostenol therapy or atrial septostomy). A substudy of 85 patients showed that

bosentan also improved haemodynamic parameters measured noninvasively by means of a transthoracic Doppler echocardiography [12].

Bosentan pilot study: 1-year results

Twenty-nine of the original 32 patients with PAH (IPAH or associated with SSc) who participated in the pilot 12-week study participated in an open-label extension study [13]. All patients received bosentan open-label (62·5 mg twice daily for 4 weeks and then 125 mg twice daily). At month 6, assessed patients continuing bosentan treatment maintained the improvement in walk distance observed at the end of the previous study (60 ± 11 m), and patients starting bosentan treatment improved their walk distance by 45 ± 13 m. Long-term treatment with bosentan for > 1 year was associated with an improvement in haemodynamic parameters and modified WHO functional class. The long-term results confirmed sustained benefits on exercise capacity and haemodynamics [13].

Survival analysis 1: first-line bosentan in IPAH patients vs. historical controls

Recently, we published the survival analysis of idiopathic PAH patients, who were from both the bosentan randomized trials and the open-label extensions treated with first-line bosentan [14]. Of the 245 patients enrolled in the placebo-controlled studies, PAH was considered primary in 177, and analyses were performed in 169 of these patients with PPH (IPAH) who received bosentan as first-line therapy for their disease, either during the placebo-controlled study or its extension. Eight patients initially randomized to placebo, seven of whom were withdrawn and treated with alternative therapies and one who died before the end of the placebo-controlled trial, did not receive bosentan as first-line therapy and were excluded from the analysis. Decisions on other treatments were taken according to the discretion of the treating physician. During the placebo-controlled studies, patients requiring prostanoid therapy were withdrawn from the study; during the extension studies, prostanoid or other alternate oral therapies could be administered with continued bosentan therapy. Data on vital status and alternative treatments were collected from September 1999 (start of the first placebo-controlled study) to 31 December 2002 (data cut-off), whether or not the patients remained on study treatment throughout. Table 2 shows the baseline characteristics of all 169 patients included in the analysis. Survival was assessed from the start of bosentan treatment to death or data cut-off. All bosentan-treated PPH patients were included in the analyses (intent to treat); patients lost to follow up were considered dead at the last known contact, the most conservative assumption. Changes in treatment did not affect the survival analysis. The annual death rate was obtained by interpolation of the observed data assuming an exponential distribution.

Mean follow-up period was 2·1 ± 0·5 years. The majority of patients were on the recommended bosentan 125 mg b.i.d. dose, 1% were on a quarter of this dose, 11·3% on half this dose and 10·1% were on double this dose. Table 3 summarizes the outcomes of bosentan-treated patients. Kaplan-Meier survival estimates were 96% at 1 year and 89% at 2 years (Fig. 1). The annual death rate of patients on bosentan was 5·5%. Furthermore, 85% and 70% of patients, respectively, remained alive and on bosentan monotherapy at 1 and 2 years (Fig. 2) [14]. The observed survival rates compared favourably with predicted survival, which was determined for each patient according to the National Institutes of Health (NIH) Registry formula. This formula, published in 1987, is based on the outcomes from 187 PPH patients in the NIH registry and reflects the natural history of disease at a time when no specific treatment was available [15]. It has been validated prospectively in a different cohort of 61 PPH patients [16]. Using the equation in our dataset, the predicted 1- and 2-year survival rates were 69% and 57%, respectively, and thus substantially lower than those observed on bosentan.

Table 2 Demographic and baseline characteristics of 169 bosentan-treated patients with idiopathic pulmonary arterial hypertension

Subjects (*n*)	169
Sex male/female (%)	21/79
Age (years)	
Mean ± SD	46 ± 16
Range	13–80
WHO functional class (%)	
I/II	1/8*
III/IV	82/9
Time from diagnosis (months)†	
Mean ± SD	32 ± 41
Range	0·3–326
Haemodynamics (mean ± SD)†	
Cardiac index (L min^{-1} m^{-2})	2·35 ± 0·80
PVR (Wood units)	12·9 ± 8·4
mPAP (mmHg)	57·1 ± 16·0
mRAP (mmHg)	10·1 ± 5·9
Walk test (m)	
Mean ± SD	345 ± 87

*All patients entered the pivotal studies in functional class III or IV, but 15 (9%) patients in the placebo group improved before being switched to bosentan in the extension study.

†Time from diagnosis and haemodynamic data were available for 157–169 bosentan-treated patients; for most of these patients, data were available only at the start of the placebo-controlled study.

Patients from the bosentan pivotal studies and their open-label extensions.

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PPH, primary pulmonary hypertension (= idiopathic PAH); WHO, World Health Organization; PVR, pulmonary vascular pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure.

Survival analysis 2: first-line bosentan in PAH-SSc patients vs. registry data

A similar analysis to that of IPAH patients was carried out on the patients with PAH-SSc who participated in the above

Table 3 Outcomes in bosentan-treated patients with idiopathic pulmonary arterial hypertension (IPAH)*

Subjects (*n*)	169
Duration of observation for survival (years)	
Mean ± SD	2·1 ± 0·5
Range	0·1–3·3
Patients lost to follow up (*n*)	1
Lung transplantations (*n*)	3
Deaths *n* (%)	20 (13)†
Transfers to/additions of prostanoids or alternative oral PPH therapies *n* (%)	39 (24)‡
Patients who received alternative treatment in addition to bosentan (*n*)	19
Discontinuations of bosentan without other event or treatment (*n*)	4

*According to the classification applicable during the initiation of the pivotal studies, these were patients with primary pulmonary hypertension (PPH) patients.

†Includes the one patient lost to follow up; ‡includes the one patient lost to follow up and three patients with a period of unknown treatment.

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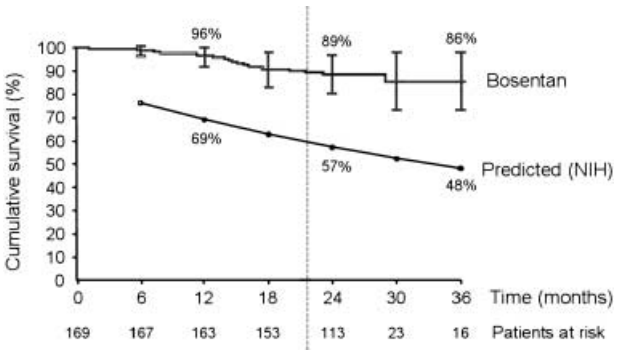

Figure 1 Survival in first-line bosentan therapy vs. predicted survival using National Institutes of Health (NIH) Registry formula for pulmonary arterial hypertension (PAH). Dashed line: observed survival; solid line: predicted survival. Adapted with permission from McLaughlin *et al.* 2005 [14].

placebo-controlled bosentan studies. The 50 patients in the long term dataset were predominantly female (84%), with a mean age of 59·4 ± 10·5 years. Four per cent, 90% and 6% of patients were in WHO functional class II, III, and IV, respectively. In this cohort, mean bosentan exposure was 1·6 ± 0·9 years and mean duration of observation was 1·8 ± 0·8 years. Eight patients (16%) received epoprostenol as add-on therapy and seven patients (14%) received it after discontinuation of bosentan. Survival was 82% after 1 year, 67% after 2 years and 64% after 3 years [17]. These data were compared with the registry data of Koh *et al.*, who reported survival rates in PAH-SSc patients of ~45%, ~35% and ~28% at 1, 2 and 3 years, respectively [18]. According to the authors' conclusion, long-term treatment may stabilize the disease and appears to have a favourable effect on long-term outcomes in comparison with registry data [16].

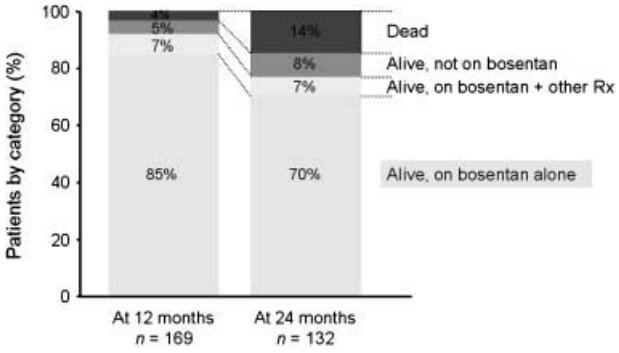

Figure 2 Vital status and treatment at 12 and 24 months of follow up in the bosentan cohort. All 169 patients were followed for 12 months; 132 patients were followed for at least 24 months. Percentages are based on the number of patients followed. Adapted with permission from McLaughlin *et al.* 2005 [14].

Survival analysis 3: first-line bosentan in IPAH class III patients vs. a retrospective cohort on first-line epoprostenol

The survival data of the two prospective, double-blind, placebo-controlled bosentan studies and their open-label extensions were also compared with a cohort of patients that received epoprostenol as initial treatment [19]. The data on epoprostenol were taken from patient records in five major referral centres which also participated in the bosentan trials. To ensure comparability of regimens, the analysis was restricted to 139 bosentan and 346 epoprostenol IPAH patients in WHO functional class III. While demographics were similar in both cohorts, patients in the epoprostenol cohort had more severe disease (lower 6-min walk test of 335 vs. 351 metres) and a lower cardiac index (2·0 vs. 2·4 L min^{-1} m^{-2}). Kaplan-Meier survival estimates in the bosentan cohort at 1 and 2 years were 97% and 91%, respectively, and in the epoprostenol cohort were 91% and 84%, respectively (log-rank *P*-value = 0·022). Cox regression to adjust for differences in baseline factors showed a greater probability of death in the epoprostenol cohort (hazard ratios: 2·3, $P = 0·006$ independent step-wise model, 1·7–2·7 alternate analyses). In all Cox regression models used, the probability of death was never higher in the bosentan cohort compared with the epoprostenol cohort, regardless of the factors imputed for adjustment. In a matched-pair analysis of cohorts of 83 patients in each, survival estimates of bosentan and epoprostenol were nearly identical (Fig. 3). In the bosentan cohort, 87% and 75% of patients followed for 1 and 2 years, respectively, remained on monotherapy [18].

Discussion

In all current, randomized, placebo-controlled trials investigating disease-specific therapy for PAH, such as bosentan,

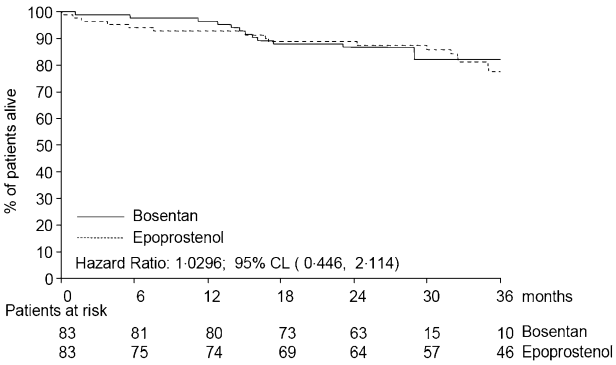

Figure 3 Kaplan-Meier survival curves for matched cohorts of functional class III patients with idiopathic pulmonary arterial hypertension (PAH) treated with bosentan or epoprostenol. Kaplan-Meier survival curves for class III idiopathic PAH patients treated with bosentan (solid line) or epoprostenol (dashed line) – a matched pair analysis. CL, confidence limits. From Sitbon *et al.* with permission [19].

epoprostenol, beraprost, treprostinil, sildenafil and others, treatment duration was short and exercise-related endpoints were chosen as the primary end point, usually the 6-min walk test [5]. Immediate relief by symptomatic improvements is important for the patient; however, other treatment goals are equally or more important. The patient's perspective is reflected by measurements of quality of life, which has been increasingly addressed in clinical studies, including those regarding bosentan [20]. But these are first steps, and augmenting survival is the paramount goal [21].

In patients with a significant acute response to a short-acting vasodilator, calcium-channel blocker (CCB) treatment, usually in IPAH patients in WHO functional class II or III, has been shown to increase survival compared with historical data in a limited number of adults or children, respectively [22–24]. However, only approximately 10–20% of adults respond and an even lower proportion gain a sustained benefit from CCB therapy [22,25].

Chronic intravenous epoprostenol (synthetic prostacyclin) has previously been shown to improve prognosis: in a series of uncontrolled studies in WHO functional class III or IV, survival was improved compared with historical controls [24,26–28]. Furthermore, a randomized, controlled trial showing improved survival has also been published but is limited to severe cases followed up over 12 weeks [29]. In the two recent cohort analyses of IPAH patients, the one conducted at our institution revealed an observed survival with epoprostenol at 1, 2, 3 and 5 years of 88%, 76%, 63% and 47%, respectively [26]. In the other series, at Béclère/Clamart, the corresponding rates were 85%, 70%, 63% and 55%, respectively [27]. Currently, epoprostenol is recommended as first-line for patients with WHO class III and IV [1,30]. However, the drug is costly, inconvenient and associated with major morbidity, especially owing to catheter-based infections. The inhaled prostacyclin alternative iloprost, which has a longer half-life and is less expensive than epoprostenol, has shown improvement in symptoms and haemodynamics in IPAH for up to 2 years [31], but in a recent 5-year study only a minority of patients could be stabilized on first-line iloprost monotherapy [4]. The oral prostacyclin beraprost did not improve survival [3].

Against the background of the considerable limitations of existing therapies, it is of major importance that the ET receptor antagonist bosentan shows a favourable effect on survival that seems at least comparable to that of epoprostenol in WHO class III IPAH patients. As ethical and practical considerations prevent placebo-controlled long-term trials, the predicted survival is calculated based on a regression equation. This equation was developed in the 1980s from the large NIH registry of PPH patients to predict the survival chances of patients on the basis of haemodynamic variables [15]. It has been validated in an independent series of patients [16] and still represents the best available tool for long-term survival analysis [32]. Thus, it was used in subsequent indirect comparisons with patients treated with various PAH drugs as well as in the bosentan dataset described earlier [4,14,26–28]. The predictive value of the NIH formula, however, may be compromised by an improvement of standards of care for PAH therapy (e.g. earlier diagnosis, improved background therapy such as widespread use of anticoagulation). Other issues to be considered in the interpretation of the data are the limited number of bosentan patients that have been followed for 3 years and the low number of patients in WHO functional class IV. There were various add-on or switch therapy strategies that were possible in addition to bosentan monotherapy, which may have contributed to the overall treatment effect [32]. Nevertheless, this reflects the current, practical approach to the medical therapy of PAH.

Survival in bosentan-treated patients was lower in SSc patients than in IPAH patients, which confirms earlier data from untreated SSc patients reported by Koh *et al.* [18] and data from patients treated with current medical therapies by Kawut *et al.* [33] Although the results in the small dataset on bosentan did not reach significance, they indicated both improvements in exercise capacity as well as enhanced prognosis. In conclusion, the present analyses suggest that first-line bosentan therapy, followed by the addition of other disease-specific therapies as required, improves survival in patients with advanced PAH.

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