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ORIGINAL CLINICAL SCIENCE

Predictors of long-term survival in pulmonary hypertension treated with bosentan

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KEYWORDS:
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BACKGROUND: Pulmonary arterial hypertension (PAH) is associated with decreased functional capacity, right ventricular failure and often early death. The recent introduction of advanced therapies has brought new opportunities for patients with PAH. In The Netherlands, bosentan is distributed in a controlled fashion through a single pharmacy. This allows for the registration and prospective follow-up of all patients in a central database. The aim of this study was to evaluate the 6-year survival rates of all Dutch PAH patients treated with bosentan.

METHODS: We analyzed the 6-year survival characteristics of the entire Dutch cohort of idiopathic PAH (iPAH; $n = 209$), collagen vascular disease–associated PAH (CVD-PAH; $n = 161$), congenital heart disease–associated PAH (CHD-PAH; $n = 224$) and inoperable chronic thromboembolic pulmonary hypertension (iCTEPH; $n = 175$) patients, who treated with bosentan between 2002 and 2009.

RESULTS: A total of 913 patients were treated with bosentan during the study period. Altogether, 769 patients were included for analysis. Survival rates (for all indications) at 1, 3 and 6 years, respectively, were as follows: overall, 90.7% ($n = 486$), 78.4% ($n = 261$) and 57.9% ($n = 34$); for iPAH, 86.9%, 71.8% and 54.6%; for CVD-PAH, 85.7%, 65.1% and 37.3%; for CHD-PAH, 93.5%, 87.9% and 64.2%; and for iCTEPH, 95.3%, 84.5% and 68.7%. Multivariate analysis showed iCTEPH, female gender, younger age, treatment initiation after 2006 and treatment at an expert center to all be independently and significantly correlated with better outcome.

CONCLUSIONS: This is the first study on a national scale to show 6-year survival rates of bosentan-treated patients for three major PAH and iCTEPH subgroups. Survival rates in the respective subgroups from the Dutch bosentan cohort are comparable to earlier reported rates from selected patient cohorts.

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Pulmonary arterial hypertension (PAH) is a rare syndrome with dyspnea, fatigue, chest pain and syncope caused by a progressive increase in pulmonary vascular resistance (PVR) and defined by a sustained elevation of mean pulmonary arterial pressure to >25 mm Hg at rest.[1] It is

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clinically characterized by progressive dyspnea, decreased functional capacity and right ventricular failure, and is associated with a shortened life expectancy.[2,3] PAH is either idiopathic or occurs in association with a series of conditions, including collagen vascular disease (CVD), congenital heart disease (CHD) with systemic-to-pulmonary shunt,[4,5] portal hypertension, human immunodeficiency virus (HIV) infection and persistent pulmonary hypertension of newborns.[3]

Despite advances brought about by the introduction of specific therapies during the past decade,[6] the prognosis of PAH remains poor, with estimated survival rates of approximately 50% for idiopathic PAH (iPAH), and 80% for CHD-PAH at 5 years and 50% for CVD-PAH at 2 years.[7] Chronic thromboembolic pulmonary hypertension (CTEPH) is another major cause of pulmonary hypertension and results from incomplete resolution of the vascular obstruction caused by pulmonary thromboembolism.[8] The prognosis of untreated CTEPH is poor, much like PAH, but the condition is surgically curable in approximately 50% to 60% of patients.[8–10] CTEPH has been estimated to occur in approximately 1% to 4% of patients within 2 years after a first episode of symptomatic pulmonary embolism,[11] which equates to up to 20,000 cases per year in the USA.[12,13] Success has been achieved with the use of therapies targeted against the underlying pathophysiologic pathways that unite the aforementioned forms of pulmonary hypertension.[14–16] The dual endothelin receptor antagonist bosentan was the first oral drug to demonstrate improvement in hemodynamics and exercise capacity in patients with PAH in WHO Functional Classes II, III and IV.[17–20] The aim of this study was to evaluate the 6-year survival rates of all Dutch PAH patients treated with bosentan.

Methods

Study subjects

All bosentan-treated patients with either PAH or inoperable CTEPH (iCTEPH) from January 2002 to December 2009 were included in a post-marketing surveillance registry. For each patient, the following data were collected: a unique identifying number; date of birth; name of the prescribing physician and hospital affiliation; indication (diagnosis); date of bosentan delivery (the assumed treatment start date); date of last bosentan delivery (the assumed treatment discontinuation date); and the reason for discontinuation.

Data collection

Bosentan has been available in The Netherlands since 2002, and obtained a position as first-line oral therapy for PAH patients with New York Heart Association (NYHA) Functional Class III status. The Dutch health insurance system has approved reimbursement of bosentan for PAH and iCTEPH patients in NYHA Classes III and IV. Bosentan is distributed in a strictly controlled fashion. This allows for the registration and prospective follow-up of all patients in a central database. Prescriptions are distributed through a single pharmacy, directly to the patient's home, or, in cases of hospital admission, to the hospital pharmacist on a named-patient basis. The diagnosis of PAH and iCTEPH was established following the most recent expert consensus algorithms.[1,6,21] Upon new prescriptions (new diagnoses) or safety signals (e.g., treatment discontinuation or dose change), the prescribing physician was contacted by the manufacturer to collect the relevant information. The anonymous data were collected for each individual patient within a data warehouse.

Statistical analysis

Statistical analyses were conducted to determine survival from start of bosentan treatment and discontinuation per subgroup (iPAH, CVD-PAH, CHD-PAH and iCTEPH). Results are expressed as mean ± SD for descriptive data. Differences in outcome measures and hazard ratios were analyzed using a linear regression model in which explanatory variables were entered into a stepwise regression model. Survival curves were estimated using the Kaplan–Meier method, and differences were analyzed using Pearson's chi-square test. For all statistical analyses $p < 0.05$ was considered significant. To determine survival differences in time, we divided the follow-up period into treatment initiation before and after 2006. We chose 2006 because sildenafil became available as advanced therapy for PAH and combination with bosentan was introduced during that year. Analyses were performed on treatment discontinuation per indication. The corresponding p-values indicate significant differences between a distinct PAH indication and the combination of all other indications.

Results

Patient demographics

A total of 913 patients were exposed to bosentan during the study period (Figure 1). Altogether, 769 patients were included for analysis; 136 patients were treated for other indications and 8 had insufficient data to allow analysis (see flow diagram). Patient were recruited from 8 university-based expert centers and 26 community centers lo-

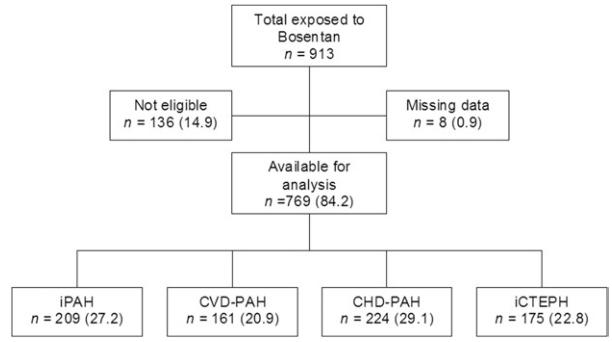

Figure 1 Patient inclusion. iPAH, idiopathic pulmonaryarterial hypertension; CVD-PAH, connective tissue disease–associated PAH; CHD-PAH, congenital systemic-to-pulmonary shunt/congenital heart disease–associated PAH; iCTEPH, inoperable chronic thromboembolic pulmonary hypertension. Percentages are showed in parentheses.

Table 1 Baseline Characteristics

Variable	Total group (n = 769)	Patients alive (n = 614; 79.8%)	Patients who died (n = 155; 20.2%)
Female, n (%)[a]	516 (67.1)	418 (81)	98 (19)
Age, mean (SD), years	53.3 (19.3)	52.1 (19.0)	58.2 (20.0)
Indication, n (%)			
iPAH	209 (27.2)	163 (78.0)	46 (22.0)
CVD-PAH	161 (20.9)	111 (68.9)	50 (31.1)
CHD-PAH	224 (29.1)	190 (84.8)	34 (15.2)
iCTEPH	175 (22.8)	150 (85.7)	25 (14.3)
NYHA functional class, n (%)			
II	10 (1.3)	9 (90)	1 (10)
III	737 (95.8)	593 (80.5)	144 (19.5)
IV	22 (2.9)	12 (54.5)	10 (45.5)
Bosentan initiation before 2006, n (%)	337 (43.8)	230 (68.2)	107 (31.8)
Patients treated at expert centers, n (%)	715 (93.0)	579 (81.0)	136 (19.0)

Values in parentheses in the second and third columns are percentages within the variable. CHD-PAH, congenital heart disease pulmonary arterial hypertension; CVD-PAH, collagen vascular disease pulmonary arterial hypertension; iCTEPH, inoperable chronic thromboembolic pulmonary hypertension; iPAH, idiopathic pulmonary arterial hypertension; NYHA, New York Heart Association.

[a]Gender was unknown in 4 patients.

cated throughout the country. The mean age of all included patients was 53 ± 19 years (range 0 to 90 years), and 21% were >71 years of age. Baseline characteristics are presented in Table 1. The mean duration of follow-up was 40.3 months, representing a total of 2,582 patient-years. A total of 155 patients died during the follow-up period, giving a cumulative mortality rate of 6.0 deaths per 100 patient-years. In total, 155 patients died and 230 patients discontinued treatment during follow-up. Forty patients stopped due to increased liver transaminases. Table 2 summarizes the reasons for discontinuation per indication. Bosentan treatment was more often discontinued in iPAH patients compared with the other subgroups ($p < 0.001$). Discontinuation due to lack of response was significantly higher in the CVD-PAH patients compared with all other indications combined ($p = 0.04$). Discontinuation due to increased liver transaminases was more frequently observed in patients with CVD-PAH ($p = 0.04$) and less frequently in patients with CHD-PAH ($p = 0.03$). The mean time from initiation of treatment to the moment of discontinuation, however, did not differ between the groups, and varied from 6 to 17 months. The rates of all-cause treatment discontinuation after 6 years of follow-up were: 62.7% for CVD-PAH; 62.7% for iPAH; 41.7% for iCTEPH; and 35.7% for CHD-PAH.

Table 2 Treatment Discontinuation

	Total group (n = 385)	iPAH (n = 131)	CVD-PAH (n = 102)	CHD-PAH (n = 79)	iCTEPH (n = 73)
Death	155 (40.3)	46	50[d]	34[b]	25[b]
Alive patients who discontinued	230 (59.7)	85[d]	52	45[d]	48
Unknown	43 (11.1)	16	10	10	7
Increased liver transaminases	40 (10.4)	16	14[b]	3[b]	7
Switch to other therapy[a]	32 (8.3)	13	4	4	11[b]
No response on bosentan	29 (7.5)	11	11[b]	5	2[b]
Patient request	26 (6.8)	9	4	11[c]	2
Adverse event/drug reaction	17 (4.4)	7	4	3	3
Operation	9 (2.3)	1	0	0	8[d]
Lung transplantation	6 (1.6)	1	0	1	4[b]
Lost to follow-up	4 (1.0)	1	1	1	1
Hospitalization	4 (1.0)	1	0	0	3[b]
Miscellaneous	20 (5.2)	9	4	7	0[c]

Percentages are presented in parentheses.

[a]There were 24 patients switched to epoprostenol, 8 patients to sildenafil.

[b]$p < 0.05$,

[c]$p < 0.01$,

[d]$p < 0.001$.

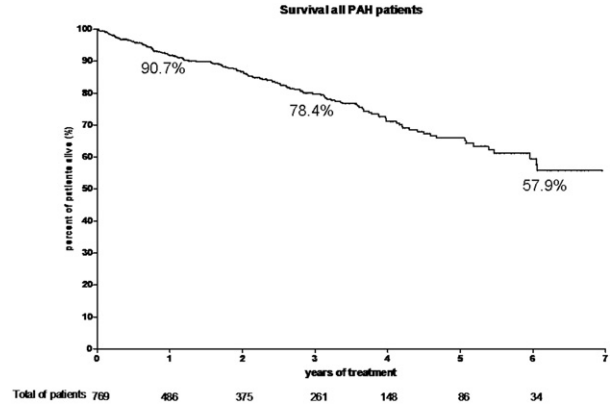

Figure 2 Survival of all PAH patients. PAH, pulmonary arterial hypertension.

Survival and risk factors

Kaplan–Meier estimates of overall survival at 1, 3 and 6 years were 90.7%, 78.4% and 57.9%, respectively (Figure 2). One-, 3- and 6-year survival rates per indication were as follows: iPAH, 86.9%, 71.8% and 54.6%; CVD-PAH, 85.7%, 65.1% and 37.3%; CHD-PAH, 93.5%, 87.9% and 64.2%; and iCTEPH, 95.3, 84.5% and 68.7% (Figure 3), respectively. Survival rate by age groups is presented in Figure 4. For the combined end-point of treatment discontinuation (death, switch to other therapy, adverse events), the 1-, 3- and 6-year estimates were 69.2%, 53.0% and 34.9%, respectively. In the multivariate analysis, iCTEPH, female gender, younger age at treatment initiation, treatment initiation after 2006 and treatment at an expert center were independently and significantly correlated with favorable survival (Table 3). Younger age at treatment initiation correlated with improved survival in adult patients. However, children (patients between 0 and 17 years of age) showed survival rates similar to those of patients between 61 and 70 years of age (Figure 4).

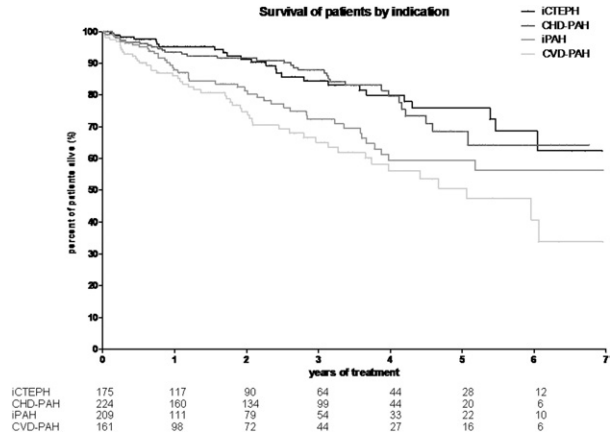

Figure 3 Survival of patients by indication. iPAH, idiopathic pulmonary arterial hypertension; CVD-PAH, connective tissue disease–associated PAH; CHD-PAH, congenital systemic-to-pulmonary shunt/congenital heart disease–associated PAH; iCTEPH, inoperable chronic thromboembolic pulmonary hypertension.

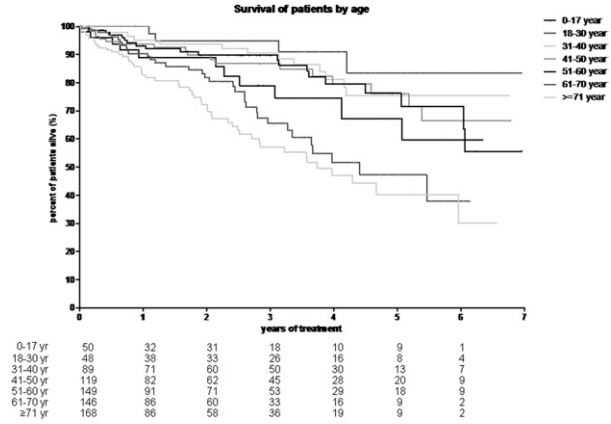

Figure 4 Survival of patients by age.

Discussion

In this study we have reported observed 6-year survival of 769 patients with PAH and iCTEPH who were treated with bosentan. Three major groups with PAH (iPAH, CVD-PAH and CHD-PAH) and iCTEPH were included in this study. Our unique registry provides clinical data in a "real-life" setting of an unbiased and comprehensive bosentan patient cohort, which is representative of the entire Dutch PAH population, except for iCTEPH patients, for whom treatment was initiated exclusively by expert centers.[22]

Our main finding was that overall 6-year survival was 57.9%, with worst outcome for the CVD-PAH subgroup, which had a 6-year survival of only 37.3%. Most published PAH studies featured single-center or single-indication observations using mixed treatment regimens; moreover, most studies were retrospective in design and with a relatively short follow-up. There has been a paucity of data on long-term survival data of PAH patients.[23] The survival rates of bosentan-treated PAH in the present study were generally comparable to previously reported observations,[7,24–27] with the expected worst prognosis for the CVD-PAH subtype.[28,29] Keogh et al recently published survival data from a comparable Australian bosentan registry consisting 528 patients with either iPAH or CVD-PAH and reported an overall 2-year survival of 89%.[23] Two-year survival in our cohort was somewhat lower at 74% and 80% in the iPAH and CVD-PAH patients, respectively. However, in the present study, iPAH observations were strikingly similar to those recently reported by Thenappan et al.[30] The observed 1-year survival of 95% in bosentan-treated iCTEPH patients is comparable with other studies.[31,32]

The present study has confirmed previously reported mortality data about PAH, with the best prognosis for CHD-PAH and iCTPEH and worst prognosis for CVD-PAH. The reason for the better survival in iCTEPH patients remains unclear. The iCTEPH patients were exclusively treated at expert centers; however, both iCTEPH and treatment at an expert center were independent predictors for better survival. This might be explained, at least in part, by a difference in pathophysiology in CTEPH compared with PAH, with CTEPH patients showing a decreased tendency for plexiform lesion formation, despite some overlapping mor-

Table 3 Independent Predictors for Survival

	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.03	1.02–1.04	<0.001	1.03	1.02–1.04	<0.001
Indication iCTEPH vs no iCTEPH	0.58	0.38–0.89	<0.05	0.41	0.26–0.64	<0.001
Female gender	0.73	0.53–1.01	0.06	0.59	0.42–0.83	<0.01
Bosentan initiation in or after 2006 vs before 2006	0.62	0.43–0.89	<0.01	0.62	0.43–0.90	<0.01
Expert vs community centers	0.30	0.18–0.48	<0.001	0.49	0.30–0.82	<0.01
Indication CVD-PAH vs no CVD-PAH	2.00	1.43–2.81	<0.001			
Indication CHD-PAH vs no CHD-PAH	0.59	0.40–0.87	<0.01			
Indication iPAH vs no iPAH	1.34	0.96–1.92	0.08			

CHD-PAH; pulmonary arterial hypertension associated with congenital heart disease; CVD-PAH; collagen vascular disease pulmonary arterial hypertension; HR; hazard ratio, iCTEPH; inoperable chronic thromboembolic pulmonary hypertension; iPAH, idiopathic pulmonary arterial hypertension.
[a]Using a stepwise regression model excluding NYHA functional class.

phologic lesions.[32] Furthermore, our results show better survival in female patients. Launay et al, however, did not observe a gender-related difference in 3-year survival in patients with systemic sclerosis-associated PAH.[26] In two other studies, sub-analyses of the influence of gender on survival were not reported.[23,30]

Younger age at treatment initiation correlated with improved survival in adult patients. However, children showed less favorable survival. In total, 11 of 50 (22%) children in this registry died after a 6-year follow-up. The worse outcome in the children was likely caused by a more severe, rapidly progressing disease in childhood. van Loon et al compared treatment response to bosentan in adults versus children with CHD-PAH and demonstrated that the decline in treatment effect was most pronounced in the children. Moreover, at baseline, children tended to have more severe disease.[16] As expected, life expectancy was found to be decreased in patients >70 years of age.

Another noteworthy observation is the significant survival benefit in patients with treatment initiation after 2006, particularly in patients with CVD-PAH and iPAH. Such an improvement in prognosis may have resulted from earlier diagnosis, a multidisciplinary approach to treatment of the disease, and a greater awareness of expert opinion in the treatment of patients. Moreover, sildenafil became available for PAH therapy during the course of 2006 and combination therapy is fully reimbursed in The Netherlands. Thus, combination therapy with bosentan and sildenafil may have contributed to the better survival after 2006. However, until now, there have been no large, randomized, controlled trials to support this hypothesis, although smaller studies reported that combination treatments improve clinical status and survival.[33,34]

We also observed better survival when patients were treated at expert centers. This finding supports the recommendation of the European Cardiology Society expert consensus guidelines to refer PAH patients to dedicated PH clinics with experience and expertise in the management of the disease.[35] A number of discontinuation reasons were observed among the PAH subgroups. Interestingly, discontinuation due to increased liver transaminases occurred most frequently in patients with CVD-PAH, and was observed in 9% of the patients. This observation, however, is in line with the study by Launay et al, where bosentan treatment was permanently stopped in 10% of CVD-PAH patients due to elevated liver transaminases.

Limitations

There are several limitations to this study that should be acknowledged. Due to the design of the drug registry, our investigation was limited by the lack of hemodynamic data such as pulmonary vascular resistance and pulmonary artery pressure. Confirmed diagnosis by right heart catheterization could not be verified in this cohort. However, Dutch centers adhere closely to the current guidelines for the diagnosis and treatment of PAH and iCTEPH, so an overestimation related to less strict diagnostic procedures appears unlikely. Therefore, we may assume that PAH diagnosis was made after right heart catheterization, except probably for some patients with Eisenmenger syndrome (ES), in whom right heart catheterization is not routinely performed as PH is clearly evident on echocardiography. ES patients are known to be at high risk for complications due to this invasive procedure. A second limitation is that relevant data on baseline characteristics are missing, such as time to PAH diagnosis and failure of prior therapy, causes of death, and reporting of possible co-medication with other advanced PAH therapies. At the start of the study and/or during the study period, prostanoids, sildenafil and also other endothelin receptor antagonists (sitaxentan, ambrisentan) were available in The Netherlands. There seems to be an underrepresentation of patients with NYHA Class IV status. In the study by Keogh et al, 19% of their patients were in NYHA Class IV, compared with 4% in the present study.[23] This difference was caused by the prescription-derived design of the registry, as Dutch PAH patients with NYHA Class IV are predominantly treated with epoprostenol intravenously.

In conclusion, this is the first time that 6-year survival rates of bosentan-treated patients for three major subgroups of PAH and iCTEPH have been reported on a national and comprehensive scale. iCTEPH, female gender, treatment at an expert center, younger age at treatment initiation and treatment initiation after 2006 were all found to be independently and sig-

nificantly correlated with better survival. Survival rates in the respective subgroups from the Dutch cohort are comparable to earlier reported rates from selected patient cohorts. Although CHD-PAH and iCTEPH patients have a relatively acceptable prognosis, there is still ample room for improvement among patients with iPAH and CVD-PAH.

Disclosure statement

The first two authors (P.B. and J.C.V.) contributed equally to this study. We thank J. Pfeil (Estimate Medical Statistics BV) for performing statistical analyses. This work was supported by Actelion Pharmaceuticals Nederland B.V. Actelion also provided the data from their national registry for this research.

The authors have no conflicts of interest to disclose.

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