Ambrisentan Improves Exercise Capacity and Symptoms in Patients with Portopulmonary Hypertension

Ambrisentan verbessert die Belastbarkeit und Symptomatik bei Patienten mit portopulmonaler Hypertonie

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Schlüsselwörter
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- cirrhosis
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- pulmonary hypertension

Zusammenfassung

Einleitung: Ambrisentan, ein selektiver Endothelinrezeptor-Antagonist, ist in vielen Ländern zur Therapie der pulmonal-arteriellen Hypertonie zugelassen. Daten, die eine verbesserte Belastbarkeit bei Patienten mit einer portopulmonalen Hypertonie (PoPH) zeigen, wurden bisher nicht publiziert.

Patienten und Methoden: Wir untersuchten retrospektiv die Sicherheit und Effektivität von Ambrisentan bei Patienten mit einer PoPH. Die Untersuchung erfolgte an 4 deutschen Universitätskliniken.

Ergebnisse: 14 Patienten mit einer moderaten bis schweren PoPH wurden eingeschlossen. Die mediane Beobachtungszeit betrug 16 Monate (IQR, 12 – 21). Nach 6 und 12 Monaten stieg die Gehstrecke im 6-Minuten-Gehtest signifikant von 376 Meter (IQR, 207 – 440) vor Therapiebeginn auf 415 Meter (IQR, 393 – 475; p = 0,011) bzw. auf 413 Meter (IQR, 362 – 473, p = 0,005) an. Die WHO-Funktionsklasse verbesserte sich ebenfalls signifikant (p = 0,014). Die Blutgasanalysen und die Leber-Funktionstests (Aspartat-Aminotransferase, Alanin-Aminotransferase, Total-Bilirubin, International Normalized Ratio) wurden nicht signifikant durch die Ambrisentantherapie beinflusst.

Schlussfolgerung: Die vorliegende Studie zeigt eine Verbesserung der Belastbarkeit und der Symptomatik unter Therapie mit Ambrisentan bei Patienten mit einer PoPH ohne Hinweise auf relevante Nebenwirkungen.

Abstract

Introduction: Ambrisentan, a selective endothelin receptor antagonist has been approved in several countries for pulmonary arterial hypertension. No data have been published on the efficacy of ambrisentan on improvement of exercise capacity in patients with portopulmonary hypertension (PoPH).

Patients and Methods: We retrospectively analyzed the safety and efficacy of ambrisentan in patients with PoPH in four German university hospitals.

Results: 14 patients with moderate to severe PoPH were included. The median follow-up was 16 months (IQR, 12 – 21). 6 minute walk tests after 6 and 12 months improved from 376 meters (IQR, 207 – 440) at baseline to 415 meters (IQR, 393 – 475; p = 0.011) and 413 meters (IQR, 362 – 473, p = 0.005), respectively. WHO- functional class after 1 year of therapy with ambrisentan also improved significantly (p = 0.014). No significant changes in blood gas analysis and liver function tests (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and international normalized ratio) during therapy with ambrisentan were detectable.

Conclusions: The present study demonstrates significant improvement of exercise capacity and clinical symptoms without relevant safety concerns during ambrisentan treatment in patients with PoPH.

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Introduction

Portopulmonary hypertension (PoPH) is a unique disorder characterized by the presence of both portal hypertension and pulmonary arterial hypertension (PAH) [1 – 3]. As cirrhosis is the most common cause of portal hypertension, PoPH is typically seen in patients with cirrhotic liver disease although it also occurs in patients with non-cirrhotic portal hypertension. The pathogenetic link between portal and pulmonary hypertension is still unknown, especially as only 1 – 6%

of patients with portal hypertension develop pulmonary arterial hypertension [1, 4].

Left untreated, PoPH carries a poor prognosis with 1-year mortality rates ranging between 24 and 60% [5]. In most referral centers, these patients are now being treated similarly to those with other forms of PAH, i.e., with phosphodiesterase (PDE)-5 inhibitors, prostacyclin derivatives and endothelin receptor antagonists (ERAs) [4–9]. Patients with PoPH, however, have usually been excluded from randomized, controlled clinical trials so that the safety and efficacy of these drugs has not been thoroughly investigated in this patient population. Small, uncontrolled case series have suggested that the non-selective endothelin receptor A (ET_A) and B (ET_B) antagonist bosentan may have beneficial effects in patients with PoPH and mildly impaired liver function, i.e., Child class A [5, 9]. Although bosentan was found to be safe in these series, the drug has a well-recognized hepatotoxic potential [10]. We therefore explored the safety and efficacy of ambrisentan, a selective ET_A antagonist with a low risk of liver toxicity [11].

Patients and Methods

A retrospective cohort study of newly diagnosed PoPH patients who were referred to four German university hospitals (University Hospitals of Dresden, Greifswald, Hannover and Leipzig), and started with ambrisentan treatment before January 1st 2010 was performed. The analysis was based on medical record reviews. All patients were carefully informed about the lack of clinical experience with ambrisentan in PoPH, and gave informed consent. There was no formal study protocol, and treatment of patients was performed at the discretion of their local specialist physicians. All patients were seen in the outpatient clinics of the university hospitals at about 3-monthly intervals for clinical investigation, including assessment of World Health Organization (WHO) functional class (FC), exercise tests and laboratory controls including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, international normalised ratio (INR), creatinine and N-terminal pro-brain natriuretic peptide (NTpro-BNP) levels.

Right heart catheterization during follow-up was performed at the discretion of the local physician. The diagnosis of PoPH was established by clinical evidence of portal hypertension and/or liver cirrhosis by hepatologists together with an elevated PAPm (≥ 25 mmHg), elevated PVR (> 240 dyn × s × cm^{-5}) and an elevated transpulmonary gradient (> 12 mmHg; PAPm – pulmonary capillary occlusion pressure) confirmed during right-heart catheterization, according to the diagnostic criteria reported by Krowka [12]. Other forms of pulmonary hypertension with elevated PVR were excluded by scintigraphy (chronic thromboembolic pulmonary hypertension), echocardiography and right heart catheterization (left heart disease, congenital systemic-to-pulmonary shunts), computed tomography of the lung and pulmonary function studies (lung disease) and serological testing (connective tissue disease, HIV infection) according to the European guidelines for the diagnosis and treatment of pulmonary hypertension [13]. Exercise capacity was examined by six-minute walk distance (6-MWD) and/or by cardiopulmonary exercise testing (CPT). 6-MWD was performed not encouraged according to American Thoracic Society recommendations [14] and CPT was performed symptom-limited on a cycle ergometer, following a standardised protocol [15].

Statistical analysis

All continuous data are summarized as medians (interquartile range, IQR). Categorical data are summarized as medians (interquartile range, IQR). Categorical data are given as percentages. Differences between baseline and follow-up were tested with Wilcoxon`s sign rank test (if the number of available measurements was n = 6 or more). Marginal homogeneity test was used to evaluate changes in the WHO-FC. A p value of < 0.05 (two-sided) was considered statistically significant. SPSS software (version 17.0) was used for all analyses.

Results

15 PoPH patients were identified as being treated with ambrisentan before January 1st 2010 in four German tertiary care referral centers for patients with pulmonary hypertension. All but one patient were enrolled. The patient who was excluded was initially in WHO FC IV and ambrisentan therapy was simultaneously started with sildenafil and inhaled iloprost and an initial exercise test was missing. The main etiology of portal hypertension was cirrhosis (13 cases, 93%), one other case had portal vein thrombosis. The most common etiology of cirrhosis was alcohol (8 cases, 62%), followed by cryptogenic cirrhosis (3 cases, 23%) and one case each of hepatitis B and primary biliary cirrhosis. Before starting therapy with ambrisentan, 3 patients had a history of treatment for variceal bleeding and 6 for ascites. The baseline clinical and hemodynamic characteristics of the patients are depicted in **Table 1**.

Overall, 14 patients were treated with ambrisentan. In 13 of them, ambrisentan was started as initial PAH therapy; one patient received ambrisentan in addition to sildenafil. In one additional patient tadalafil was added after 6 months of ambrisentan therapy because of insufficient clinical improvement; all other patients remained on ambrisentan monotherapy. The median follow-up was 16 months (IQR, 12 – 21). One patient discontinued ambrisentan after 4 weeks due to peripheral oedema, which resolved after the drug had been discontinued. No other patient stopped ambrisentan therapy due to side-effects. The daily doses of ambrisentan at the end of the observation time were 5 mg in 9 patients and 10 mg in 4 patients.

Two patients died during the study period, one from liver failure and one presumably from right heart failure. The patient who died from liver failure was female, suffered from cryptogenic cirrhosis and the median model for end-stage liver disease score (MELD score) was 16 when PoPH was diagnosed and treatment with ambrisentan initiated. Dyspnoea initially improved and VO_2 peak value increased from 8.2 to 10.3 mL/kg/min after 6 months of therapy with 5 mg ambrisentan, but 11 months after initiating this treatment the patient presented with progressive and finally therapy-resistant ascites without other signs of a possible right heart failure and without increased transaminases. Ambrisentan was discontinued and decompensated liver cirrhosis was diagnosed by the presence of deteriorating liver synthesis parameters. Two months later, the patient died due to progressive hepatic dysfunction. An offered liver or liver-lung transplantation was refused by the patient.

Liver failure was considered by the physician in charge to be unrelated to ambrisentan therapy as aminotransferase levels remained within the normal range throughout drug exposure. The origin of liver failure remained unclear. No other patient suffered from cirrhotic complications during the study period.

Table 1 Baseline characteristics of 14 patients with diagnosed porto-pulmonary hypertension.[1]

clinical characteristics	n = 14 patients
age (years), median (IQR)	57 (46 – 63)
female gender, n (%)	9 (64 %)
BMI (kg/m²), median (IQR)	30 (25 – 33)
cirrhosis, n (%)	13 (93 %)
alcoholic cirrhosis, n	8 (62 %)
MELD score, median (IQR)	10 (9 – 13)[2]
Child A classification, n (%)	12 (86 %)
6 MWD (m), median (IQR)	360 (227 – 435)[3]
VO_2peak (mL/kg/min), median (IQR)	12,7 (9.7 – 15.3)[4]
FVC (% predicted), median (IQR)	92 (70 – 106)
FEV1 (% predicted), median (IQR)	72 (61 – 83)
paO_2 (mm Hg), median (IQR)	66 (57 – 72)
$paCO_2$ (mm Hg), median (IQR)	32 (29 – 35)
DLCO (%predicted), median (IQR)	64 (47 – 83)
WHO functional class, median (IQR)	3 (2.8 – 3.0)
NT-proBNP (pg/mL) median (IQR)	1118 (134 – 2 331)[3]
PAPm (mm Hg), median (IQR)	44 (40 – 53)
RAP (mm Hg), median (IQR)	7 (4 – 12)[2]
cardiac output (L/min), median (IQR)	4.2 (3.6 – 5.2)[3]
PAOP (mm Hg), median (IQR)	7.5 (6.5 – 12.5)
PVR (dyn s cm^{-5}), median (IQR)	741 (516 – 809)[3]

[1] IQR: interquartile range, n: number, BMI: body mass index, MELD: model for endstage liver disease, 6 MWD: 6 minute walk distance, VO2peak: peak oxygen uptake, FVC: forced vital capacity, FEV1: forced expiratory volume in one second, paO2: partial oxygen tension, paCO2: partial carbon dioxide tension, DLCO: carbon monoxide diffusing capacity, WHO: World Health Organization, NT-proBNP: N terminal pro brain natriuretic peptide, PAPm: mean pulmonary arterial pressure, RAP: right atrial pressure, PAOP: pulmonary arterial occlusion pressure, PVR: pulmonary vascular resistance.

[2] N = 13.

[3] N = 12.

[4] N = 8.

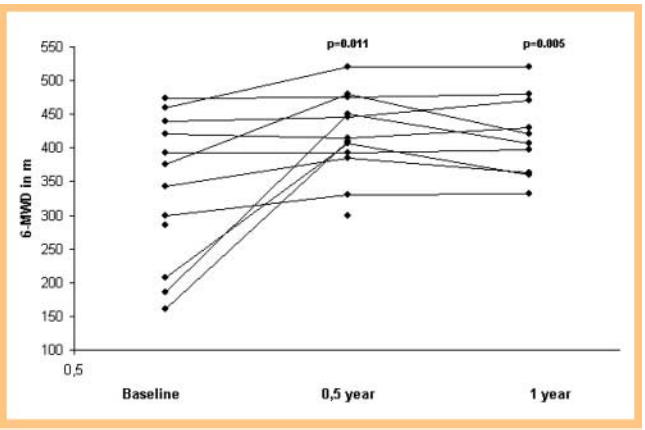

Fig. 1 6-minute walk distances before and after initiating therapy with ambrisentan.

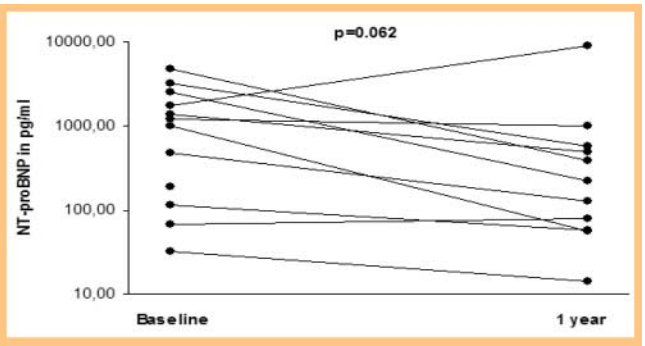

Fig. 2 NT-proBNP levels at baseline and during follow-up.

The patient who died from right heart failure had been non-compliant with his therapy and stopped ambrisentan approximately two months before his death.

Follow-up examinations of 6-minute walk tests after 6 and 12 months performed in 11 and 10 patients, respectively, revealed an apparent clinical benefit from ambrisentan treatment. After 6 months, the 6 MWD increased from 376m (IQR, 207 – 440; n = 11) at baseline to 415 meters (IQR, 393 – 475; p = 0.011 versus baseline); after 1 year, the 6 MWD results were virtually unchanged (413m; IQR, 362 – 473; p = 0.005 versus baseline; n = 10) as shown in **Fig. 1**. WHO-FC data after 1 year of therapy with ambrisentan were available from 11 patients. Initially, 3 of them presented in WHO-FC II, 7 in WHO-FC III, and 1 in WHO-FC IV. After 12 months, 1 patient was in WHO-FC I, 6 patients in WHO-FC II and 4 patients in WHO-FC III (p = 0.014 versus baseline).

Data from cardiopulmonary exercise testing at baseline and during follow-up were available from 6 patients. Peak VO_2 at baseline was 12.7 mL/kg/min (IQR, 8.9 – 15.1, n = 6) and increased to 15.1 (IQR, 12.0 – 17.3, p = 0.027 vs. baseline) after 6 months.

Data from NT-pro BNP levels at baseline and during follow-up were available from 11 patients. In 9 of 11 patients blood levels decreased with one marked upwards outlier. The median NT-proBNP was 1,226 pg/mL (IQR: 113 – 2,521; n = 11) at baseline and decreased by trend to 224 pg/mL (IQR, 59 – 583; p = 0.062 vs. baseline) after 12 months as shown in **Fig. 2**.

Right heart catheterization data at baseline and during follow-up were available from only 5 patients. Median cardiac output increased from 4.1 L/min (IQR, 4.0 – 5.2) to 5.9 L/min (IQR, 4.5 – 10.1) after a median treatment duration of 425 days (IQR, 241 – 511), median mean pulmonary arterial pressure (PAPm) decreased from 44 mmHg (IQR, 42 – 54) to 36 mmHg (IQR, 30 – 50), median pulmonary vascular resistance (PVR) decreased from 780 dyn × s × cm^{-5} (IQR, 611 – 808) to 347 dyn × s × cm^{-5} (IQR, 173 – 830), and median mixed venous oxygen saturation (SvO_2) increased from 70 % (IQR, 66 – 78) to 74 % (68 – 81). Mean systemic arterial pressure remained unchanged (data not shown). No symptomatic hypotension and no episodes of syncope were reported.

Blood gas analysis performed in 11 patients did reveal a slight but not significant worsening of arterial oxygenation. Median PaO_2 was 69 mmHg at baseline (IQR, 57 – 76) and 63 mmHg after 1 year (IQR, 58 – 84, p = 0.306). Likewise no significant change in liver transaminases was documented after initiation of therapy with ambrisentan (**Table 2**). Values for median MELD score available from 12 patients in the course of 1 year were 10 (IQR, 9 – 13) at baseline and 10 (IQR, 8 – 16; p = 0.96 vs. baseline) after 1 year ambrisentan therapy, respectively. Data for relevant laboratory safety parameters during ambrisentan therapy are shown in **Table 2**. Neither a clear trend nor a significant change was detectable for any of these parameters.

Table 2 Longitudinal analysis of relevant laboratory safety parameters in the course of 1 year ambrisentan treatment.[1]

parameters	baseline	after Ambrisentan Treatment	p value
INR, median (IQR)	1.17 (1.10 – 1.20)	1.15 (1.10 – 1.25)	0.77
Total bilirubin, mg/dL, median (IQR)	1.35 (0.87 – 1.59)	1.04 (0.67 – 1.49)	0.56
Creatinine, mg/dL, median (IQR)	1.19 (0.95 – 1.89)	1.18 (0.82 – 1.55)	0.94
ALT, µmol/(s × L), median (IQR)	0.34 (0.24 – 0.47)	0.47 (0.22 – 0.56)	0.92
AST, µmol/(s × L), median (IQR)	0.60 (0.45 – 0.75)	0.79 (0.52 – 0.87)	0.79

[1] INR: international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Discussion

This multicenter retrospective study for the first time demonstrates that ambrisentan therapy significantly increases exercise capacity assessed by 6-MWD and/or CPT in patients with PoPH. Additionally, symptoms (WHO-FC) were significantly improved. None of our patients showed symptomatic reduction in systemic blood pressure, relevant elevation of hepatic transaminases as hint for any dose-dependent toxic side effect of ambrisentan therapy, deterioration of liver function tests or significant impairment of gas exchange as a consequence of ambrisentan therapy.

In accordance with published data in our patients alcohol abuse was the most frequent cause of PoPH [16].

Partly conflicting results respecting the improvement of exercise capacity in PoPH patients have been published for other specific PAH treatments. Whereas Reichenberger et al. demonstrated a significant increase of the 6-MWD after 1 year of therapy with sildenafil, Hemnes et al. in 8 patients with PoPH could not confirm this result ($p = 0.29$) [7, 8]. The reason for this might be the lower dose of sildenafil (mean dose 31 ± 14 mg thrice daily) used in the trial of Hemnes et al. in comparison to Reichenberger et al. (50 mg thrice daily) [7, 8]. Melgosa demonstrated a significant increase of 6-MWD by 67 ± 59m after 12 months of therapy with inhaled iloprost ($p < 0.001$), whereas no significant change was detectable in the trial of Hoeper et al. ($p = 0.278$) [5, 6]. The reason for the different results is unclear and cannot be explained by different doses of inhaled iloprost. For the oral unselective endothelein receptor A and B antagonist bosentan two case series were published, both demonstrating an improvement of exercise capacity. Both trials also demonstrated an improvement of hemodynamics. BNP or NTpro-BNP levels, reflecting the degree of heart insufficiency, were not reported in these trials [5, 9].

In our patients, NTpro-BNP levels dropped after 1 year of therapy in the majority of patients with available data, but this change did not reach statistical significance ($p = 0.062$). The reason for this may be one outlier (patient who interrupted medication), in whom the value increased from 1761 pg/mL at baseline to 8.931 pg/mL.

Dose escalation of ambrisentan was not routinely performed in our patients. The maximum daily recommended dose is 10 mg, which 4/14 of our patients received. A very recently published trial in which dose uptitration to 10 mg of ambrisentan was performed routinely in 11/12 PoPH patients, demonstrated a significant improvement of hemodynamics and a significant reduction of BNP. However, data regarding the effect of ambrisentan therapy on exercise capacity or gas exchange are missing in this trial [17].

Ambrisentan was well tolerated in all our patients except the one with pronounced edema after 4 weeks of therapy, and no relationship with the therapy was seen in the patient who died due to liver insufficiency.

It is important to stress that most of our patients, like the patients in the study of Cartin-Ceba et al. [17], suffered from mild liver disease with the same initial median MELD score of 10. Safety data for ambrisentan in patients with higher MELD scores are lacking.

The question as to which drug should be used for treatment of PoPH is open due to the lack of placebo-controlled and head-to-head trials. Intravenous prostanoids are afflicted with the potentially serious side effects of catheter infection and malfunction of the pump. No survival benefit was found in CHILD Pugh A PoPH patients treated with intravenous epoprostenol [4].

Whether the unselective endothelin A and B receptor antagonist bosentan or the selective endothelin A receptor antagonist ambrisentan should be preferred in PoPH patients cannot be answered by the available data. There are safety concerns regarding the administration of bosentan in patients with known liver disease due to the well-known side-effect of potential hepatotoxicity of this substance [18]. But a number of case series and case reports suggested safety and efficacy of bosentan treatment in PoPH patients [5, 9, 19 – 25]. It is important to underline that all these patients where in Child class A, where no impairment of metabolism of bosentan is expected [26]. In addition it needs to be kept in mind that bosentan is not approved for patients with Child class B or C cirrhosis. Contrary to bosentan, ambrisentan does not inhibit human hepatic transporters, which provides a potential mechanism for the improved hepatotoxic profile of ambrisentan in comparison to bosentan [27]. With respect to safety concerns, this could be an advantage of ambrisentan over bosentan if treatment with an ET-receptor blocker is considered, especially in patients with moderate impairment of hepatic function. 5/13 patients in the trial of Cartin-Ceba al. [17] and 2/14 patients in our study treated with ambrisentan were in Child class B or C, and none of them experienced an elevation of transaminases above two times the upper level of normal. Another advantage of ambrisentan is the once daily dosing in comparison to twice daily dosing of bosentan.

The present study has the following limitations: (i) the number of patients was small (although the present series represents the largest population of PoPH patients treated with ambrisentan); (ii) the study was retrospective and neither patients nor investigators were blinded; (iii) there was no formal study protocol and thus dose escalation was performed by the investigators decision and assessments were not carried out at the same time-points and were not complete; (iv) no control group existed; (v) the impact of ambrisentan on portal hypertension was not investigated; (vi) the impact of ambrisentan on the hemodynamics could not sufficiently be evaluated due to the small number of patients ($n = 5$).

Despite these limitations, the present study confirmed the safety of ambrisentan in patients with PoPH and demonstrated an improvement of exercise capacity and symptoms as relevant markers for treatment efficacy with this drug. Thus, ambrisentan should be added to the list of medications that should be further investigated for this condition.

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