Peer reviewed article

Bosentan therapy for chronic thromboembolic pulmonary hypertension

A national open label study assessing the effect of Bosentan on haemodynamics, exercise capacity, quality of life, safety and tolerability in patients with chronic thromboembolic pulmonary hypertension (BOCTEPH-Study)

Silvia Ulrich[a,b], *Rudolf Speich*[a,b], *Guido Domenighetti*[c], *Thomas Geiser*[d], *John-David Aubert*[e], *Thierry Rochat*[f], *Lars Huber*[a], *Ursula Treder*[a], *Manuel Fischler*[a]

[a] Clinics of Internal Medicine, University Hospital, Zurich, Switzerland
[b] Clinic of Pulmonology, University Hospital, Zurich, Switzerland
[c] Critical Care Unit and Division of Internal Medicine, Regional Hospital, Locarno, Switzerland
[d] Clinic of Pulmonology, University Hospital, Bern, Switzerland
[e] Clinic of Pulmonology, University Hospital, Lausanne, Switzerland
[f] Clinic of Pulmonology, University Hospital, Geneva, Switzerland
For the Swiss Society for Pulmonary Hypertension SSPH

Summary

Study objectives: we performed an open-label national study to evaluate the effects of Bosentan on haemodynamics, exercise capacity, quality of life, safety and tolerability in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Patients and methods: fifteen patients with CTEPH not eligible or waiting for surgery were enrolled. The primary endpoint was the change in pulmonary vascular resistance (PVR). Secondary endpoints included quality of life (measured by the Minnesota living with heart failure questionnaire, MLHF), 6 minute walk distance (6MWD), World Health Organization (WHO) functional class, Borg dyspnoea scale, plasma endothelin, serum values of disease severity such as uric acid, N-terminal-pro brain natriuretic peptide (NT-proBNP), C-reactive protein measured by a highly sensitive method (CRPs) and other serum and haemodynamic parameters.

Results: after six months of treatment with bosentan, the PVR decreased from 852 (319) to 657(249) dyn*s*m-5 (p = 0.02). Quality of life considerably improved from a mean total score of 48(14) to 35(17) (p = 0.003) with improvements in the physical (from 25(5) to 17(7)) and emotional (from 11(6) to 6(5)) subscores (p = 0.005 and 0.011), respectively. The 6MWD improved from 389(78) to 443(79) meters (p = 0.005). 4 patients (27%) improved and 11 patients (73%) maintained their WHO class with no deterioration during the six months of bosentan treatment (p = 0.02). Uric acid serum levels declined from 525(145) to 453(151) µmol/l (p = 0.006), NT-proBNP and CRPs declined insignificantly. Endothelin serum levels increased from 4.3(1.5) to 5.9(2.2) pg/ml (p = 0.025). Patients tolerated the treatment well, and there were no severe adverse events or deaths.

Conclusion: this open-label study suggests a beneficial effect of bosentan therapy not only on pulmonary haemodynamics, but also on quality of life and exercise capacity for patients with severe CTEPH.

Key words: pulmonary hypertension; chronic thromboembolic pulmonary hypertension; endothelin receptor antagonist; bosentan

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Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the most frequent causes of pulmonary hypertension characterised by intraluminal thrombus organisation, fibrous stenosis and complete obliteration of pulmonary arteries leading to right heart failure and impaired survival [1, 2]. The true incidence of CTEPH might be underestimated, as up to 4% of patients with persistent dyspnoea after acute pulmonary embolism develop CTEPH and many affected patients do not have a history suggestive of episodes of pulmonary embolism [3]. Although surgical desobliteration of the pulmonary vascular tree by pulmonary endarterectomy (PEA) is con-

sidered the treatment of choice due to its curative potential, only a subgroup of patients can benefit from this procedure [4, 5]. Many patients with CTEPH either suffer from a surgically inaccessible disease due to a distribution of the organised embolic material mainly to the subsegmental and smaller branches of the pulmonary vascular bed, or suffer from severe medical co-morbidities precluding surgery [1, 2]. In addition, an unknown number of operated patients may exhibit persistent or recurrent pulmonary hypertension not amenable to repeated surgery [2]. Furthermore, the histopathological vascular changes of many patients with CTEPH resemble those seen in pulmonary arterial hypertension (PAH) including endothelial proliferation and formation of plexiform lesions [6, 7], Moreover, CTEPH and PAH may share acute vasoreactivity properties [8]. Left untreated, the prognosis of CTEPH is poor with a reported 5-year mortality approaching 90% when the mean pulmonary artery pressure (MPAP) is >30 mm Hg [9]. Taken together it seems reasonable to postulate that patients with CTEPH might benefit from medical therapy with drugs that have been shown to be effective in PAH. At present, there are no licensed medical therapies for CTEPH. Case series and smaller uncontrolled studies have reported improvements in exercise capacity, markers of disease severity and pulmonary haemodynamics with the use of oral, inhaled or intravenous prostanoids, the phosphodiesterase inhibitor sildenafil and recently bosentan [10–19]. One randomised controlled trial showing a favourable effect of inhaled iloprost in pulmonary hypertension has included patients with CTEPH, but subgroup analyses of these subjects has not been reported [20].

Endothelin (ET)-1 plays a key role in pulmonary arterial vessel remodelling as seen in patients with PAH and CTEPH [7]. Circulating endothelin levels are elevated in correlation to disease severity and ET receptor subtypes (ETA and ETB) are upregulated in PAH and possibly CTEPH [21–24]. The dual endothelin receptor antagonist bosentan has been shown to improve exercise capacity and right ventricular function in PAH [2, 17, 25], with sustained improvements and survival shown in open label follow up studies up to three years [26]. The aim of the present national open-label, non-controlled six month trial was to characterise the effects of bosentan on pulmonary haemodynamics, quality of life exercise capacity, safety and tolerability in severely ill patients with CTEPH.

Patients and methods

Subject selection and inclusion criteria

Consecutive patients with CTEPH either not eligible for surgery or scheduled for PEA not earlier than 6 months and being orally anticoagulated for at least 6 months were included in this open-label, prospective study conducted under the auspices of the Swiss Society for Pulmonary Hypertension (SSPH) upon written informed consent. The study was conducted in accordance with the Declaration of Helsinki 1975 and was approved by the ethical review boards of the involved and actively recruiting centres. All patients had established pulmonary hypertension confirmed by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg and a pulmonary artery occlusion pressure ≤15 mm Hg at rest during right heart catheterisation. Other inclusion criteria were severe limitation in daily activity and exercise capacity assessed as WHO functional class III-IV and a six minute walk distance (6MWD) between 150–500 meters, a pulmonary vascular resistance (PVR) above 500 dyn*s*m^{-5} and a stable clinical condition including no changes in any potentially vasoactive medication over the last three months (eg, calcium channel blockers and angiotensin converting enzyme inhibitors or other antihypertensive therapy, prostanoids, sildenafil, longterm oxygen therapy). Exclusion criteria were other forms of pulmonary hypertension, child-bearing potential without an acceptable method of contraception and aspartate- and/or alanine aminotransferases levels above three times the upper limit of normal. The diagnosis of CTEPH was based on ventilation perfusion scanning and pulmonary angiography in all patients. All patients were evaluated for PEA by an interdisciplinary team consisting of pulmonologists, specialists in intensive care, radiologists and thoracic surgeons familiar with PEA. Included patients were either not eligible for surgery due to distal disease, suffered from significant comorbidities precluding surgery or were not willing to undergo surgery within the next 6 months for personal reasons. In these cases, the study was considered as a bridging period prior to potential PEA.

Study assessments, treatment and outcomes

All patients were orally anticoagulated with phenprocoumon (vitamin K antagonist, Marcoumar®) for at least 6 months prior to study onset. After obtaining written informed consent, all patients underwent a clinical assessment including the determination of WHO functional class by a standard questionnaire, completed the Minnesota living with heart failure (MLHF) questionnaire for evaluation of quality of life [1, 27], performed the 6MWD according to standard clinical practice with assessment of blood pressure, heart rate and oxygen saturation before and after the test, determination of the Borg dyspnoea scale immediately after the 6MWD, pulmonary function testing and right heart catheterisation for haemodynamic measures. Additionally, peripheral blood samples for complete haematogram, endothelin, C-reactive protein assessed by a highly sensitive method (CRPs), N-terminal pro-brain natriuretic peptide (here referred to as pro-BNP), D-dimer, uric acid, bilirubin, liver function tests and arterial blood gas assessment were obtained. For endothelin measurement, blood samples were immediately centrifuged and the serum frozen at –20 °C. All endothelin levels were then measured at once by enzyme-linked immune assay according to the manufactures instructions.

All patients meeting the inclusion criteria were then started on bosentan (kindly provided by Actelion Pharma Schweiz AG, Baden, Switzerland) 62.5 mg bid for the first

4 weeks and then continued at the target dose of 125 mg bid. Liver function tests were monitored every 2 weeks over the first month and every 4 weeks thereafter according to the treatment guidelines for bosentan. Patients were evaluated on an outpatient basis at 4 week intervals until the study end dated at 6 months. Every follow up visit encompassed a clinical assessment with special attention to potential adverse events, venous blood analysis of liver enzymes and markers of disease severity (CRP, pro-BNP, uric acid), determination of WHO functional class, 6MWD and Borg dyspnoea scale. The study end visit at 6 months additionally included a follow-up right heart catheterisation with a full haemodynamic profile, pulmonary function tests and assessment of quality of life. Patients were followed 2 and 6 weeks after completion of the study for safety assessments.

Since it was an open label study, the primary endpoint was chosen to be the change in PVR after 6 months of bosentan treatment. Secondary endpoints were the change in WHO functional class, 6MWD, Borg dyspnoea scale, the MLHF scores (total score, physical- and emotional-subscores), biochemical markers of disease severity (CRP, pro-BNP, uric acid), changes in mPAP and other haemodynamic values, changes in gas exchange and pulmonary function testing.

Statistics

Patients' characteristics at baseline and after treatment are expressed as means and standard deviation (SD) for continuous variables or number of subjects. Wilcoxon signed rank test analysis was used to compare baseline and end of study continuous variables. The Friedman test was additionally applied where more than two consecutive continuous variables were available (6MWD, biochemical markers of disease severity). Patients with and without vasodilatative combination therapy were compared using the Mann-Whitney-U-Test. A p-value of <0.05 was considered statistically significant.

Results

Patients

22 patients with CTEPH not eligible for surgery within the next 6 months were screened for the study. Five patients had to be excluded due to a 6MWD >500 meters, 1 patient was excluded because of a PVR <500 dyn*s*m^{-5} and 1 patient was

Table 1

Characteristics of 15 patients with Chronic Thromboembolic Pulmonary Hypertension at baseline and after 6 months of Bosentan therapy.

	Baseline	After 6 months of Bosentan	P-value
Age (yr)	67 (9)		
Gender females/males	7 / 8		
BMI (kg/m^2)	24 (4)	24 (3)	0.70
WHO functional class II / III /IV	0 / 8 / 7	2 / 9 / 4	0.02
6MWD (m)	389 (78)	443 (79)	0.005*
MLHF total score	48 (14)	35 (17)	0.003*
MLHF physical subscore	25 (5)	17 (7)	0.005*
MLHF emotional subscore	11 (6)	6 (5)	0.011*
Haemodynamic parameters			
Heart rate (beats/minute)	76 (10)	74 (16)	0.47
Mean systemic BP (mm Hg)	89 (15)	82 (11)	0.09
mPAP (mm Hg)	44 (8)	38 (7)	0.001*
Cardiac index (l/min/m^2)	2.0 (0.5)	2.2 (0.5)	0.03*
PVR (dyn*sec*m^{-5})	852 (319)	657 (249)	0.02*
SVR (dyn*sec*m^{-5})	1897 (542)	1534 (349)	0.01*
RAP (mm Hg)	10 (4)	8 (5)	0.11
PAOP (mm Hg)	9 (3)	10 (4)	0.72
SaO_2 (%)	89 (3)	89 (4)	0.35
$SmvO_2$ (%)	54 (6)	55 (6)	0.18
Biochemical markers			
Uric acid (µmol/l)	526 (145)	453 (151)	0.006*
Pro-BNP (ng/l)	3126 (2746)	2558 (2714)	0.158
CRPs (mg/l)#	10 (12)	8 (8)	0.11
Bilirubin (µg/l)	19 (3)	15 (2)	0.15
D-Dimer (mg/l)##	0.6 (0.7)	0.7 (0.6)	0.833
Troponin-T (normal <0.01 µg/l)	2	0	

Data are presented as number of patients or mean values and standard deviation (SD). # = data of 3 patients missing. ## = data of 5 patients missing. BMI: Body mass index , 6MWD: 6 minute walk distance, MLHF: Minnesota living with heart failure questionnaire for Quality of Life assessment, BP: blood pressure, mPAP: Mean pulmonary arterial pressure, CI: Cardiac index, PVR: Pulmonary vascular, resistance, RAP: Right atrial pressure, PAOP: Pulmonary artery occlusion pressure, Sa02: Arterial oxygen saturation, Sv02: Mixed venous oxygen saturation, pro-BNP: NT-pro brain natriuretic peptide, CRPs: C-reactive protein assessed by a sensitive method. *significant changes with $p<0.05$.

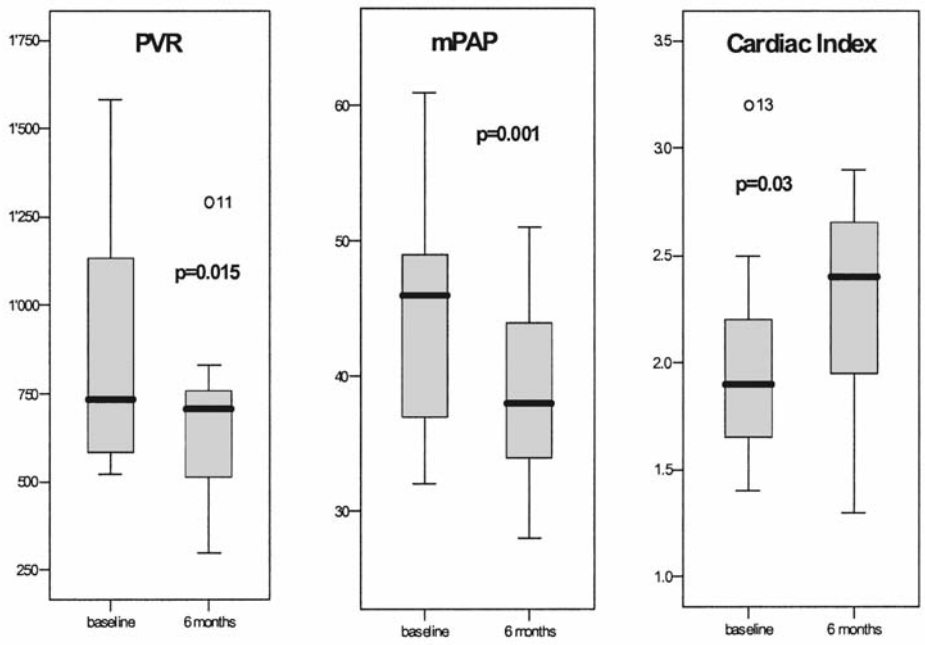


Figure 1

PVR, mPAP and CI at baseline and after six months of Bosentan treatment in 15 patients diagnosed with CTEPH.

Data are presented as box plots, with the box representing the two middle quartiles (25–75%), the bar in the box the median and the lengths of the whisker-lines represent the 1.5 fold interquartile ranges. Outliers are represented separately as dots (adjacent numbers represent patient numbers). The p-values are calculated by using the Wilcoxon test for two consecutive measurements. mPAP: Mean pulmonary arterial pressure, CI: Cardiac index, PVR: Pulmonary vascular, resistance.

already on bosentan therapy. Thus, a final number of 15 patients were included in the study. The baseline characteristics are presented in the table 1. Subjects were severely ill and all of them were receiving chronic diuretics and long term oral anticoagulation. Four patients (27%) were on continuous long term oxygen therapy. Six patients (40%) were on stable therapy with inhaled iloprost for more than 3 months (25(17) months), none of the patients was taking sildenafil. Significant comorbidities in a stable condition were arterial hypertension (2 patients), mild chronic obstructive pulmonary disease (2), renal cell carcinoma (1), and polycythaemia vera (1). Only 6 patients (40%) had a history of past acute pulmonary embolism, and 2 patients (13%) recalled a deep leg vein thrombosis. Except of the one with carcinoma, none of the patients suffered from coagulopathy or thrombophilia. None of the patients had elevated liver enzymes at baseline.

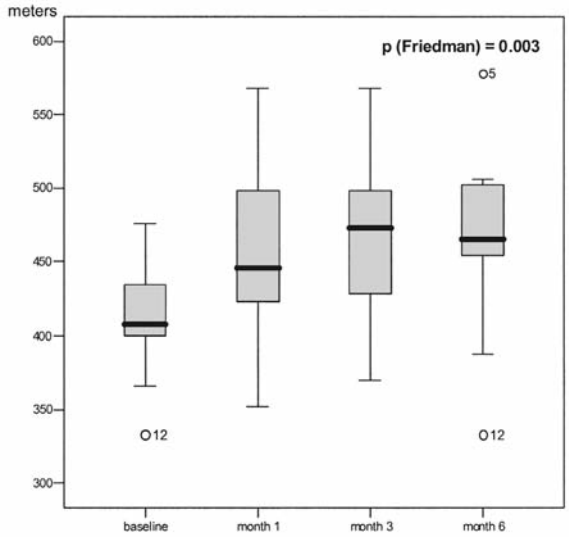


Figure 2

Six minute walk distance during different time points of a six month treatment period with bosentan.

Data are presented as box plots, with the box representing the two middle quartiles (25–75%), the bar in the box the median and the lengths of the whisker-lines represent the 1.5 fold interquartile ranges. Outliers are represented separately as dots (adjacent numbers represent patient numbers). The y-axis represents metres, the x-axis the different time points as marked. The p-values are calculated by using the Wilcoxon test for two consecutive measurements. 6MWD: 6 minute walk distance.

Haemodynamic response

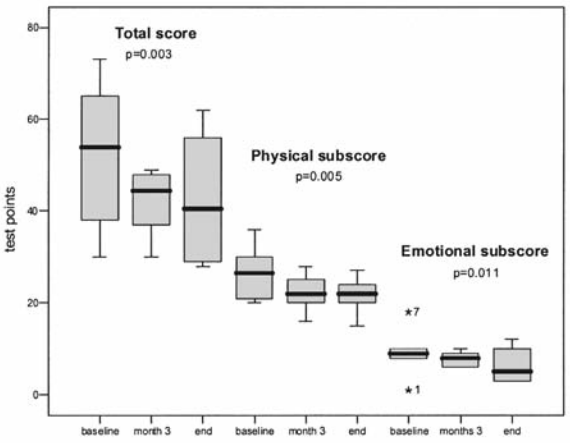
Results of cardiac catheterization at baseline and after 6 months of bosentan treatment are shown in the table and in figure 1. The primary endpoint, the PVR, significantly declined from 852(319) to 657(249) dyn*s*m^{-5} (p = 0.02). The mPAP fell from 44(8) to 38(7) mm Hg (p = 0.001) and cardiac index rose from 2.0(0.5) to 2.2(0.5) l/min/m–2 (p = 0.03). The systemic vascular resistance significantly decreased from 1897(542) to 1534(349) dyn*s*m^{-5} (p = 0.01). There were, however, no significant changes in mean blood pressure, heart rate, right atrial and pulmonary artery occlusion pressure, as well as arterial and mixed venous blood saturation. The mean haemodynamic changes over 6 months did not differ between the six patients on stable combination therapy with inhaled Iloprost compared with the other nine patients.

Functional assessments, exercise capacity and quality of life

At baseline, 8 patients were in WHO functional class III and 7 patients in class IV. After 6 months of treatment, one patient each improved from functional classes IV and III to class II and two patients from class IV to class III. The re-

Figure 3

Quality of life measured by the Minnesota living with heart failure questionnaire at baseline, three and six month of Bosentan treatment.



Data are presented as box plots, with the box representing the two middle quartiles (25–75%), the bar in the box the median and the lengths of the whisker-lines represent the 1.5 fold interquartile ranges. Outliers are represented separately as dots (adjacent numbers represent patient numbers). The y-axis represent test points (higher numbers represent worse quality of life), the x-axis the different time points as marked. The p-values are calculated using the Wilcoxon test for consecutive measurements.

maining patients were assigned the same functional class as at baseline.

As shown in figure 2, the 6MWD significantly increased from 389(78) to 443(79) meters (p-Wilcoxon = 0.005, p-Friedman = 0.003), whereas the Borg dyspnoea scale remained unchanged (4.3(1.3) at baseline vs 4.6(1.7) at study end, p = 0.8). Quality of life measured by the MLHF questionnaire significantly improved from a mean total score of 48(14) to 35(17) (p = 0.003) (figure 3). The physical as well as the emotional subscore improved significantly from 25(5) to 17(7) and from 11(6) to 6(5) (p = 0.005 and 0.011), respectively. There were no significant changes in lung function parameters during the study period.

Laboratory values

Uric acid serum levels were elevated above the normal limit of 350 µmol/l in all patients at baseline with a mean level of 525(145). They decreased to 453(151) µmol/l (p = 0.006) during the study and normalised in 6 patients (40%). The endothelin-1 serum level could be measured in 8 patients (53%). The mean endothelin-1 serum level increased from 4.26(1.5) to 5.86(2.2) pg/ml (p = 0.025) during the six month of bosentan treatment. Serum levels of pro-BNP were elevated above the upper normal limit (334 ng/l) in 13 (87%) patients at baseline and study end. Mean pro-BNP serum levels insignificantly decreased from 3126(2746) to 2558(2714) ng/l (p = 0.16) during the study. Serum levels of CRPs at baseline were missing in 3 patients. Of the remaining 12, none had a normal level (<1 mg/l). Ten showed moderately (1–10 mg/ml) and 2 highly (>10 mg/l) elevated serum levels of CRPs. The mean levels slightly decreased during the study from 9.65(12) to 7.73(9) mg/l (p = 0.11), respectively, with one patient with normal, 8 with moderate and 3 with high CRP-levels at study end. Bilirubin serum levels were elevated above the normal limit of 17 µg/l in 7 patients (47%) at baseline and 5 patients (33%) at study end, the mean levels did not decrease significantly during the study (19(3) vs 15(2) µg/l, p = 0.15). D-Dimers measures were missing in five patients at baseline. Of the remaining 10 patients, two had levels above the laboratory norm of 0.5 mg/l at baseline and four at study end. The mean levels insignificantly increased from 0.6(0.7) to 0.7(0.6) mg/l (p = 0.833). Serum levels of troponin T were slightly above the detection limit of 0.01 µg/l in two patients at baseline (0.02 and 0.04 µg/l), and were undetectable in all patients at study end.

Side effects and adverse events

The liver enzymes alanine and aspartate aminotransferases were within normal limits at baseline and remained there during the 6 months study period in all patients. Systemic blood pressure, heart rate, body weight and haemoglobin did not change significantly during the study and no patient experienced episodes of right heart failure or symptomatic hypotension during the study period. The study medication was tolerated very well. The most frequent side effect was slight ankle oedema in 5 patients and one patient developed mild ascites during the 5th month of treatment. Minor adverse events during the study were respiratory tract infections in two patients. There were no serious adverse events during the whole 6 months study period. The patient included with previously stable renal cell carcinoma developed rapid tumour progression and died within three months of study end. Another patient died three weeks after completing the study after unsuccessful cardiopulmonary resuscitation due to ventricular tachycardia. The patient was on continued bosentan therapy, and his death was judged not to be correlated with the study drug but due to CTEPH itself.

Discussion

Our study confirms the favorable effect of bosentan therapy to improve pulmonary haemodynamics and exercise capacity in CTEPH not eligible for PEA. In addition, a positive effect on quality of life could be demonstrated. Although PEA is the only curative therapy for patients with CTEPH, many patients do not qualify for this surgical option due to distal pulmonary vascular

disease, contraindications or significant comorbidity [4, 8]. Currently, no specific randomised trial-based therapeutic recommendations exist for these patients. Although the pathogenesis of CTEPH still remains incompletely understood, it is becoming increasingly clear that beside a possibly initiating thromboembolic obstruction of pulmonary vessels, vascular remodeling plays a important role in CTEPH as well [7, 28]. The morphological changes of the vessel wall resemble those found in PAH and may also lead to endothelial dysfunction. Thus, the use of vasoactive treatment in chronic thromboembolic disease in analogy to PAH seems reasonable. Several pharmacological strategies have been employed in patients with CTEPH not eligible for PEA or as a bridge to surgery. Smaller studies demonstrated a favourable effect of prostanoids and sildenafil on pulmonary haemodynamics and/or exercise capacity in these patients [10, 12, 15, 20]. Another therapeutic option in patients with PAH is endothelin antagonism [23]. As plasma levels of big-endothelin-1, the precursor of endothelin-1, are increased in patients with CTEPH compared to control subjects and upregulation of endothelin B receptors have been demonstrated in pulmonary arterial smooth muscle cells of patients with this disease [29], a treatment with an endothelin receptor antagonist in patients with CTEPH seems reasonable. The increased endothelin levels may also suggest that CTEPH and PAH share pathogenic pathways. Therefore, endothelin antagonism may be important in the treatment of CTEPH as well, as supported by the present study. Indeed, recently a beneficial effect of bosentan therapy on exercise capacity and functional class in CTEPH was demonstrated in three small prospective trials [16, 17, 19], one of which also demonstrated an amelioration of pulmonary haemodynamics [17]. Additionally, a sustained favourable effect of bosentan in inoperable CTEPH was demonstrated by a retrospective chart review of 47 patients after one year [18].

Our study confirms these favourable results of bosentan therapy in CTEPH not eligible for PEA. Pulmonary haemodynamics significantly improved after 6 months of treatment with significant decreases in PVR, the primary endpoint. There was a significant mean increase in the 6MWD of 58 m, and thus comparable to the study of Hoeper and Hughes and colleagues [17, 18]. The mean Borg dyspnoea scale immediately after the test remained unchanged. This may be attributed to a similar effort for the increased distance walked at study end compared with baseline.

Beside the improvements in haemodynamics and exercise capacity, this study is the first to show a significant improvement in quality of life in CTEPH under bosentan therapy. Nowadays, quality of health parameters are becoming increasingly relevant, especially in serious disorders requiring difficult and costly treatments. Recently, we were even able to demonstrate that quality of life belongs to the most important predictors of disease progression, with the MLHF total score is the sole factor predicting subsequent outcome in a multivariate analysis [26]. Although its measurement is subjective, amelioration of quality of life is the parameter considered most important for the patients' well being and correlates with prognosis. Moreover, it is one of the most important factors for patients and decision making in health authorities [30, 31].

Hyperuricaemia has been shown to be associated with elevated right and left heart filling pressures and correlates with disease severity and mortality in patients with pulmonary arterial hypertension [32–35] and uric acid serum levels were shown to decrease in about two third of patients under intravenous prostanoid therapy [35]. In the present study, we found elevated baseline uric acid serum levels in all patients, with a significant decrease in mean uric acid serum levels, and a normalisation of the values in 6 patients (40%) at study end. It can be speculated, that in analogy to PAH, these findings might be associated with a improved prognosis [32]. Another important marker of disease severity in right and left heart failure is pro-BNP [36]. In our cohort, pro-BNP serum levels were elevated at baseline in all but one patient, and decreased during the treatment period. As experimental data suggest that blockage of ET could directly reduce BNP levels independently of the haemodynamic effect, the interpretation of this marker seems to be difficult [37]. However, in contrast to other published observational studies, the mean serum level decrease during this study did not reach statistical significance. A high level of CRPs is a marker of endothelial dysfunction in the systemic circulation [38, 39]. We found high to very high levels of CRPs levels in 11 of the 12 tested patients (92%) at baseline. During the study, CRPs levels decreased in 7 patients (58%), however, the change of overall mean levels not being significant. The considerably high baseline CRPs levels in this small CTEPH-cohort are remarkable and reinforce the implication of inflammatory mechanisms in the pathogenesis of CTEPH. Elevation of proinflammatory mediators have also been reported in patients with idiopathic pulmonary arterial hypertension and CTEPH [40–44]. Whether CRPs is a marker of endothelial dysfunction in the pulmonary circulation analogous to the systemic circulation has only been studied in a limited fashion to date [45]. The findings of this small cohort support the possible value of CRPs as a marker of disease severity in CTEPH.

Six of the fifteen study patients were on stable therapy with inhaled Iloprost. The mean changes in all assessed parameters were not different in this subgroup compared with the remainder. This may indicate that even patients on stable vasodilator therapy with another drug could further profit by adding Bosentan therapy. However, the

presently investigated cohort was not intended to answer the question about vasodilator combination therapy in CTEPH. Therefore, further larger clinical studies are warranted to enlighten this question.

Bosentan therapy was very well tolerated in this study population. None of the patient had quit therapy or decreased the target dose due to side effects or elevated liver enzymes. Reported side effects were minor leg oedema and ascites in one patient. These data are in concordance with previous studies of bosentan in patients with PAH and CTEPH, showing that doses up to 250 mg twice daily can be safely administered under strict monitoring [16–18, 23].

The limitation of the present study is the lack of a control population and it's limited sample size. Thus, it can not be excluded that the observed improvements in functional class, exercise capacity and quality of life were due to a placebo effect. However, the significant improvements in the objective primary study end point, namely the PVR, as well as uric acid serum levels reflecting another important parameter of disease severity, can hardly be attributed to a placebo effect only and underscore the efficacy of bosentan in a cohort of CTEPH with proximal and distal involvement.

In conclusion, the results of this study suggest that therapy with the dual Endothelin receptor antagonist bosentan is well tolerated and can result in a sustained improvement in pulmonary haemodynamics, quality of life, WHO functional class, exercise capacity and markers of disease severity in a broad collective of CTEPH not suitable for PEA for various reasons or as a bridge to PEA in some patients. Nevertheless, all patients with CTEPH should first be evaluated for the potentially curative PEA procedure and receive anticoagulation therapy.

Correspondence:
Dr. med. Silvia Ulrich
Department of Internal Medicine
Rämistrasse 100
CH-8005 Zurich
Switzerland
E-Mail: silvia.ulrich@usz.ch

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