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)

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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 (3)) 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

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-
Considered 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 hemodynamics with the use of oral, inhaled or intravenous prostanooids, 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 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 hemodynamics with the use of oral, inhaled or intravenous prostanooids, 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.

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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 six informed consent, all patients underwent a clinical as-essment including the determination of WHO func-tional class by a standard questionnaire, completed the Minnesota living with heart failure (MLHF) question-naire for evaluation of quality of life [1, 27], performed 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 func-tion tests and arterial blood gas assessment were obtained. For endothelin measurement, blood samples were imme-diately 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>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of 15 patients with Chronic Thromboembolic Pulmonary Hypertension at baseline and after 6 months of Bosentan therapy.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>After 6 months of Bosentan</strong></td>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>67 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender females/males</strong></td>
<td>7 / 8</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>24 (4)</td>
<td>24 (3)</td>
</tr>
<tr>
<td><strong>WHO functional class II / III /IV</strong></td>
<td>0 / 8 / 7</td>
<td>2 / 9 / 4</td>
</tr>
<tr>
<td><strong>6MWD (m)</strong></td>
<td>389 (78)</td>
<td>443 (79)</td>
</tr>
<tr>
<td><strong>MLHF total score</strong></td>
<td>48 (14)</td>
<td>35 (17)</td>
</tr>
<tr>
<td><strong>MLHF physical subscore</strong></td>
<td>25 (5)</td>
<td>17 (7)</td>
</tr>
<tr>
<td><strong>MLHF emotional subscore</strong></td>
<td>11 (6)</td>
<td>6 (5)</td>
</tr>
<tr>
<td><strong>Haemodynamic parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate (beats/minute)</strong></td>
<td>76 (10)</td>
<td>74 (16)</td>
</tr>
<tr>
<td><strong>Mean systemic BP (mm Hg)</strong></td>
<td>89 (15)</td>
<td>82 (11)</td>
</tr>
<tr>
<td><strong>mPAP (mm Hg)</strong></td>
<td>44 (8)</td>
<td>38 (7)</td>
</tr>
<tr>
<td><strong>Cardiac index (l/min/m²)</strong></td>
<td>2.0 (0.5)</td>
<td>2.2 (0.5)</td>
</tr>
<tr>
<td><strong>PVR (dyn<em>sec</em>m⁻⁵)</strong></td>
<td>852 (119)</td>
<td>657 (249)</td>
</tr>
<tr>
<td><strong>SVR (dyn<em>sec</em>m⁻⁵)</strong></td>
<td>1897 (542)</td>
<td>1334 (349)</td>
</tr>
<tr>
<td><strong>RAP (mm Hg)</strong></td>
<td>10 (4)</td>
<td>8 (5)</td>
</tr>
<tr>
<td><strong>PAOP (mm Hg)</strong></td>
<td>9 (3)</td>
<td>10 (4)</td>
</tr>
<tr>
<td><strong>SaO₂ (%)</strong></td>
<td>89 (3)</td>
<td>89 (4)</td>
</tr>
<tr>
<td><strong>SmvO₂ (%)</strong></td>
<td>54 (6)</td>
<td>57 (6)</td>
</tr>
<tr>
<td><strong>Biochemical markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uric acid (µmol/l)</strong></td>
<td>526 (145)</td>
<td>453 (151)</td>
</tr>
<tr>
<td><strong>Pro-BNP (ng/l)</strong></td>
<td>3126 (2746)</td>
<td>2538 (2714)</td>
</tr>
<tr>
<td><strong>CRPs (mg/l)</strong></td>
<td>10 (12)</td>
<td>8 (8)</td>
</tr>
<tr>
<td><strong>Bilirubin (µg/l)</strong></td>
<td>19 (3)</td>
<td>15 (2)</td>
</tr>
<tr>
<td><strong>D-Dimer (mg/l)</strong></td>
<td>0.6 (0.7)</td>
<td>0.7 (0.6)</td>
</tr>
<tr>
<td><strong>Troponin-T (normal &lt;0.01 µg/l)</strong></td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

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, SaO₂: Arterial oxygen saturation, SmvO₂: 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.
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.

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-
remaining 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 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...
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...quality of health parameters are becoming increasingly relevant, especially in serious disorders such as PAH and CTEPH. This study is the first to show a significant improvement in exercise capacity and functional class in CTEPH with bosentan therapy. Indeed, recently a beneficial effect of bosentan therapy on exercise capacity and functional class in CTEPH was demonstrated in small prospective trials, one of which also demonstrated a normalization of pulmonary haemodynamics [17]. Additionally, a sustained improvement in exercise capacity was observed in 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 bosentan. 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 being 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 normalization 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 is BNP, but BNP values in CTEPH are normal or even increased in about half of the patients [36]. During the study, BNP 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 systemic circulation has been questioned [37]. 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 decreased 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 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 ascerts 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 cannot 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 anti-coagulation therapy.

References


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