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Long-term treatment with sildenafil in chronic thromboembolic pulmonary hypertension

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ABSTRACT: For chronic thromboembolic pulmonary hypertension not amenable to pulmonary endarterectomy, effective medical therapy is desired.

In an open-label uncontrolled clinical trial, 104 patients (mean±SEM age 62±11 yrs) with inoperable chronic thromboembolic pulmonary hypertension were treated with 50 mg sildenafil *t.i.d.* At baseline, patients had severe pulmonary hypertension (pulmonary vascular resistance 863±38 dyn·s·cm^{-5}) and a 6-min walking distance of 310±11 m. Eight patients were in World Health Organization functional class II, 76 in class III and 20 in class IV.

After 3 months' treatment, there was significant haemodynamic improvement, with reduction of pulmonary vascular resistance to 759±62 dyn·s·cm^{-5}. The 6-min walking distance increased significantly to 361±15 m after 3 months' treatment, and to 366±18 m after 12 months' treatment. A subset of 67 patients received a single dose of 50 mg sildenafil during initial right heart catheterisation. The acute haemodynamic effect of this was not predictive of long-term outcome.

In this large series of patients with inoperable chronic thromboembolic pulmonary hypertension, open-label treatment with sildenafil led to significant long-term functional improvement. The acute effect of sildenafil may not predict the long-term outcome of therapy.

KEYWORDS: Chronic thromboembolism, pulmonary hypertension, sildenafil

Chronic thromboembolic pulmonary hypertension (CTEPH) is a known complication of pulmonary thromboembolism, affecting up to 3.8% of patients with persistent symptoms following acute major pulmonary embolism [1]. CTEPH is regarded as a distinct diagnostic entity of pre-capillary pulmonary hypertension (PH) characterised by pulmonary vascular obstructions due to persistence and fibrous organisation of thromboembolic material within the pulmonary vasculature [2]. If untreated, CTEPH leads to progressive PH with additional pulmonary vascular remodelling in the nonobstructed pulmonary vessels, which share homologies with pulmonary arterial hypertension (PAH) [3, 4]. Furthermore, it leads to subsequent right heart failure and early death [5].

For obstructions in the central pulmonary arteries, the treatment of first choice is pulmonary thromboendarterectomy (PTE) [6]. However, if the peripheral vascular obstructions are not considered amenable to surgical removal or the presence of pulmonary microvascular obstruction is suggested due to significant imbalance between the severity of CTEPH and morphological obstructions on pulmonary angiography, pharmacological therapy beyond oral anticoagulation may be indicated [7].

Data regarding the use of specific pulmonary vasoactive treatments in CTEPH are sparse. In most of the randomised controlled trials of new therapies for PAH, CTEPH has been explicitly excluded [8, 9]. To date, only a single study, which examined the effects of inhaled iloprost on severe PH, included a subset of patients with inoperable CTEPH. In this study, the response to study drug in CTEPH patients was not significantly different from that in the other subgroups, although the magnitude of the response appeared smaller compared to that in idiopathic PAH patients [10]. Successful use of intravenous epoprostenol and bosentan in inoperable CTEPH has also been reported in case series [11–15]. Recently, a small inoperable CTEPH patient series treated with oral sildenafil was described; however, few data are available concerning long-term therapy [16].

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A previous report demonstrated an acute pulmonary haemodynamic effect of sildenafil and inhaled iloprost in a group of patients that included a considerable number of inoperable CTEPH patients, suggesting that phosphodiesterase 5 is involved in the vasoconstrictive process; however, the long-term clinical relevance of this finding has not yet been evaluated [17].

In the present report, a single-centre study on the efficacy and safety of long-term treatment with oral sildenafil and the relevance of the acute haemodynamic effect of sildenafil to long- term outcome in patients with CTEPH who are not candidates for PTE are detailed.

PATIENTS AND METHODS

In the Giessen PH clinic (University of Giessen Lung Centre, Dept of Internal Medicine, Giessen University Hospital, Giessen, Germany), a specialised referral centre, patients with PH were diagnosed and evaluated with respect to their underlying disease and treatment options. Diagnosis of chronic thromboembolism was made using thoracic computed tomography, computed tomographic pulmonary angiography and pulmonary perfusion scintigraphy. When proximal pulmonary vascular obstructions were suspected in either test, patients additionally underwent conventional pulmonary angiography. In all patients, the possibility of PTE was assessed by a multidisciplinary panel including an experienced surgeon (E. Mayer) [7].

Only patients who were not considered candidates for surgery were included in the present study. Other forms of PH and additional cardiopulmonary diseases were excluded according to current recommendations [18], by means of echocardiography, pulmonary function tests, blood gas analyses, screening for HIV and collagen vascular diseases, coronary angiography or sleep studies, as clinically indicated. The diagnosis of pre-capillary PH was confirmed on initial right heart catheter investigation by a mean pulmonary arterial pressure ($\bar{P}_{pa}$) of >25 mmHg, a pulmonary arterial wedge pressure (P_{paw}) of <15 mmHg and a pulmonary vascular resistance (PVR) of >240 dyn·s·cm^{-5}. Pulmonary haemodynamics were re-evaluated after 3 months of treatment in all patients. Patients were further assessed by World Health Organization (WHO) functional classification and the 6-min walking distance (6MWD), according to current guidelines and use in clinical trials [9–15, 18, 19].

Treatment with sildenafil was initiated in patients with a diagnosis of inoperable CTEPH, WHO functional class II–IV and impaired exercise tolerance, with a 6MWD of <450 m at baseline, despite conventional treatment with oral anticoagulation therapy for ⩾6 months, diuretics and oxygen supplementation if indicated.

No patient received β-blocking agents, nitric oxide donor substrates, endothelin receptor antagonists, or inhaled or systemic prostanoids.

Sildenafil treatment was started in increasing doses, reaching 50 mg *t.i.d.* on day 3.

Follow-up investigations were performed after 3 and 12 months, including a clinical assessment, and evaluation of side-effects and the 6MWD.

Patients were asked to participate in the evaluation of the acute haemodynamic effects of oral sildenafil during initial right heart catheterisation. After recording of baseline haemodynamics, these patients received a single 50-mg dose of sildenafil. The haemodynamic measurements were repeated after 45 min, when the maximum acute effect of oral sildenafil is expected [17]. Patients were categorised as showing a major or minor acute haemodynamic effect. A major haemodynamic effect was defined as when the PVR reduction was greater than the median drop in PVR in the whole study population. Both groups were followed-up concerning the long-term outcome of sildenafil therapy.

Patients gave written informed consent for assessment of the acute haemodynamic effect and long-term compassionate treatment with sildenafil. The present study was approved by the Ethics Committee of Giessen University Hospital.

Statistical analysis

All data were analysed for normal distribution by means of the Kolmogorov–Smirnov test. Data on patients lost to follow-up were included using last-observation-carried-forward analysis. Parameters with normal distributions are presented as mean±SEM. In order to test for significant differences between groups, a two-tailed unpaired t-test was used. In cases of multiple testing, correction according to Bonferroni was applied in order to avoid a Type I error. Correlations between two variables were analysed using Pearson's correlation coefficient [20].

RESULTS

Between 2002 and 2005, sildenafil treatment was initiated in 104 patients with definite inoperable CTEPH (45 males and 59 females; mean (range) age 62 (34–83) yrs).

The reason for inoperability was a peripheral location of the pulmonary vascular obstruction or the presence of thromboembolic microvascular disease [7, 21].

Patients detailed in the study of McLAUGHLIN *et al.* [14] were not included in the present investigation. Prior to inclusion, all patients had received oral anticoagulation therapy for ⩾6 months.

At baseline, patients were placed in WHO functional classes II (n=8), III (n=76) and IV (n=20; overall functional class 3.1±0.05). The 6MWD was 310±11 m. Haemodynamic parameters indicated severe pre-capillary PH, with a $\bar{P}_{pa}$ of 47±1 mmHg, P_{paw} of 8±1 mmHg, PVR of 863±38 dyn·s·cm^{-5} and cardiac index (CI) of 2.1±0.1 L·min^{-1}·m^{-2}.

After 3 months of treatment, 104 patients were re-evaluated using the WHO classification, 6MWD and right heart catheterisation. Patients were placed in WHO functional classes II (n=11), III (n=83) and IV (n=10), with a mean functional class of 3.0±0.04 (p=0.01). Thus 10 patients improved from class IV to III, and three from class III to II.

There was a significant increase in 6MWD to 361±15 m (p=0.0001). $\bar{P}_{pa}$ decreased to 46±2 mmHg (p=0.1), CI increased to 2.4±0.1 L·min^{-1}·m^{-2} (p=0.006) and PVR decreased to 759±62 dyn·s·cm^{-5} (p=0.0002; table 1).

After 12 months of treatment, 102 patients were reassessed using the WHO classification and 6MWD, since two patients had been lost to follow-up. Patients were placed in WHO functional classes II (n=12), III (n=83) and IV (n=7), with a mean of 2.9±0.04 (p=0.001 *versus* baseline). Three patients improved from class IV to III and four from class III to II, whereas three deteriorated from class II to III.

The 6MWD was 366±18 m (p=0.0005 *versus* baseline; figs 1 and 2). None of the 102 patients died during the 12-month observation period. Seven patients requiring additional therapy with inhaled iloprost due to clinical worsening stabilised with regard to clinical and functional parameters on combination therapy.

Analysing the functional capacity of the 95 patients who remained on sildenafil monotherapy over the whole study period, the 6MWD increased from 306±20 m at baseline to 362±27 m after 3 months (p<0.0005 *versus* baseline) and 397±26 m after 12 months (p<0.001 *versus* baseline).

Among the whole study population, 67 patients (28 males and 39 females; mean (range) age 62 (38–83) yrs) consented to the evaluation of the acute effects of sildenafil during right heart catheterisation at baseline. In this subgroup, the median acute reduction in PVR after oral administration of sildenafil was 27%. Accordingly, the major acute effect group comprised of 35 patients and the minor acute effect group 32 patients with a >27 and a <27% acute reduction in PVR, respectively (table 2). Both patient groups exhibited comparable baseline haemodynamics and functional capacity (table 3).

After 3 months of treatment, the 6MWD increased from 310±18 to 358±26 m (p=0.005) and PVR decreased from 916±66 to 632±112 dyn·s·cm^{-5} (p=0.002) in the major acute effect group. In the minor acute effect group, the 6MWD increased from 301±21 to 379±26 m (p=0.02) and PVR decreased from 770±61 to 624±82 dyn·s·cm^{-5} (p=0.03). There was no correlation between the acute change in PVR at baseline and the change in PVR after 3 months' therapy compared with baseline (r=0.16; p=0.22; table 3).

After 12 months of sildenafil treatment, the 6MWD was 386±24 m in the major acute effect group (p=0.002 *versus* baseline) and 379±41 m in the minor acute effect group (p=0.07 *versus* baseline). There were no significant differences between the two patient groups (fig. 3).

TABLE 1 Baseline characteristics and 3-month follow-up in 104 patients with inoperable chronic thromboembolic pulmonary hypertension

	Baseline	3 months	p-value
6MWD m	310±11	361±15	0.0001
$\bar{P}_{pa}$ mmHg	47±1	46±2	0.1
CI L·min^{-1}·m^{-2}	2.1±0.1	2.4±0.1	0.006
PVR dyn·s·cm^{-5}	863±38	759±62	0.0002

Data are presented as mean±SEM. 6MWD: 6-min walking distance; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

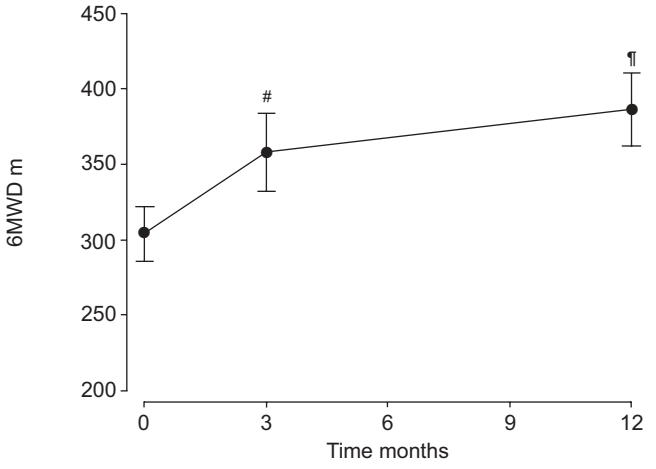

FIGURE 1. 6-min walking distance (6MWD) at baseline (0 months; start of sildenafil therapy) and after 3 and 12 months of follow-up in the whole study group, including seven patients on sildenafil and inhaled iloprost combination therapy at 12 months. Data are presented as mean±SEM. #: p=0.0001; ¶: p=0.00005 *versus* baseline.

There were no major systemic side-effects related to sildenafil therapy; in particular, no visual disturbances or bleeding complications were observed. Minor side-effects included transient flush (n=8), transient palpitations (n=10), symptoms of gastro-oesophageal reflux (n=24), epistaxis (n=8) and lower back pain (n=12), and did not require specific interventions. No patient denied therapy due to side-effects or noncompliance.

DISCUSSION

In the present single-centre uncontrolled open-label study on the effects of sildenafil in inoperable CTEPH, significant functional and haemodynamic improvement were observed after 3 months of sildenafil monotherapy, with a sustained clinical response over 1 yr of treatment.

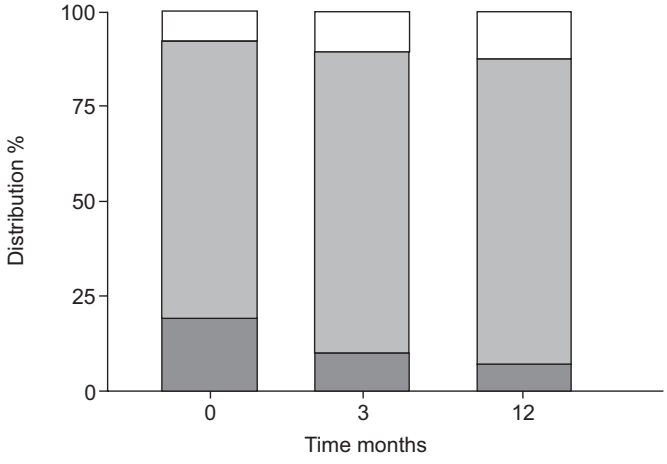

FIGURE 2. World Health Organization (WHO) functional class (□: II; ■: III; ■: IV) distribution at baseline (0 months) and after 3 and 12 months of follow-up.

TABLE 2 Acute haemodynamic changes in response to sildenafil[#]

	Major acute effect group	Minor acute effect group
Subjects n	35	32
$\Delta\bar{P}_{pa}$ %	23±1	13±2
ΔPVR %	34±1	12±2

Data are presented as mean±SEM, unless otherwise stated. Classification of the acute response was according to the degree of reduction in pulmonary vascular resistance (PVR; cut-off 27%). Δ: change; $\bar{P}_{pa}$: mean pulmonary arterial pressure. [#]: in a subset of 67 patients.

It was notable that none of the included patients died during the 1-yr observation period; however, in 7% of patients, combination therapy with inhaled iloprost was required [17].

Although inoperable CTEPH represents one of the largest subgroups of pre-capillary PH, data on pharmacological therapy in this disease are sparse. Inhaled iloprost has been studied in inoperable CTEPH in a subgroup within a randomised controlled trial; however, the study was not powered for subgroup analysis [8]. New oral compounds for the treatment of PH have been studied in patients with PAH, but patients with inoperable CTEPH were explicitly excluded [8, 9].

Small case series of intravenous epoprostenol and bosentan in inoperable CTEPH demonstrated a significant improvement in 6MWD after 3 months of therapy [11, 12, 14, 15]. A sustained improvement over 12 months' treatment with bosentan was recently described in a mixed patient population with inoperable CTEPH and residual PH after PTE [13].

In the present large series of patients with inoperable CTEPH, it was shown that monotherapy with sildenafil results in significant haemodynamic, functional and clinical improvement after 3 months of therapy, and sustained clinical and functional stabilisation over 12 months of treatment. This is in accordance with an initial small case series in inoperable CTEPH, in which an increase in 6MWD of 54 m was observed after 6 months of treatment [16].

The effects on functional capacity and haemodynamic parameters after 3 months of treatment in the present study (6MWD increase 51 m, PVR decrease 217 dyn·s·cm^{-5}) are comparable to the results of a large randomised controlled study in PAH (6MWD increase 46 m, PVR decrease 192 dyn·s·cm^{-5}) [9], suggesting that inoperable CTEPH patients may be as suitable for sildenafil treatment as PAH patients. Although WHO functional class is influenced by subjective perception of functional capacity, the 6MWD is regarded as currently being the best measure for assessing aerobic exercise capacity in PH [22].

The long-term haemodynamic response, on average, was very similar to the acute response to sildenafil; however, on an individual basis, there was no significant correlation between the acute and long-term response.

TABLE 3 Long-term changes on sildenafil therapy by acute sildenafil response[#]

	Baseline	3 months	p-value
Major acute effect group[¶]			
WHO class II/III/IV n	2/30/3	3/31/1	
6MWD m	310±18	358±26	0.005
$\bar{P}_{pa}$ mmHg	47±2	42±3	0.05
CI L·min^{-1}·m^{-2}	2.0±0.1	2.5±0.2	0.001
PVR dyn·s·cm^{-5}	916±66	632±112	0.002
Minor acute effect group[+]			
WHO class II/III/IV n	1/25/6	2/30/0	
6MWD m	301±21	379±26	0.02
$\bar{P}_{pa}$ mmHg	46±2	43±2	0.4
CI L·min^{-1}·m^{-2}	2.3±0.1	2.7±0.2	0.005
PVR dyn·s·cm^{-5}	770±61	624±82	0.03

Data are presented as mean±SEM, unless otherwise stated. WHO: World Health Organization; 6MWD: 6-min walking distance; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance. [#]: in a subset of 67 patients; [¶]: n=35; [+]: n=32.

A deliberate decision was made to include only patients with inoperable chronic thromboembolic disease to receive sildenafil monotherapy, and to exclude patients with operable CTEPH and those who had received prior therapy with inhaled iloprost or bosentan, in order to minimise heterogeneity within the study group. Despite initial improvement within 3 months, 7% of patients required combination therapy with inhaled iloprost due to clinical worsening within 1 yr. In all of these patients, combination therapy resulted in stabilisation of the disease, as previously shown [17]. Failure of sildenafil monotherapy should be expected in ~7% of patients with inoperable CTEPH within 1 yr of treatment.

A sildenafil dosage of 50 mg *t.i.d.* was used based on previous clinical experience [16, 23, 24]. This higher dose, compared with

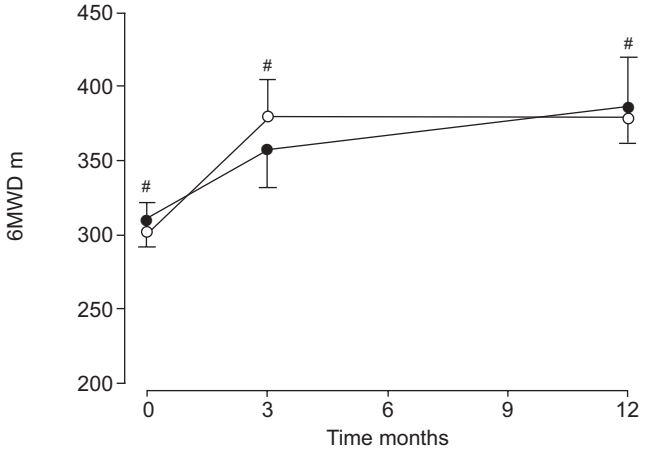

FIGURE 3. Development of 6-min walking distance (6MWD) in 67 patients stratified by major (>27% reduction in pulmonary vascular resistance (PVR); ○) or minor (<27% reduction in PVR; ●) acute haemodynamic response to sildenafil at baseline (0 months; start of sildenafil therapy). Data are presented as mean±SEM. [#]: nonsignificant.

the currently licensed dose for the treatment of PAH (20 mg *t.i.d.*), was not associated with a higher rate of side-effects.

In general, the observed side-effects of sildenafil therapy included minor epistaxis in eight patients, which may have been due to a combination of sildenafil and intense oral anticoagulation therapy. Other reported side-effects included flush, symptoms of gastro-oesophageal reflux and lower back pain that was responsive to analgesics or proton pump inhibitors. None of these side-effects required special intervention or hospitalisation.

Haemodynamic or other markers predictive of the individual long-term response to therapy are required for all forms of PH; however, published data are only available for high-dose calcium channel blockers and epoprostenol therapy in idiopathic PAH [18, 25]. Although the acute response is predictive of response to long-term calcium channel blocker therapy, it is not predictive of the long-term epoprostenol response. There is no information regarding the prospective value of the acute sildenafil response in inoperable CTEPH.

In a subgroup within the present study population, a remarkable acute haemodynamic effect of sildenafil was found, with a 27% decrease in PVR, but only a 4% decrease in $\bar{P}_{pa}$. This effect was similar to the haemodynamic improvement after 3 months of therapy (tables 2 and 3).

Although CTEPH is regarded as an obstructive pulmonary vascular disease, the acute pulmonary vasodilative properties speak in favour of significant pulmonary vascular changes (remodelling) in the nonobliterated pulmonary vasculature [3]. One component of the remodelling is acutely reversible vasoconstriction, as has previously been shown in CTEPH patients [4]. Indeed, in 13 out of the 67 subgroup patients, a reduction in $\bar{P}_{pa}$ of >10 and <40 mmHg was observed. According to current guidelines, this would be regarded as a significant acute haemodynamic response in idiopathic PAH. However, sildenafil is not established for acute vasoreactivity testing and such tests are of no clinical consequence in patients with CTEPH.

In the present patient population, the acute haemodynamic effect of sildenafil did not predict the long-term result of therapy. Although the acute haemodynamic effects were considerably different between individuals and within the minor and major acute effect groups, as defined in the present study, there was comparable long-term haemodynamic improvement after 3 months. More importantly, the functional and clinical responses after 3 and 12 months were unrelated to the acute sildenafil response.

The major limitation of the present study is the single-centre uncontrolled design, with lack of a control group. However, the haemodynamic and clinical response to sildenafil treatment was apparent and consistent in the long run. Nevertheless, the findings of this open-label uncontrolled study warrant confirmation in a randomised controlled trial of sildenafil in inoperable CTEPH.

In conclusion, in the present single-centre uncontrolled trial, sildenafil therapy led to significant and sustained long-term functional and haemodynamic improvement in patients with inoperable chronic thromboembolic pulmonary hypertension. The acute effect of sildenafil may not predict the long-term outcome of therapy.

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