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ORIGINAL ARTICLE

The efficacy and safety of sildenafil in Chinese patients with pulmonary arterial hypertension

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Sildenafil has been suggested to be a cost-effective treatment for pulmonary arterial hypertension (PAH). On account of the lack of data confirming its benefit in PAH patients, sildenafil has not been adopted in China for the treatment of PAH. The purpose of this study was to evaluate the efficacy, safety and 1-year survival of Chinese patients with PAH treated with sildenafil. Sixty Chinese patients with PAH were enrolled in this preliminary study. Their 6-min walk distance, WHO functional class and hemodynamic parameters (such as right atrial pressure, pulmonary arterial pressure, cardiac index and pulmonary vascular resistance) at both baseline and 16 weeks after initiation of sildenafil treatment were recorded. In addition, 1-year overall survival was assessed in this cohort. The 6-min walk distance improved from 392.13 ± 91.35 to 467.22 ± 80.38 m during the course of treatment ($P<0.001$). There was a significant decrease in the mean pulmonary vascular resistance (15.28 ± 8.12–14.99 ± 7.88 Woods units; $P=0.02$) and a significant increase in the mean cardiac index (2.39 ± 0.90–2.75 ± 0.92 l/min/m^2, $P=0.006$) of the included patients at 16 weeks. The mean systemic oxygen saturation improved significantly at 16 weeks (91.44 ± 7.54%–94.11 ± 4.28%; $P=0.002$). No serious adverse reactions were reported. The Kaplan–Meier analysis showed that the 1-year survival rate improved significantly in the sildenafil-treated cohort compared with predicted survival (94.7% compared with 63.3%, $P=0.03$). In conclusion, sildenafil may be a safe and effective treatment for Chinese PAH patients. Sildenafil, when added to conventional therapy, was associated with improvements in exercise capacity, hemodynamic parameters and overall survival in a cohort of Chinese patients with PAH.
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INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by a remodeling of the pulmonary arterial microvasculature with an associated progressive increase in pulmonary vascular resistance, resulting in right ventricular failure and premature death if left untreated.[1–3] Without targeted therapy, the prognosis of PAH is very poor. Overall survival rates for primary pulmonary hypertension have been reported to be in the ranges of 68–77, 52–57, 39–41 and 21–27% at 1, 2, 3 and 5 years, respectively.[4,5] According to the idiopathic and familial PAH registry study in China, in which patients received only conventional therapy, the survival at 1, 2, 3 and 5 years was found to be 68.0, 56.9, 38.9 and 20.8%, respectively.[6] Although iloprost and bosentan have been approved for the treatment of PAH in China, for economic reasons, few patients have been treated with these agents.

Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor that has been approved for the treatment of PAH in the United States and European Union since 2005.[7] A 1-month supply of conventional sildenafil therapy (20 mg t.i.d.) costs only US$300 in China, which is much less than bosentan and iloprost, which cost about US$3000 per month. However, as no clinical study has confirmed its efficacy and safety in PAH in China, sildenafil has not been approved for the treatment of PAH in China.

The objective of our open-label study was to assess the effects of sildenafil therapy on the exercise capacity, hemodynamic parameters and overall survival of Chinese patients with PAH.

METHODS

Study population

Consecutive patients with PAH seen at the Aviation Industry Central Hospital, Fu Wai Hospital, Shanghai Pulmonary Hospital, Beijing Shijitan Hospital and Parkway Health Medical Centers during the period from September 2006 to December 2008 were considered for entry into the study.

Patients were enrolled if they met the following criteria: (1) World Health Organization (WHO) functional class II, III or IV; (2) PAH, either idiopathic, associated with connective tissue disease, or occurring at least 3 years after the surgical or interventional repair of the congenital systemic-to-pulmonary

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shunts; and (3) age ⩾16 years. Pulmonary arterial hypertension was defined as the resting mean pulmonary artery pressure (mPAP) >25 mm Hg, a pulmonary capillary wedge pressure <15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood Units.[8]

Patients were excluded if they responded acutely to pulmonary vasoreactivity testing or if they had received treatment with oral bosentan or inhaled iloprost in the preceding 6 months. Additional exclusion criteria included a baseline 6-min walk distance of less than 150 m or more than 500 m and interstitial pulmonary fibrosis resulting in total lung capacity of <60%. Sildenafil was administered to all patients after enrollment. Conventional therapies permitted in addition to sildenafil included anticoagulants, diuretics, digoxin and supplemental oxygen.

The study was performed according to the 1975 Declaration of Helsinki (modified in 1983) and in adherence to local guidelines for good clinical practice. The protocol was approved by the local ethics committees, and written informed consent was obtained from all patients.

Study design

This was an open-label, uncontrolled, fixed-dose study conducted on PAH patients at five centers in China. After a screening period of 3–14 days, 60 eligible patients were enrolled in this study. Eligible patients were given sildenafil 20 mg t.i.d. in addition to the conventional therapies noted above. Six-min walk distance, WHO functional class, echocardiographic parameters, serum markers and hemodynamic assessments were determined at baseline and after 16 weeks of sildenafil therapy. All patients continued to take sildenafil after the end of the 16-week study period and additional data were collected during the extended treatment period.

Data collection and follow-up

Patients were re-evaluated 16 weeks after initiation of sildenafil therapy and every 3–6 months thereafter. The primary outcome measure was the change in the 6-min walk distance at week 16. Secondary end points included WHO functional class, echocardiographic parameters and hemodynamic indices at week 16. Hemodynamic indices that were measured included cardiac index (CI), PVR, mPAP and pulmonary capillary wedge pressure, all of which were measured by right heart catheterization at baseline and at week 16. CI was computed as cardiac output divided by body surface area; cardiac output was measured using the thermodilution technique; PVR was calculated using the standard formula: PVR=(mPAP−PCWP)/cardiac output.[9] Physical examinations and laboratory tests were performed at each visit, and investigators recorded adverse events throughout the study.

After week 16, all patients were treated for an extended follow-up period. The primary end point of the follow-up period was overall survival compared with predicted survival, which was calculated using the National Institute of Health formula.[4]

Six-min walk test

Six-min walk tests were performed by patients in accordance with the American Thoracic Society Guidelines.[10]

Right heart catheterization

Right heart catheterization was performed in all 60 patients at baseline according to standardized protocol. Follow-up right heart catheterizations were performed in all patients at week 16.

Data analysis

All data are expressed as mean ± s.e.m. SPSS 13.0 for Windows was used for all statistical analyses (SPSS Inc., Chicago, IL, USA). As every patient served as his or her own control, a paired sample *t*-test was used to compare data points at baseline and at 16 weeks (6-min walk distance, echocardiography and invasive hemodynamic parameters). All reported *P*-values were two-tailed. *P*-values <0.05 were considered statistically significant.

Survival was assessed from the start of therapy to death or the end of follow-up. The Kaplan–Meier survival curves were plotted for both the actual survival rate of the sildenafil-treated patients and the expected survival rate of the enrolled patients (calculated for each patient on the basis of the NIH formula). The log-rank test was used to compare survival probabilities.

RESULTS

Study sample characteristics

A total of 60 patients were enrolled in this study. Twenty of them (33.3%) were male and forty (66.7%) were female patients. The mean age was 33.56 ± 14.12 years. Table 1 describes the patients' baseline clinical characteristics, including sex, weight, body surface area, WHO functional class and diagnosis. The etiology of PAH included 40 patients (66.67%) with idiopathic pulmonary arterial hypertension, 12 patients (20.00%) with PAH associated with repaired congenital systemic-to-pulmonary shunts and eight patients (13.33%) with PAH associated with connective tissue diseases. Thirty-four patients (56.67%) were significantly symptomatic, as defined by having a WHO functional class III or IV. All patients received additional medications concomitantly, including anticoagulants, digoxin and diuretics.

Treatment effect

None of the patients died during the first 16 weeks of treatment. Complete follow-up data were obtained in all patients. Three patients were started on bosentan after the initial 16-week study period because of a worsening of the clinical symptoms. The remainder of the patients remained on sildenafil alone during the extended follow-up period.

Exercise capacity and WHO functional class

The median baseline 6-min walk distance was 392.13 m. A significant improvement in the 6-min walk distance was observed after 16 weeks of sildenafil treatment (467.22 ± 80.38 m at 16 weeks *vs.* 392.13 ± 91.35 m at baseline; $P<0.001$) (Figure 1).

Sildenafil treatment improved the WHO functional class of the PAH patients enrolled in this study (Figure 2). At baseline, there were 26 patients with class II, 32 patients with class III, and two patients with class IV WHO functional status. Following 16 weeks of sildenafil therapy, the distribution of WHO classifications was as follows: six patients with class I, 42 patients with class II, 12 patients with class III and 0 patients with class IV functional status.

Cardiopulmonary hemodynamics

At baseline, the median mPAP was 63.52 mm Hg, the median systemic systolic blood pressure was 107.29 mm Hg, the median CI was

Table 1 Baseline characteristics of the study sample

Characteristics	*Study sample (n=60)*
Age, years	33.56 ± 14.12
Male, *n* (%)	20 (33.33)
Weight, kg	56.78 ± 12.09
Body surface area, m^2	1.61 ± 0.18
Etiology of pulmonary arterial hypertension, n (%)	
Idiopathic	40 (66.67)
Associated with repaired congenital S–P shunts, *n* (%)	12 (20.00)
Associated with connective tissue disease, *n* (%)	8 (13.33)
WHO functional class, n (%)	
II	26 (43.33)
III	32 (53.34)
IV	2 (3.33)

$2.391\,min^{-1}\,m^{-2}$ and the median PVR was 16.01 Wood Units (Table 2). After 16 weeks of sildenafil treatment, all 60 patients underwent repeated right heart catheterization. Compared with baseline, there was a significant improvement in PVR, mPAP, CI and systolic blood pressure after oral sildenafil therapy. Systemic arterial oxygen saturation increased significantly as well. Improvements in the hemodynamic parameters observed with sildenafil were not associated with the clinically relevant changes in the heart rate (Table 2).

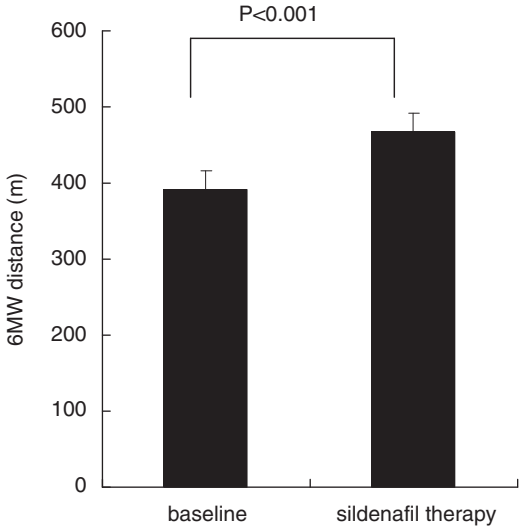

Figure 1 Change in 6MW distance from baseline. The baseline 6MW distance was 392.13 ± 91.35 m, increased to 467.22 ± 80.38 m at week 16 ($P<0.001$, $n=60$).

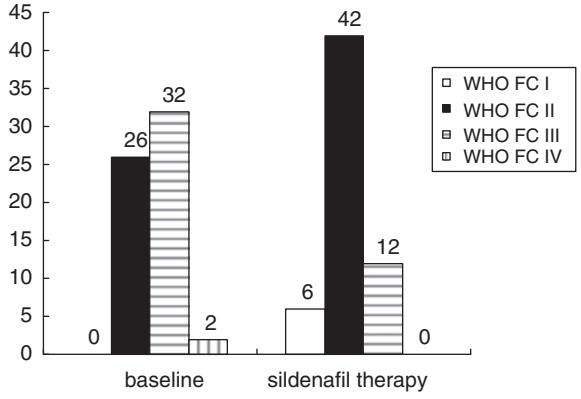

Figure 2 Effects of sildenafil therapy on WHO functional class: change in number of patients from baseline to week 16.

Echocardiographic parameters and serum biomarkers

All patients had severe right ventricular dilatation and hypertrophy on echocardiography with moderate to severe tricuspid regurgitation. Patients treated with sildenafil showed improvements in their left ventricular end-diastolic diameter and right ventricular diameter. In patients treated with sildenafil, there was a significant reduction in the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at 16 weeks compared with baseline ($332.73 \pm 170.01\,pg\,ml^{-1}$ and $276.13 \pm 144.12\,pg\,ml^{-1}$, respectively; $P=0.01$). Plasma uric acid and big endothelin-1 (big ET-1) levels did not differ between baseline and week 16 (Table 3).

Safety

All patients tolerated the drug well without any major adverse events. Minor side effects included self-limited headache (38 patients, 63.3%), dyspepsia (six patients, 10.0%) and blurry vision (two patients, 3.33%). None of the patients reported an allergic skin rash. No patient had to discontinue sildenafil because of intolerance or adverse events.

Survival analysis

No patients were lost to follow-up in this study. The mean duration of follow-up was 12.52 ± 4.38 months. Two patients with WHO functional class IV PAH died of progressive right heart failure. The Kaplan–Meier analysis revealed a 1-year survival rate of 94.7% in this cohort of sildenafil-treated patients. This differed significantly from the predicted survival rate (calculated for each patient on the basis of the NIH formula) of 63.3% (Figure 3) ($P=0.03$, log-rank test).

DISCUSSION

Earlier studies have shown that there is an abundance of PDE-5 in the smooth muscle of the lung vasculature.[11,12] PDE-5 inhibitors cause a relaxation of the pulmonary vasculature smooth muscle by activating large-conductance, calcium-activated potassium channels.[13] Moreover, PDE-5 inhibitors, such as sildenafil, have been shown to reduce the mean pulmonary arterial pressure and pulmonary vascular resistance, resulting in improved ventilation–perfusion mismatch, arterial oxygenation and functional capacity in PAH patients in Western countries.[7,13] Despite these data on the beneficial effects of PDE-5 inhibitors in PAH, the specific effects of sildenafil on the clinical and hemodynamic parameters in Chinese patients with PAH had not been reported earlier.

In this open-label study, 16 weeks of sildenafil therapy (20 mg orally, three times/day) was well tolerated in PAH patients and was associated with a significant improvement in the exercise capacity, WHO functional class and hemodynamic indices. During the

Table 2 Hemodynamics characteristics for 60 patients treated with sildenafil

	Baseline (n=60)	*After 16 weeks of treatment with sildenafil (n=60)*	P-*value*
Heart rate, beats per min	81.96 ± 16.26	80.75 ± 12.08	0.70
Systolic blood pressure, mm Hg	107.29 ± 12.65	115.62 ± 13.12	<0.01
Diastolic blood pressure, mm Hg	70.54 ± 12.03	74.02 ± 9.89	0.30
Mean pulmonary artery pressure, mm Hg	63.52 ± 17.28	58.62 ± 13.29	0.02
Cardiac index, liters per min m^{-2}	2.39 ± 0.90	2.75 ± 0.92	0.005
Pulmonary vascular resistance, Wood Units	16.01 ± 7.24	14.99 ± 7.88	0.02
Right atrial pressure, mm Hg	7.03 ± 4.71	4.91 ± 4.20	0.15
Arterial oxygen saturation, %	91.44 ± 7.54	94.11 ± 4.28 %	0.002

Table 3 Effects of oral sildenafil on echocardiography parameters and serum biomarkers: change from baseline to week 16

	Baseline (n=60)	*After 16 weeks of treatment with sildenafil (n=60)*	P-*value*
LVEDD, mm	36.89 ± 6.25	39.64 ± 4.91	0.02
RV, mm	36.25 ± 7.26	33.12 ± 6.95	0.04
UA, mg dl^{-1}	6.56 ± 2.04	6.43 ± 1.35	0.90
NT-proBNP, pg ml^{-1}	332.73 ± 170.01	276.13 ± 144.12	0.01
Big ET-1, pg/ml^{-1}	3.70 ± 2.45	5.13 ± 3.20	0.24

Abbreviations: LVEDD: left ventricular end-diastolic diameter, RV: right ventricular, UA: uric acid, NT-proBNP: N-terminal pro-brain natriuretic peptide, Big ET-1: Big endothelin-1.

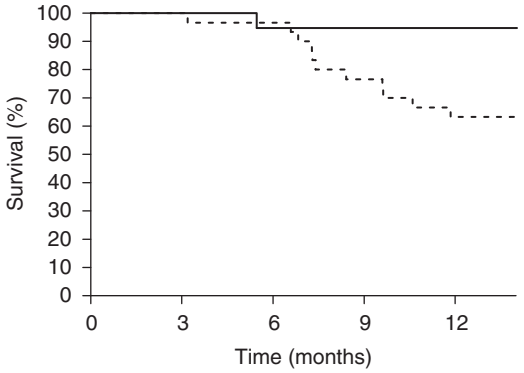

Figure 3 Observed survival (—) in 60 oral sildenafil-treated PAH patients (with baseline hemodynamics available) *vs.* predicted survival (---) by the National Institute of Health equation. One-year survival estimate was 94.7% *vs.* predicted survival rate of 63.3% (P=0.03).

extended treatment period, the survival rate was found to have improved significantly compared with the survival rate predicted by the National Institute of Health formula, and sildenafil continued to be well tolerated during this period.

The 6-min walk distance is an independent predictor of death in patients with idiopathic pulmonary arterial hypertension, and has been used as the primary end point in a number of studies of pulmonary arterial hypertension.[14,15] In Michelakis's 2003 open-label study of sildenafil in PAH, a treatment-related improvement in the 6-min walk distance of 128 m was observed.[15] In Galiè's 2005 study, there was a treatment-related increase in the six-minute walk distance of 45–50 m.[7] In our study of sildenafil-treated Chinese PAH patients, the 75 m improvement in the 6-min walk distance was similar to that seen in earlier studies. The improvement in exercise capacity that occurred with sildenafil treatment in this study was associated with an increase in cardiac output as well as with an improvement in other hemodynamic parameters at 16 weeks compared with baseline data.

The observed reduction in pulmonary arterial pressure and increase in cardiac index were similar to those reported in earlier studies examining sildenafil therapy in PAH patients.[13,15,16] Several mechanisms may account for the improvement in hemodynamic parameters seen with sildenafil therapy. In addition to directly reducing pulmonary vascular resistance (by the aforementioned mechanism), sildenafil treatment also leads to an increase in cardiac output owing to a reduction in right ventricular afterload caused by dilatation of the pulmonary vasculature. Sildenafil's anti-proliferative properties may also reverse the remodeling of the pulmonary resistance vessels in patients receiving long-term treatment.[17,18]

Sastry *et al.*[18] have shown that oral sildenafil therapy in PAH patients leads to 1-, 3- and 5-year survival rates of 93, 75 and 54%, respectively. These rates are significantly higher than the expected survival rates of 89, 43 and 19% calculated on the basis of the NIH formula. In historical PAH patients receiving only conventional therapy in China, survival at 1 year has been documented to be 68.0%.[6] In this study, the survival of patients who received sildenafil treatment was 94.7% at the end of 1 year. This result suggests that sildenafil treatment might improve the prognosis in Chinese PAH patients in a manner similar to the results that have been reported in Western patients.

Study limitations

This was an open-label study without a control group. Although all patients showed improvement in functional class and exercise capacity, a double-blind, placebo-controlled trial should be undertaken to assess the effect of the drug on exercise capacity and functional status in Chinese PAH patients. A longer follow-up period should also be included in future studies to more effectively determine the impact of sildenafil therapy on long-term survival among Chinese PAH patients. In Simonneau's study in 2008, the improvement of the 6-min walk distance was most prominent among patients with baseline 6-min walk distances of 325 m or more. The median 6-min walk distance in our study was 392.13 m at baseline, which showed that more patients with mild and moderate symptoms were enrolled in this study compared with others.[19]

Conclusions

Oral sildenafil therapy may be a cost-effective, well-tolerated approach to achieving selective pulmonary vasodilatation in Chinese PAH patients. In this study, sildenafil therapy improved the 6-min walk distance, WHO functional class, echocardiography parameters, serum markers, hemodynamics and 1-year survival of included PAH patients. These clinical, biochemical and hemodynamic improvements suggest that sildenafil therapy may be beneficial for Chinese patients with PAH and provide the rationale for performing a larger, placebo-controlled clinical trial.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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