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Sildenafil Improves Walk Distance in Idiopathic Pulmonary Fibrosis

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Abstract

Pulmonary hypertension is a common finding in patients with idiopathic pulmonary fibrosis (IPF), and is associated with increased morbidity and mortality. Therapy with sildenafil has been shown to decrease pulmonary vascular resistance in patients with pulmonary fibrosis and may improve functional status. Patients with IPF and documented pulmonary hypertension were followed up in an open-label study of sildenafil. The 6-min walk test distance (6MWD) was obtained before and after 3 months of sildenafil therapy. Fourteen patients were followed up in the study; 11 patients completed both 6-min walk tests. The mean improvement in walk distance was 49.0 m (90% confidence interval, 17.5 to 84.0 m). When all 14 patients were dichotomized into groups of “responders” (*ie*, $\geq 20\%$ improvement in 6MWD) or “nonresponders” (*ie*, $< 20\%$ change or unable to complete), 57% were classified as responders. Sildenafil is a promising and well-tolerated therapeutic agent for use in patients with IPF and pulmonary hypertension, and should be studied in a large, well-controlled trial.

Keywords

clinical trial; pulmonary fibrosis; pulmonary hypertension; sildenafil; therapeutics

Idiopathic pulmonary fibrosis (IPF) is the most common form of chronic, diffuse lung disease and is associated with a particularly poor prognosis.^{1,2} Recent data have suggested that many patients with IPF have pulmonary arterial hypertension (PAH). Two large studies^{3,4} of patients undergoing formal evaluation for lung transplantation found that 33 to 50% of patients demonstrated PAH at rest, as assessed by right-heart catheterization.

The presence of PAH in IPF patients is associated with poor survival.^{4–6} Sildenafil (Viagra or Revatio; Pfizer; New York, NY), a phosphodiesterase-5 inhibitor, appears to cause clinically significant pulmonary vasodilation in patients with pulmonary fibrosis.⁷ The long-term effects of sildenafil on functional measures such as 6-min walk test distance (6MWD) have not been

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studied in patients with IPF and PAH. We tested the hypothesis that treatment with sildenafil would improve 6MWD in patients with IPF and PAH.

Materials and Methods

All patients were transitioned into this open-label study from a randomized trial of sildenafil at the University of California Los Angeles (ClinicalTrials.gov identifier: NCT00352482). Written informed consent was obtained from each patient. Patients had an established diagnosis of IPF, determined according to accepted criteria,⁸ and evidence of pulmonary hypertension defined by either (1) a mean pulmonary artery (PA) pressure of ≥ 25 mm Hg on right-heart catheterization ($n = 10$), or (2) a PA systolic pressure of ≥ 35 mm Hg on echocardiography ($n = 4$). Patients with contraindications to phosphodiesterase inhibitor therapy were excluded from the study.

Patients performed two baseline 6-min walk tests (6MWTs) according to modified American Thoracic Society standards⁹ on the day of screening to control for potential learning effects. Testing was uncoached, and rest periods were allowed. At the end of 6 min, the total distance walked was recorded. As recommended by American Thoracic Society guidelines,⁹ the test was terminated if the pulse oximetric saturation fell to $< 80\%$ and the distance walked prior to termination was recorded. In all patients, the best baseline 6MWD was recorded as the pretreatment value. Patients were then treated with open-label sildenafil (dosed between 20 and 50 mg tid, depending on the formulation available) with a follow-up 6MWT planned for 12 weeks. The primary end point was change in 6MWD (in meters) over time. Secondary end points were clinically meaningful response to sildenafil (defined as a $\geq 20\%$ improvement in 6MWD) and incidence of adverse events. The mean change in 6MWD was reported along with a 90% confidence interval based on nonparametric bootstrap estimates.¹⁰ All analyses were performed using a statistical software package (SAS, version 9.2; SAS Institute; Cary, NC).

Results

Fourteen patients were enrolled in the open-label study (Table 1). Eleven patients successfully completed both the baseline and follow-up 6MWTs. The median time between initial and follow-up testing was 91 days.

Individual walk data on all 14 patients are presented in Table 2. Nine patients showed improvement in their 6MWD; only two patients showed a decline. The mean improvement in the 6MWD among those completing both walk tests ($n = 11$) was 49.0 m (90% confidence interval, 17.5 to 84.0 m). When all 14 patients were dichotomized into groups of “responders” (*ie*, $\geq 20\%$ change in 6MWD) or “nonresponders” (*ie*, $< 20\%$ change in 6MWD or was unable to complete the second 6MWT), 57% of patients were classified as responders. There was no change in the perceived level of exertion during 6MWT with sildenafil therapy ($p = 0.52$).

Sildenafil therapy was stopped in two patients due to side effects that were attributed to the medication (*ie*, diarrhea and transient hypotension), and one patient was unable to complete the second 6MWT due to chest discomfort (this patient continued to receive therapy with sildenafil). Of the 11 patients completing the study, 1 patient reported mild intermittent diarrhea and headaches, a second patient reported mild intermittent headaches, and a third patient reported blurry vision.

Discussion

Historical data suggest the majority of patients with IPF have PAH. PAH at rest (*ie*, a mean PA pressure of > 20 mm Hg on right-heart catheterization) was reported in 55% of patients

with IPF.¹¹ In that cohort, 80% of IPF patients had PAH with exercise (mean PA pressure > 30 mm Hg). Pre-lung transplantation evaluations have corroborated these early findings.^{3,4} Importantly, the presence of PAH in patients with IPF is a predictor of worse survival.^{4–6}

This study demonstrates significant improvement in 6MWD after treatment with sildenafil in patients with IPF and PAH. More than half of patients (57%) improved their 6MWD by $\geq 20\%$, which we believe demonstrates a clinically meaningful increase in functional status. These findings are consistent with the results of smaller reports^{7,12,13} showing the effects of sildenafil on pulmonary hemodynamics and walk distance in patients with pulmonary fibrosis. In a group of eight patients with pulmonary fibrosis and PAH undergoing right-heart catheterization, treatment with a single dose of oral sildenafil (50 mg) lowered the mean PA pressure, improved ventilation/perfusion matching, and improved gas exchange.⁷ A report¹² of three patients with IPF and PAH treated with 8 weeks of sildenafil therapy showed a significant increase in mean 6MWD (80 to 120 m; $p = 0.03$). Data published in abstract form only reported the effects of sildenafil in 10 patients with IPF and PAH.¹³ Right heart catheterization during the initial dose of sildenafil showed a reduction in pulmonary vascular resistance of 28%; during a median follow-up time of 8.4 months, significant improvements in dyspnea, gas exchange, and quality of life were reported.

The 6MWD is a relevant outcome measure in patients with IPF and PAH.^{14,15} Recently, a retrospective review¹⁶ of 454 patients with IPF who had undergone formal 6-min walk testing at the time of referral for lung transplantation found that a lower 6MWD was associated with an increased risk of death (adjusted rate ratio, 4.7; $p < 0.0001$). In contrast to traditional therapies in IPF patients, sildenafil appears to be generally well-tolerated.^{7,12} Only one patient in our protocol had a serious adverse event (transient hypotension) that was attributable to sildenafil. Based on the results of this study, we believe sildenafil is a promising therapy for patients with IPF and PAH. The results of this study should be confirmed in a large, randomized, placebo-controlled trial.

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Abbreviations

IPF	idiopathic pulmonary fibrosis
PA	pulmonary artery
PAH	pulmonary arterial hypertension
6MWD	6-min walk test distance
6MWT	6-min walk test

Table 1**Clinical Characteristics***

Variables	Values
Age, yr	72 (7); 71 (63, 85)
Female gender	6 (43)
Smoking history	10 (71)
Duration of symptoms, mo	40.4 (30.0); 34.5 (10, 84)
Surgical lung biopsy-proven disease	6 (43)
Right-heart catheterization performed	10 (71)
Mean PA pressure, [†] mm Hg	30.7 (5.7); 29.5 (29.0, 43.0)
FVC	
L	2.65 (1.18); 2.39 (0.99, 5.31)
% predicted	69.6 (18.4); 71.5 (41.0, 100.0)
D _{LCO}	
mL/min/mm Hg	7.39 (3.92); 7.25 (2.90, 17.80)
% predicted	32.4 (17.0); 33.0 (13.0, 79.0)

* Values are given as the mean (SD); median (minimum, maximum) or No. (%). DLCO = diffusing capacity of the lung for carbon monoxide.

[†] Values reported based on the number of patients who underwent right-heart catheterization (n = 10).

Table 2

Change in 6MWD by Patient*

Patient No.	RHC	Dose (tid), mg	6MWD, m			BDI		AEs
			Baseline	Follow-up	Change	Baseline	Follow-up	
1	Y	50	40	60	20	15	13	None
2	Y	50	60	100	40	15	13	None
3	Y	50	382	374	-8	7	7	None
4	N	50	100	140	40	11	13	None
5	N	50	135	95	-40	12	12	None
6	Y	20	55	100	45	12	11	None
7	Y	20	75	90	15	10	7	Headache and diarrhea
8	Y	20	60	185	125	11	9	None
9	N	50	518	525	7	6	6	None
10	Y	20	70	85	15	13	12	Headache
11	Y	40	65	270	205	6	7	Blurry vision
12	Y	40	155			15		Chest pain during follow-up 6MWT [†]
13	Y	20	105			11		Diarrhea (medication stopped)
14	N	25	250			8		Transient hypotension (medication stopped)

* RHC = right-heart catheterization; BDI = Borg dyspnea index; AE = adverse event; Y = yes; N = no.

[†] Stopped at 30 m due to chest pain.