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The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial

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1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2016.04.010

KEYWORDS:
pulmonary hypertension;
chronic obstructive pulmonary disease;
sildenafil;
BODE index;
end-stage lung disease;
lung transplantation

BACKGROUND: Pulmonary hypertension (PH) is a well-known independent prognostic factor in chronic obstructive pulmonary disease (COPD) and a sufficient criterion for lung transplant candidacy. Limited data are currently available on the hemodynamic and clinical effect of phosphodiesterase 5 inhibitors in patients with severe PH associated with COPD. This study assessed the effect of sildenafil on pulmonary hemodynamics and gas exchange in severe PH associated with COPD.

METHODS: After screening, this multicenter, randomized, placebo-controlled double-blind trial randomized patients to receive 20 mg sildenafil or placebo 3 times a day (ratio 2:1) for 16 weeks. The primary end point was the reduction in pulmonary vascular resistance. Secondary end points included BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, 6-minute walk test, and quality of life questionnaire. Changes in the partial pressure of arterial oxygen were evaluated as a safety parameter.

RESULTS: The final population included 28 patients, 18 in the sildenafil group and 10 in the placebo group. At 16 week, patients treated with sildenafil had a decrease in pulmonary vascular resistance (mean difference with placebo –1.4 WU; 95% confidence interval, $\leq$ –0.05; $p = 0.04$). Sildenafil also improved the BODE index, diffusion capacity of the lung for carbon monoxide percentage, and quality of life. Change from baseline in the partial pressure of arterial oxygen was not significantly different between the sildenafil and placebo groups.

CONCLUSIONS: This pilot study found that treatment with sildenafil reduced pulmonary vascular resistance and improved the BODE index and quality of life, without a significant effect on gas exchange.

J Heart Lung Transplant 2017;36:166–174

Pulmonary hypertension (PH) is a condition frequently observed in chronic obstructive pulmonary disease (COPD).[1–3] Usually, PH-COPD is mild or moderate (mean pulmonary artery pressure, 25-35 mm Hg), but severe PH (mean pulmonary artery pressure [mPAP] > 35 mm Hg) occurs in 3% to 5% of COPD patients.[3,4] The clinical effect of PH in COPD is relevant because it represents an independent predictor of poor prognosis and a sufficient criterion for lung transplant candidacy.[4–6]

The pathogenesis of severe PH in COPD is not completely explained by a simple hypoxic vasoconstriction mechanism,[6] and recent data from the pathologic analysis of COPD lungs explanted for transplantation showed a correlation between the type and extension of pulmonary vascular lesions and the severity of PH assessed by right-heart catheterization (RHC).[7]

Despite the independent prognostic effect of PH in COPD, only a few randomized controlled studies have addressed whether pulmonary arterial hypertension (PAH) drugs may be effective in the treatment of PH in COPD.[7–10] The overall results were generally inconclusive because their inclusion criteria (definition of PH, mPAP cutoff, severity of obstruction) varied widely and their study designs could not be compared. Moreover, a worsening of gas exchange was reported in COPD patients with mild PH treated with sildenafil.[11] In the present prospective randomized, controlled, proof-of-concept study, we investigated whether sildenafil improves rest pulmonary hemodynamics in severe PH-COPD without a detrimental effect on gas exchange.

Methods

Study overview

The study, an investigator-driven trial, was funded by Pfizer, sponsored by Associazione Italiana Pneumologi Ospedalieri (AIPO), and performed in Italy. Pfizer donated sildenafil and identical tablets containing placebo, but took no part in the study design, in the accrual or analyses of data, and in the preparation of the manuscript. The study was conducted at 7 Italian centers with expertise in the management of PH and COPD, most of which are also lung transplant centers. ISMETT (Istituto Mediterraneo per I Trapianti e Terapie ad Alta Specializzazione, Palermo, Italy) served as the data-coordinating center, and managed all aspects of the study, data management, and statistical analysis. The study was approved by the Institutional Review Boards of each center, and all the patients signed informed consent before enrollment. The trial was registered on the www.clinicaltrials.gov Web site (NCT0144193).

Study patients

We included patients between the ages of 40 and 80 years and diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines.[12] Patients were excluded if they had decompensated heart failure, a severe mental disorder preventing appropriate judgment concerning study participation, or known intolerance to or formal contraindication for the use of sildenafil.

Patients with COPD referred with symptoms suggestive of PH were screened with Doppler echocardiography: an estimated systolic pulmonary arterial pressure $\geq$ 50 mm Hg was the indication for the baseline RHC. To identify patients with significant PH with respect to airflow limitation, we enrolled patients with mPAP $\geq$ 35 mm Hg in the case of forced expiratory volume of 1 second (FEV_1) < 30% of predicted value after bronchodilator, and mPAP $\geq$ 30 mm Hg for a FEV_1 > 30% of predicted value after bronchodilator.

Other potential causes of PH, such as chronic thromboembolic pulmonary hypertension or left-sided heart disease were excluded, as was ischemic or cardiac valve disease. Also excluded were patients receiving concomitant nitrate or PAH treatment, those with liver/kidney dysfunction, or who had experienced a recent bronchial exacerbation (< 4 weeks).

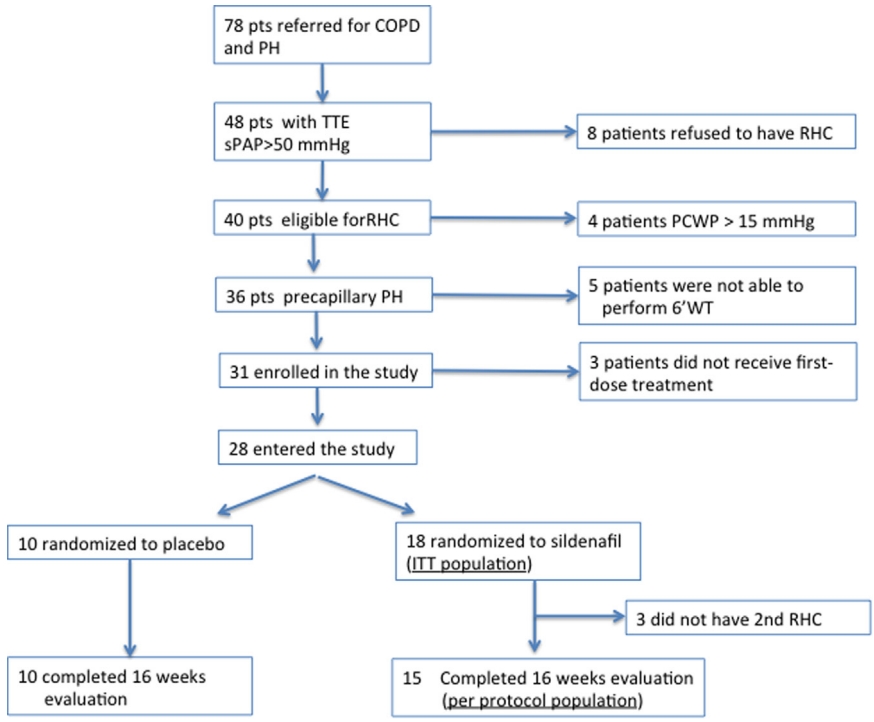

Figure 1 Flow chart of patient disposition in the study. 6'WT, 6-minute walk test; COPD, chronic obstructive pulmonary disease; ITT, intention to treat; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; RHC, right-heart catheterization; sPAP, systolic pulmonary artery pressure; TTE, transthoracic echocardiography.

Study design

Sildenafil and Pulmonary HypERtension In COPD (SPHERIC-1) was a 16-week, double-blind, multicenter, randomized, placebo-controlled trial of oral sildenafil (20 mg) given 3 times a day. Patients who met the eligibility criteria were screened with transthoracic echocardiogram, and after the baseline evaluation, including the confirmatory RHC, spirometry, arterial blood gas analysis, and 6-minute walk test (6MWT), they were randomized with a 2:1 ratio to receive sildenafil or matched placebo. A pharmacologist not involved directly in the study used an electronic system to manage randomization. At the end of study, after 16 weeks of treatment, a second clinical and hemodynamic assessment was made.

Outcome measures

The primary end point was the improvement in pulmonary hemodynamics assessed by the change in pulmonary vascular resistance (PVR) at the end of the study compared with the baseline. Additional end points included changes from baseline of partial pressure of arterial oxygen (Pao_2), BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index, 6MWT distance, and quality of life as measured by the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) questionnaire.

Safety evaluations

Because sildenafil may worsen pulmonary gas exchange in COPD,[13] the candidates were evaluated for their arterial blood gases (ABGs) in stable condition before randomization. Patients supported with long-term oxygen therapy of $\leq$ 6 liters/min flow were accepted. The cutoff value of partial pressure of arterial carbon dioxide ($Paco_2$) for inclusion was $\leq$ 55 mm Hg. For safety reasons, all patients underwent a second ABG measurement after taking the first dose of blind study medication. Patients with a drop of Pao_2 $<$ 55 mm Hg were excluded from the study.

During the study, measurements of the percentage of percutaneous oxygen saturation (Spo_2) and ABGs were repeated monthly at the same oxygen flow level of the screening assessment. The number and severity of acute COPD exacerbation episodes and any adverse event were also recorded.

Procedures

Echocardiographic screening was done according to the American Society of Echocardiography recommendations.[14] Systolic PAP was estimated by the measurement of the velocity of the tricuspid regurgitant flow in a 4-chamber view, and the estimate of right atrial pressure was measured from the dimension and collapsibility of the inferior vena cava.[14]

Hemodynamic evaluation was done with a standard technique. Pressures were measured after zeroing the system at the midchest position with a fluid-filled catheter. All pressures were measured at end expiration. Cardiac output (CO) was measured in triplicate with the thermodilution technique, and PVR was calculated with the formula PVR = (mPAP – pulmonary capillary wedge pressure)/CO.

Pulmonary function tests were done according to the European Respiratory Society standards.[15] Diffusion capacity of the lung for carbon monoxide (D_{LCO}) was measured by the single breath technique. A specimen of arterial blood was taken with the patient seated and breathing room air or oxygen supplementation. $Paco_2$, Pao_2, and pH were measured with a commercially available blood gas analyzer.

Exercise capacity was measured with the non-encouraged 6MWT done in a 30-meter-long corridor in the same environmental

Table 1 Demographics, Pulmonary Function Test Results, and Functional Capacity of Patients Who Assumed at Least One Dose of Sildenafil or Placebo: Comparison at Baseline

Variable[a]	Placebo ($n = 10$)	Sildenafil ($n = 18$)	p-value
Male gender, %	80.0	72.2	NS
Age, years	64.1 ± 11.0	66.4 ± 6.5	NS
BMI, kg/m^2	24.9 ± 4.8	27.2 ± 6.2	NS
F_{IO_2}, %	26.3 ± 7.1	28.3 ± 7.2	NS
Pa_{O_2}, mm Hg	74.4 ± 14.9	74.2 ± 14.3	NS
Pa_{CO_2}, mm Hg	44.5 ± 9.0	40.3 ± 5.2	NS
A-a O_2 gradient, mm Hg	57.5 ± 55.0	77.1 ± 54.1	NS
Pulmonary function test			
FEV_1, % predicted	48.4 ± 25.3	54.4 ± 22.4	NS
FEV_1/FVC, %	0.53 ± 0.17	0.52 ± 0.13	NS
TLC, % predicted	97.1 ± 17.8	101.2 ± 25.1	NS
D_{LCO} %, predicted	34.6 ± 23.0	32.8 ± 12.2	NS
Functional capacity			
6MWT, m	308.5 ± 99.6	229.2 ± 101.4	0.06
BODE Index, units	4.7 ± 2.0	5.2 ± 2.5	NS
MMRC scale, units	2.3 ± 0.7	3.0 ± 0.9	0.07
Hemodynamics			
RAP, mm Hg	9.0 ± 2.6	7.3 ± 3.9	NS
mPAP, mm Hg	39.1 ± 12.5	39.3 ± 7.6	NS
PCWP, mm Hg	12.2 ± 2.9	10.9 ± 2.9	NS
Cardiac index, liters/min/m^2	2.5 ± 0.7	2.4 ± 0.5	NS
Stroke volume index, ml/m^2	33.2 ± 9.9	29.4 ± 7.6	NS
Total PVR, WU	9.2 ± 3.3	9.7 ± 3.1	NS
PVR, WU	6.3 ± 3.1	7.0 ± 2.6	NS
SVR, WU	23.7 ± 8.5	21.4 ± 5.7	NS
Heart rate, beats/min	77.8 ± 15.8	82.0 ± 10.9	NS
SF-36 general health, units	44.6 ± 18.6	36.5 ± 16.1	NS

6MWT, 6-minute walk test; A-a O_2 gradient, alveolar-to-arterial gradient; BMI, body mass index; D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; F_{IO_2}, fraction of inspired oxygen; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; MMRC, Modified Medical Research Council; NS, not significant; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Pa_{O_2}, partial pressure of arterial oxygen; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVR, systemic vascular resistance; TLC, total lung capacity; PVR, pulmonary vascular resistance.

[a]Continuous data are shown as mean ± standard deviation and categoric data as indicated.

conditions and at about the same time of day (±2 h).[16] Quality of life was analyzed using the SF-36.[17]

Statistical analysis

Categoric variables are described as frequencies and percentages continuous variables as mean ± standard deviation or median (interquartile range), when appropriate. To compare baseline values, the Fisher's exact test was used for categoric variables, and the 2-sample t-test or the Wilcoxon rank sum test were used for continuous variables, when appropriate. The level of statistical significance was set at 5%, and 2-sided p-values and relative 95% confidence intervals (CIs) are reported.

The primary efficacy analysis was done on the intention-to-treat population. Safety analysis was done on the complete group of randomized patients.

For 3 patients with missing end-of-study RHC data, a missing at random mechanism was assessed.[18] The mixed-effects linear regression model with the expectation-maximization imputation method[19] was applied to assess the efficacy of sildenafil compared with placebo. The expectation-maximization method leads to unbiased estimate with the missing at random mechanism.[18] The last observation carried forward imputation method was not applied because, even under the unrealistically strong assumption of completely missing at random mechanism, the bias in the last observation carried forward estimator typically does not vanish, and even more importantly, the bias can be positive or negative.[19-22]

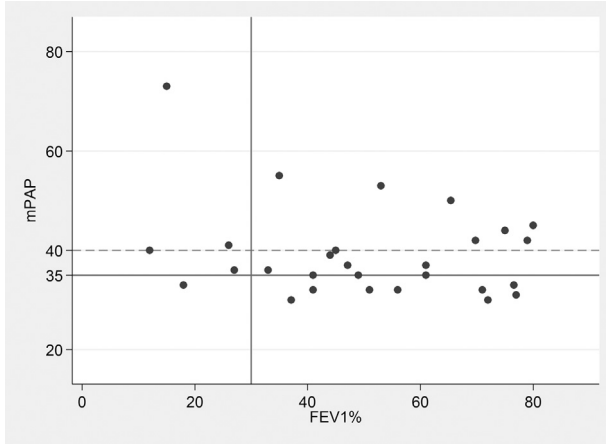

Figure 2 Plot of mean pulmonary artery pressure (mPAP) against forced expiratory volume in 1 second (FEV_1) of the patients at baseline right-heart catheterization.

Table 2 Primary End Point and Hemodynamics of Patients Who Received the Last Dose of Sildenafil or Placebo (Intention-to-Treat Analysis)

Variable	Placebo ($n = 10$) Mean (SE)	Sildenafil ($n = 18$) Mean (SE)	Difference in change (95% CI)	p-value
PVR, WU				
Baseline	6.27 (0.79)	7.01 (0.59)		
Follow-up	6.36 (0.79)	5.72 (0.62)		
Change	0.09	−1.29	−1.38 (≤ −0.05)	0.04
Total PVR, WU				
Baseline	9.21 (0.95)	9.70 (0.70)		
Follow-up	9.34 (0.95)	8.03 (0.74)		
Change	0.13	−1.67	−1.80 (≤ −0.21)	0.03
RAP, mm Hg				
Baseline	9.00 (1.24)	7.28 (0.92)		
Follow-up	8.20 (1.24)	8.56 (1.00)		
Change	−0.80	1.28	2.08 (≥ −0.86)	NS
mPAP, mm Hg				
Baseline	39.10 (2.85)	39.33 (2.13)		
Follow-up	36.70 (2.85)	35.49 (2.28)		
Change	−2.40	−3.84	−1.44 (≤ 4.44)	NS
Cardiac index, liters/min/m^2				
Baseline	2.5 (0.2)	2.4 (0.1)		
Follow-up	2.3 (0.2)	2.6 (0.1)		
Change	−0.2	0.2	0.4 (≥ 0.2)	0.004
Stroke volume index, ml/m^2				
Baseline	33.2 (2.3)	29.4 (1.7)		
Follow-up	30.3 (2.3)	34.1 (1.8)		
Change	−2.9	4.7	7.6 (≥ 3.7)	0.0007
SVR, WU				
Baseline	2.89 (0.41)	2.73 (0.31)		
Follow-up	3.33 (0.42)	2.48 (0.33)		
Change	0.44	−0.25	−0.69 (≤ −0.24)	0.006
Heart rate, beats/min				
Baseline	77.8 (3.3)	82.0 (2.4)		
Follow-up	76.5 (3.3)	75.3 (2.6)		
Change	−1.3	−6.7	−5.4 (≤ 1.13)	0.09

CI, confidence interval; mPAP, mean pulmonary arterial pressure; NS, not significant; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SE, standard error; SVR, systemic vascular resistance.

The same regression method was applied for the secondary outcome measures. To assess the efficacy of sildenafil compared with placebo, the level of statistical significance was set at 5%, and 1-sided p-values and 95% CIs are reported. Analyses were done using Stata 13.1 software (StataCorp LP, College Station, TX).

Results

Study population

The study lasted 12 months (March 2012 to March 2013), and 31 patients were recruited. After excluding from the final analysis 3 patients who did not receive the first dose of sildenafil/placebo, 28 patients thus completed the study: 18 on sildenafil and 10 on placebo. Included in the intention-to-treat analysis were 3 patients who did not perform the end-of-study RHC for refusal or technical reasons. Figure 1 shows the disposition of the patients.

Baseline demographic characteristics were similar between the two groups (Table 1). Patients had moderate airway obstruction but severely impaired DLCO, mean Pao_2 was > 70 mm Hg with low-flow oxygen requirement, and $Paco_2$ was close to the normal range. The sildenafil group had a trend toward a shorter distance at the 6MWT (229.2 ± 101.4 vs 308.5 ± 99.6 meters, $p = 0.06$). Both groups had severe precapillary hypertension, with mPAP ≥ 35 mm Hg in 19 patients (68%) and ≥ 40 mm Hg in 11 (39%), at baseline (Table 1 and Figure 2), with preserved cardiac index and right atrial pressure.

Outcome measures

Primary end-point and hemodynamic variables are reported in Table 2 and Figure 3. Changes from baseline to week 16 in the PVR were different in the 2 treatment groups, with a mild increase in the placebo arm and a decrease in the sildenafil arm. In the intention-to-treat population, the placebo-corrected difference in PVR and total PVR after 16 weeks of sildenafil was statistically

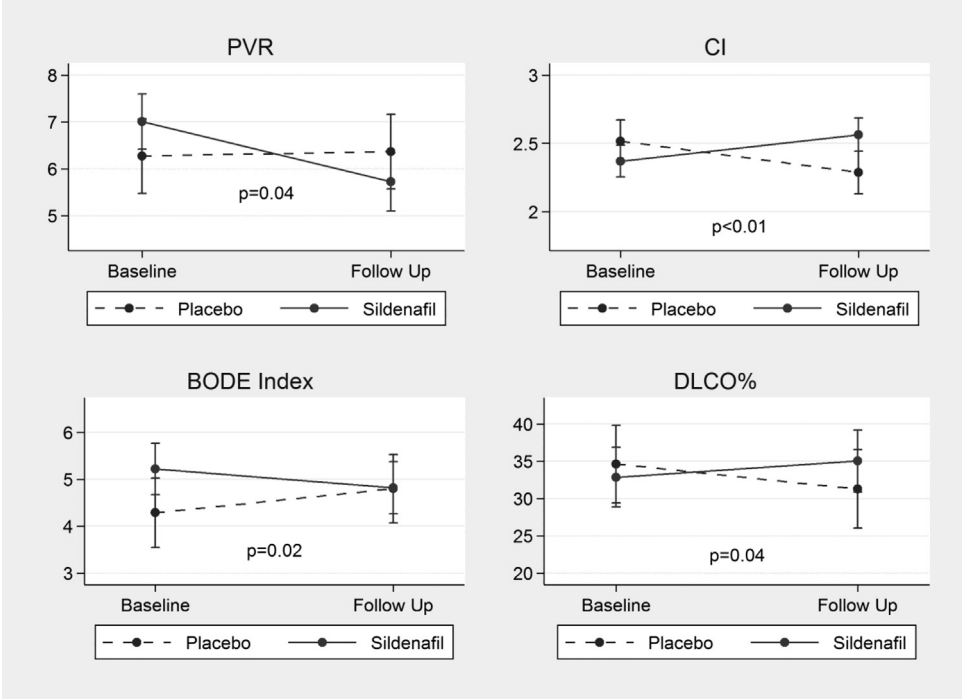

Figure 3 Primary and secondary end point variables significantly varied in patients treated with sildenafil (see also Tables 2–4). The error bars indicate the standard deviation. BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; CI, cardiac index; DLCO, diffusion capacity of the lung for carbon monoxide; PPVR, peripheral pulmonary vascular resistance.

significant (PVR: –1.38 WU; 95% CI, ≤ –0.05 WU; $p = 0.044$; total PVR: –1.8 WU; 95% CI, ≤ –0.21 WU; $p = 0.032$). In the treated group, the cardiac index increased significantly (placebo-corrected change +0.42 liters/min/m^2, 95% CI, ≥ 0.16 liters/min/m^2; $p = 0.0036$), as well as stroke volume index (+8 ml/m^2; 95% CI, ≥ 4 ml/m^2; $p = 0.0007$) without a significant reduction in mPAP (placebo-corrected change, –1.44 mm Hg; 95% CI, ≤ 4.44 mm Hg; $p = 0.3$). Right atrial pressure remained unchanged.

Secondary end points are reported in Tables 3 and 4 and in Figures 3 and 4. In the treatment group, no significant differences were observed in lung function from baseline to week 16, except for DLCO %, which increased in the sildenafil group and decreased in the placebo group. The alveolar-arterial O_2 gradient and Pa_{O_2} did not change significantly. No significant decrease occurred in Sp_{O_2} at rest at each visit during the double-blind phase (Figure 4). At the end-of-study 6MWT, no difference was found between the sildenafil and placebo groups in Sp_{O_2} desaturation (Table 3). Pa_{CO_2} slightly increased in the sildenafil group and decreased in the placebo group, although remaining in the normal range. We observed a trend toward an improvement in the 6MWT distance. The BODE index, Modified Medical Research Council (MMRC) scale, and SF-36 general health domain improved significantly in the sildenafil group compared with the placebo group.

Adverse events

Adverse events were observed in 5 patients in the sildenafil arm. The events were mild to moderate and included headache, diarrhea, flushing, limb pain, dyspnea, myalgia, and peripheral edema. None interrupted the study treatment because of adverse events. No significant adverse effects were reported in the placebo arm.

Discussion

The SPHERIC-1 randomized controlled trial provides data on the safety and the efficacy of chronic administration of sildenafil, 20 mg 3 times a day, in patients with severe PH-COPD. Our results show that sildenafil decreased PVR, with improvement in the cardiac index, stroke volume, MMRC score, BODE index, and quality of life, with no detrimental effects on gas exchange.

Previous studies showed conflicting results caused by bias in the selection of the population. In a small population of COPD patients, bosentan, a dual-endothelin receptor antagonist, failed to improve exercise capacity after 12 weeks of treatment and caused a considerable deterioration in gas exchange and functional status.[8] Most of the participants had modest PH, which was diagnosed only by means of transthoracic Doppler ultrasound imaging.

Experiences with phosphodiesterase 5 inhibitors showed similar results. Lederer et al[9] performed a small study in COPD patients with mild PH comparing sildenafil with placebo in a cross-over design over 4 weeks. Blanco et al[10] compared the effect of sildenafil and placebo in COPD patients with mild PH who were enrolled in a rehabilitation program. In both studies, sildenafil did not show any effect on effort tolerance compared with placebo but worsened gas exchange. In a more recent report, Goudie et al[13] studied a larger COPD population, using tadalafil, a different phosphodiesterase 5 inhibitor. After 12 weeks of treatment,

Table 3 Secondary End Points of Patients Who Received the Last Dose of Sildenafil or Placebo (Intention-to-Treat Analysis)

Variable	Placebo ($n = 10$) Mean (SE)	Sildenafil ($n = 18$) Mean (SE)	Difference in change (95% CI)	p-value
F_{IO_2}				
Baseline	26.30 (2.25)	28.35 (1.73)		
Follow-up	26.10 (2.25)	28.65 (1.74)		
Change	−0.20	0.30	0.50 (≥ −0.97)	NS
Pa_{O_2}				
Baseline	74.40 (4.00)	74.23 (2.98)		
Follow-up	70.24 (4.00)	69.05 (3.26)		
Change	−4.16	−5.18	−1.02 (≤ 10.58)	NS
Pa_{CO_2}				
Baseline	44.50 (2.02)	40.29 (1.51)		
Follow-up	41.24 (2.02)	42.22 (1.55)		
Change	−3.26	1.94	5.20 (≥ 2.89)	0.0001
DA-aO_2				
Baseline	57.49 (16.66)	77.10 (12.85)		
Follow-up	64.30 (16.66)	82.64 (12.95)		
Change	6.81	5.54	−1.27 (≤ 11.77)	NS
FEV_1/FVC				
Baseline	0.53 (0.04)	0.52 (0.03)		
Follow-up	0.57 (0.04)	0.51 (0.03)		
Change	0.04	−0.01	−0.05 (≤ 0.02)	NS
D_{LCO}, %				
Baseline	34.62 (5.22)	32.84 (4.01)		
Follow-up	31.27 (5.28)	35.02 (4.16)		
Change	−3.35	2.18	5.53 (≥ 0.26)	0.04
Delta O_2 6MWT				
Baseline	−8.90 (1.65)	−9.78 (1.23)		
Follow-up	−8.12 (1.70)	−10.18 (1.32)		
Change	+0.78	−0.40	1.18 (≥ −1.64)	NS
SF36 general health				
Baseline	44.6 (5.20)	36.5 (3.87)		
Follow-up	42.3 (5.20)	44.1 (4.08)		
Change	−2.30	7.55	9.85 (≥ 0.78)	0.04

CI, confidence interval; DA-aO_2, difference in the alveolar-to-arterial O_2 gradient; Delta O_2 6MWT, oxygen desaturation during 6-minute walk test; D_{LCO}, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; F_{IO_2}, fraction of inspired oxygen; FVC, forced vital capacity; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Pa_{O_2}, partial pressure of arterial oxygen; SE, standard error; SF36 general health, general health domain of the Medical Outcomes Study Short-Form 36 Health Survey.

tadalafil did not improve exercise capacity or quality of life compared with placebo.[13] The main limitation in most of these studies is that the selected COPD cohorts had borderline or mildly elevated pulmonary pressure. That the pulmonary vasodilator drugs did not have positive effect is therefore not surprising because those patients had mostly ventilatory limitation to exercise rather than reduced circulatory reserve.[23]

In the present study, we included only patients with COPD in Global Initiative for Chronic Obstructive Lung Disease Stage II or III and severe pre-capillary hypertension matching the definition of severe PH-COPD as suggested in the recent European Society of Cardiology and European Respiratory Society guidelines.[24] PH-COPD patients treated with sildenafil in the present study showed a placebo-corrected decrease in PVR similar to that obtained in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER-1) study for PAH. Because the pathophysiology of right ventricular dysfunction in severe PH is mainly due to an excessive increase in the afterload, a reduction in one component of the afterload (PVR) causes an increase in the right ventricular stroke volume and cardiac output, with trivial decrease in mPAP.

Pulmonary pressure is a well known independent prognostic factor in COPD.[2–5] Because our study was not designed to address the effect of hemodynamic changes on the prognosis of PH-COPD patients, we can not infer any conclusion about this important issue, but the significant increase in the cardiac index mainly due to the increase in stroke volume is a very favorable hemodynamic improvement.

The hemodynamic improvement does not confer an improvement in effort capacity, because we did not observe a statistically significant improvement of exercise capacity evaluated by the 6MWT. This result is different compared with what was observed in the SUPER-1 study for PAH patients[25] and could be explained by some confounding conditions such as the older age of examined population, the more severe exercise deconditioning, the higher number of

Table 4 BODE Score With Individual Components of Patients Who Received the Last Dose of Sildenafil or Placebo (Intention-to-Treat Analysis)

Variable	Placebo ($n = 10$) Mean (SE)	Sildenafil ($n = 18$) Mean (SE)	Difference in change (95% CI)	p-value
BODE index				
Baseline	4.29 (0.74)	5.22 (0.55)		
Follow-up	4.80 (0.73)	4.82 (0.56)		
Change	0.51	−0.40	−0.92 (≤ −0.20)	0.02
6MWT, m				
Baseline	308.5 (31.7)	229.2 (23.6)		
Follow-up	297.3 (32.0)	237.3 (24.2)		
Change	−11.2	8.1	−19.3(≥ −8.99)	NS
BMI, kg/m^2				
Baseline	24.93 (1.71)	27.22 (1.27)		
Follow-up	25.64 (1.71)	27.47 (1.28)		
Change	0.71	0.25	−0.46 (≤ 0.11)	0.09
MMRC scale				
Baseline	2.31 (0.28)	3.00 (0.20)		
Follow-up	2.40 (0.27)	2.49 (0.21)		
Change	0.09	-0.51	−0.60 (≤ −0.31)	0.03
FEV_1, % predicted				
Baseline	48.41 (7.11)	54.38 (5.30)		
Follow-up	45.63 (7.11)	54.60 (5.35)		
Change	−2.78	0.21	2.99 (≥ −1.58)	NS

6MWT, 6-minute walk test; BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; MMRC, Modified Medical Research Council scale; NS, not significant; SE, standard error.

comorbidities, and by some degree of ventilatory limitation due to the airways disease in PH-COPD population. Notably, the changes in the 6MWT distance and in the MMRC dyspnea score resulted in a statistically significant improvement of the BODE score, a validated composite prognostic index in COPD.[26]

A considerable finding of our investigation is the absence of a detrimental effect of sildenafil on gas exchange (alveolar-arterial O_2 gradient and Pao_2). The reduction in Pao_2 was slight in both groups, as observed acutely in other studies,[11] without clinical effect because no patients required up-titration of the fraction of inspired oxygen. Moreover, the increase in the cardiac index observed during sildenafil treatment likely had a favorable effect on oxygen delivery.

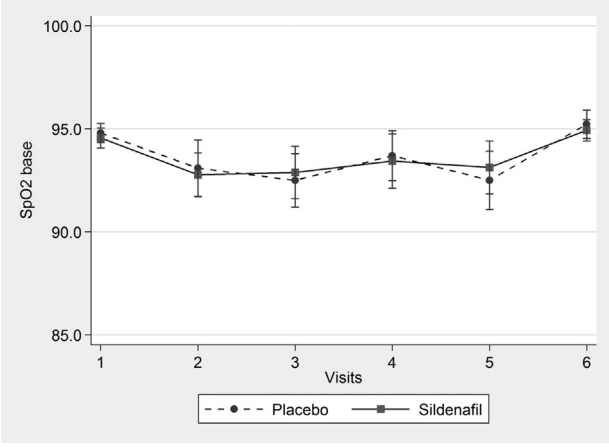

Figure 4 Trend of rest peripheral capillary oxygen saturation (Spo_2) at the scheduled visits

We report here a significant improvement in the DLCO% in the treated group. This finding and the absence of peripheral Spo_2 desaturation at rest suggest that the effect of sildenafil on the ventilation/perfusion ratio may be beneficial in severe PH-COPD. All of these results are in agreement with the improvement in the SF-36 general health domain.

The main limitation of the study is the small patient sample size. Nevertheless, it is the largest randomized controlled trial of sildenafil in COPD patients with severe PH to date. Moreover, this pilot study provides robust proof-of-concept data useful for the design of larger randomized controlled trials.

The study did not provide information on sildenafil dose titration, because a fixed dose of sildenafil (20 mg 3 times a day) was administered. A positive dose-effect relationship has been described in PAH, but we do not know if an increased dose may imply better results or more pronounced adverse effects.

Another limitation is the lack of mortality reporting and time to clinical worsening among the study end points because of the short observation time.[27] However, the BODE index is a surrogate composite end point of prognostic significance[26] with indirect implications on mortality, giving additional data on the benefit of specific PAH drugs in this particular settings.

In conclusion, the results of this pilot study suggest that sildenafil, 20 mg 3 times a day, has a favorable hemodynamic effect in severe PH-COPD, with no significant

effect on gas exchange and with a good safety profile. Specific composite end points, such as the BODE index, may be more appropriate than the 6MWT in the assessment of the efficacy of PAH drugs and should be included in larger trials.

Disclosure statement

P.V. is a member of the advisory board of GSK and Bayer, received travel fees from Actelion, Bayer, Dompé, GSK, and Pfizer, and his institution (Istituto di Ricovero e Cura a Carattere Scientifico) has received research grants sponsored by Actelion and Dompé during the last 3 years. M.B. received travel fees from Dompé during the 3 three years. M.C. received travel fees from GSK and Bayer. P.G. received travel fees from Actelion. M.D. is a member of advisory boards of Actelion, Bayer, Dompé, GSK, Pfizer, and United Therapeutics and has received speaker/travel fees from Actelion, Bayer, Dompé, GSK, Pfizer, and United Therapeutics during the last 3 years. S.G. received consulting fees from Bayer, GSK, and United Therapeutics. Pfizer sponsored a Regional Network Project in Region Lombardia headed by Policlinico S. Matteo of Pavia during the last 3 years. R.B. received fees as a speaker from Bayer, United Therapeutics, Dompé, and GSK during the last 4 years. R.P. received fees from Dompé, GSK, and Italfarmaco for serving as a consultant. P.R. received reimbursements and fees for participating in educational meetings, advisory boards, and for attending international and national congresses from InterMune-Roche, Boehringer Ingelheim, Novartis, Grifols, and Menarini group in the past 5 years. C.D.V. received fees for serving as a speaker, consultant, and an advisory board member, from Actelion, Bayer, Dompé, GSK, Italfarmaco, Lilly, Pfizer, and United Therapeutics. His institution has received research grants from Actelion, Bayer, GSK, Lilly, Pfizer, and United Therapeutics. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

This study was funded by an unrestricted grant from Pfizer.

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