Sildenafil for Pulmonary Arterial Hypertension Associated with Connective Tissue Disease

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ABSTRACT. ***Objective.*** Pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) is difficult to manage, and has a poor prognosis. The phosphodiesterase-5 inhibitor sildenafil citrate enhances vasodilatation, has antiproliferative effects, and is effective in the treatment of PAH. We examined the efficacy and safety of oral sildenafil in patients with PAH-CTD.

Methods. In a 12-week, double-blind study (SUPER-1), 278 patients with PAH were randomized to oral placebo, sildenafil 20 mg, sildenafil 40 mg, or sildenafil 80 mg 3 times daily (tid). In a post-hoc subgroup analysis of 84 patients with PAH-CTD, exercise capacity, hemodynamic measures, World Health Organization functional class, and tolerability were assessed.

Results. Forty-five percent of the patients had scleroderma, 23% had systemic lupus erythematosus, and the rest (32%) were categorized as other. Patients were predominantly functional class II (38%) or III (61%) at baseline. Sildenafil-treated patients exhibited mean increases in 6-minute walk distance at Week 12 of 42 m (95% CI 20, 64) for 20 mg, 36 m (95% CI 14, 58) for 40 mg, and 15 m (95% CI –24, 54) for 80 mg, while placebo-treated patients exhibited a mean decrease of 13 m (95% CI –36, 10). Improvement of at least 1 functional class occurred in 29%–42% of sildenafil-treated patients, compared to 5% for placebo. Significant improvements in mean pulmonary arterial pressure and pulmonary vascular resistance were observed with sildenafil 20 mg, and sildenafil was generally well tolerated.

Conclusion. In patients with PAH-CTD, sildenafil improves exercise capacity, hemodynamic measures (at the 20 mg dose), and functional class after 12 weeks of treatment. (First Release Nov 1 2007; J Rheumatol 2007;34:2417–22)

Key Indexing Terms:
SILDENAFIL CONNECTIVE TISSUE DISEASE SAFETY
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Pulmonary arterial hypertension (PAH), characterized by a progressive increase in pulmonary vascular resistance[1], can occur as a complication of connective tissue diseases (PAH-CTD) such as scleroderma, systemic lupus erythematosus (SLE), mixed CTD, and rheumatoid arthritis[2]. The pathogenesis of pulmonary hypertension varies and may involve the precapillary arteriole (PAH), interstitial lung disease, left ventricular diastolic dysfunction, thromboembolic disease, autoimmune processes, and endothelial dysfunction[2]. Patients with PAH-CTD have a poor prognosis[3,4]. In these patients, PAH is progressive and particularly difficult to manage[5], with survival rates at 2 years of 40%–60%[3,6-9]. Potential therapeutic options to treat their PAH include prostanoids, endothelin receptor antagonists (ERA), immunomodulators, and phosphodiesterase (PDE) inhibitors[2,5]. The prostanoids epoprostenol, treprostinil, and iloprost as well as the ERA bosentan and the PDE inhibitor sildenafil are approved for the treatment of PAH, which includes the subgroup of patients with PAH-CTD[10].

Sildenafil citrate, a selective PDE type 5 inhibitor[11], promotes the accumulation of intracellular cyclic guanosine monophosphate (cGMP), thereby enhancing nitric oxide

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(NO)-mediated vasodilatation[12], and reducing smooth muscle cell proliferation[13]. Sildenafil has been shown to improve exercise capacity and cardiopulmonary hemodynamics in patients with PAH[14-16]. In patients with PAH-CTD, therapy with prostanoids and ERA has shown varying levels of efficacy in randomized, controlled trials[17-20], small studies, or case series[21-26]. However, the tolerability profiles of these treatments are not ideal[19,27-29]. Preliminary reports from case studies of sildenafil therapy in patients with PAH-CTD have described improved exercise capacity, functional class (FC), and cardiopulmonary hemodynamics with short- and longterm treatment[29-32].

To evaluate the efficacy of sildenafil in PAH-CTD, therefore, we performed a post-hoc subgroup analysis of a 12-week, multicenter, multinational, randomized, double-blind, placebo-controlled study of 20, 40, and 80 mg oral sildenafil 3 times daily (tid) in patients with PAH.

MATERIALS AND METHODS

Study design. Our study was a post-hoc subgroup analysis of a 12-week, multicenter, multinational, randomized, double-blind, placebo-controlled study that examined the efficacy and safety of oral sildenafil in patients with PAH (idiopathic and associated PAH), conducted between October 2002 and November 2003[15]. The study was conducted in compliance with the principles of the Declaration of Helsinki (1989, revised Edinburgh, 2000) and with local regulations regarding the use of new therapeutic agents in the countries of conduct. The study was approved by independent ethics committees, and written informed consent was obtained from patients before entry into the study. A detailed description of the methods and the outcomes of the main study has been reported[15]. The results from the subgroup of patients with PAH-CTD are reported here.

Patients were assigned using a central randomization scheme to placebo, sildenafil 20 mg tid, sildenafil 40 mg tid, and sildenafil 80 mg tid in a 1:1:1:1 ratio. Randomization was stratified according to baseline walking distance and etiology, and conducted with a computer-generated, pseudo-random code using the method of random permuted blocks within strata. Patients randomized to sildenafil 80 mg tid received 40 mg tid for the first 7 days before uptitration to 80 mg. Patients in the other 3 groups concomitantly underwent dummy uptitration.

Patients (PAH-CTD subgroup). Adult patients (≥ 18 yrs) with PAH [defined as mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg and pulmonary artery wedge pressure ≤ 15 mm Hg at rest] associated with CTD were included in this analysis. Patients in World Health Organization (WHO) FC I–IV were included[33]. Patients were excluded if they had a 6-minute walk distance (6MWD) of ≤ 100 m or ≥ 450 m. Study medication was given in addition to patient's background therapy (e.g., anticoagulants, digoxin, calcium channel blockers, diuretics, and/or supplemental oxygen). Specific PAH treatments were not permitted, namely intravenous epoprostenol, intravenous or inhaled iloprost, subcutaneous treprostinil, oral bosentan, and L-arginine supplementation.

Outcomes. The primary efficacy outcome was change in exercise capacity from baseline to Week 12, as measured by 6MWD. Secondary outcome measures were the change from baseline to Week 12 for WHO FC and hemodynamic measures. Hemodynamic measurements, recorded using a pulmonary arterial catheter, included mPAP, mean right atrial pressure (mRAP), cardiac output, and pulmonary vascular resistance (PVR). All measurements were performed at Weeks 4, 8, and 12. All adverse events (AE) were recorded throughout the study.

Statistical analysis. The primary endpoint was evaluated for the 3 sildenafil dose groups compared to placebo using pair-wise comparisons, carried out at the prespecified 2-sided α level of 0.01 using a 2-sample t-statistic. Hemodynamic measures were analyzed using a 2-sample t-statistic with a 2-sided α level of 0.05. P values were not adjusted for multiple testing. Efficacy analyses were performed on the intention-to-treat (ITT) population using the last observation carried forward for missing data. To be included in the ITT population, a patient must have received study drug, had a baseline assessment, and had at least 1 post-baseline assessment (Week 4, 8, or 12). All patients who received at least 1 dose of study medication were analyzed for safety.

RESULTS

Patient disposition. Of the 278 patients in the main study, 84 had PAH-CTD. These were randomized to oral sildenafil (20, 40, or 80 mg tid) or placebo (Figure 1). Seventy-nine patients (94%) completed the study (Figure 1).

Baseline characteristics. The patients' baseline characteristics were not significantly different for the placebo group and the 3 sildenafil groups (Table 1). Patients were predominantly female, and scleroderma was the most common CTD diagnosis. Most patients were either FC II (38%) or FC III (61%).

Efficacy – Exercise capacity. Twelve weeks of treatment with sildenafil improved exercise capacity in patients with PAH-CTD (Figure 2). Sildenafil-treated patients exhibited mean increases in 6MWD at Week 12 of 42 m (95% confidence interval 20, 64) for 20 mg, 36 m (95% CI 14, 58) for 40 mg, and 15 m (95% CI –24, 54) for 80 mg, while placebo-treated patients exhibited a mean decrease of 13 m (95% CI –36, 10). The corresponding mean placebo-corrected improvements at Week 12 were 55 m (95% CI 24, 85) for sildenafil 20 mg, 49 m (95% CI 19, 80) for 40 mg, and 28 m (95% CI –14, 71) for 80 mg.

Efficacy – Functional class. Following 12 weeks of treatment, improvement of at least one WHO FC was seen in 6 (29%), 8 (40%), and 8 (42%) in the 20 mg, 40 mg, and 80 mg sildenafil-treated patients, respectively, compared with 1 (5%) placebo-treated patient (Figure 3).

Efficacy – Hemodynamics. Pulmonary hemodynamics improved, with statistical significance achieved only for the 20 mg group (Table 2). Both mPAP ($p < 0.01$) and PVR ($p < 0.05$) were decreased compared to placebo in patients receiving 20 mg sildenafil tid.

Safety and tolerability. Overall, sildenafil was well tolerated (Table 3). The most frequent AE was headache. The proportion of CTD patients with AE was similar in sildenafil-treated and placebo-treated patients, although headache and epistaxis did appear to occur more commonly in sildenafil-treated patients. Incidence of AE did not appear to be dose-related, with a total of 133, 123, and 96 reported for the 20 mg, 40 mg, and 80 mg doses, respectively. Five patients discontinued sildenafil treatment, including 3 who died. The 2 AE-related discontinuations were attributable to edema of the lower legs and cirrhosis of the liver. One patient in the 20 mg group died from pulmonary embolism and urosepsis. One patient who discontinued due to AE (myocardial infarction) in the 80 mg group later died. Another patient randomized to the 80 mg

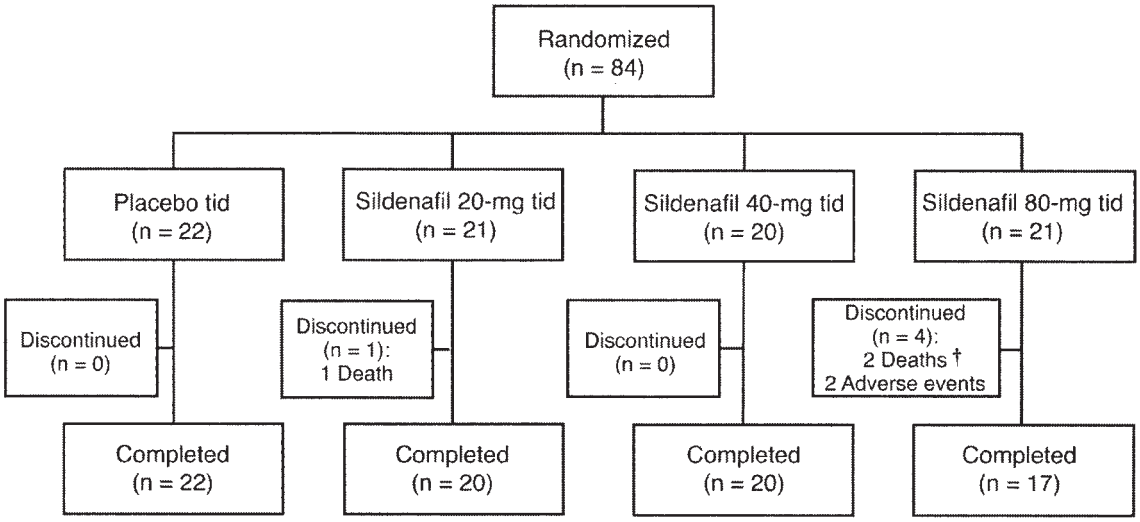

Figure 1. Patient disposition. †Includes 1 patient who discontinued due to adverse event (myocardial infarction) and later died. No deaths or adverse events were considered to be treatment-related.

group died from septic shock, although the patient had not been titrated to 80 mg at the time of death, and was still taking 40 mg sildenafil. No deaths or AE were considered to be treatment related. Although severe AE were more frequent in sildenafil (23%) compared with placebo (14%) patients, the differences were not statistically significant.

DISCUSSION

This post-hoc subgroup analysis of a multinational, randomized, double-blind, placebo-controlled study is the first report of improved clinical outcomes with sildenafil treatment in the PAH-CTD population in a clinical setting. Sildenafil treatment improved exercise capacity, hemodynamic measures (significantly for mPAP and PVR, in particular), and WHO FC across a range of CTD etiologies, and was shown to be generally well tolerated. These results are consistent with the findings of a number of case studies of short- and longterm sildenafil therapy in patients with PAH-CTD[29-32], where sildenafil appeared beneficial[29-32]. In this trial, improvements in all efficacy outcomes were seen with the 20 mg tid dose, suggesting that oral sildenafil 20 mg tid is effective and is a rational initial treatment dose in patients with PAH-CTD.

Table 1. Baseline characteristics of study subjects.

Characteristic	Placebo	Sildenafil 20 mg	Sildenafil 40 mg	Sildenafil 80 mg	Total
Patients, n	22*	21*	20*	21*	84*
Age, mean ± SD, yrs	56 ± 14	52 ± 15	50 ± 15	54 ± 14	53 ± 15
Sex, male/female, n	4/18	5/16	3/17	2/19	14/70
Primary diagnosis, n					
Scleroderma	8	9	11	10	38
Systemic lupus erythematosus	4	6	3	6	19
Other†	10	6	6	5	27
6MWD, mean ± SD m	334 ± 71	336 ± 94	349 ± 70	349 ± 68	342 ± 76
WHO functional class, n					
I	0	0	0	0	0
II	9	7	7	9	32
III	13	13	13	12	51
IV	0	1	0	0	1
mPAP, mean ± SD mm Hg	47 ± 12	51 ± 9	45 ± 11	43 ± 11	47 ± 11
mRAP, mean ± SD mm Hg	7.7 ± 3.8	7.3 ± 3.6	7.7 ± 6.3	8.1 ± 5.5	7.7 ± 4.8
Cardiac output, mean ± SD l/min	3.8 ± 1.0	4.5 ± 1.6	4.7 ± 1.8	4.8 ± 1.7	4.4 ± 1.6
PVR, mean ± SD dyn.s/cm^5	921 ± 408	902 ± 431	737 ± 444	686 ± 451	810 ± 436

* n varied slightly for each hemodynamic measure due to missing assessments. † Other diagnoses: CREST syndrome, n = 12; mixed CTD, n = 8; Sjögren's syndrome, n = 4; Still's disease, n = 1; primary biliary cirrhosis, n = 1; rheumatoid arthritis, n = 1. 6MWD: 6-min walk distance; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; PVR: pulmonary vascular resistance.

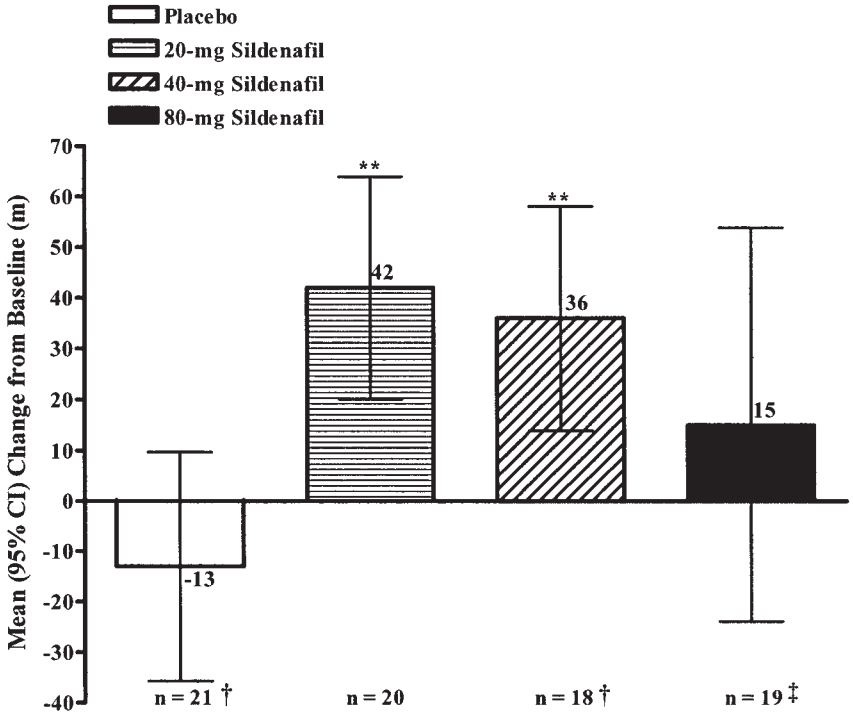

Figure 2. Mean (95% CI) change in 6MWD from baseline to Week 12. †Patients without baseline 6MWD: 1 in placebo group and 2 in 40-mg group. ‡Two patients discontinued due to adverse events after Week 4 evaluations; these data were carried forward for analysis. **p < 0.01 vs placebo.

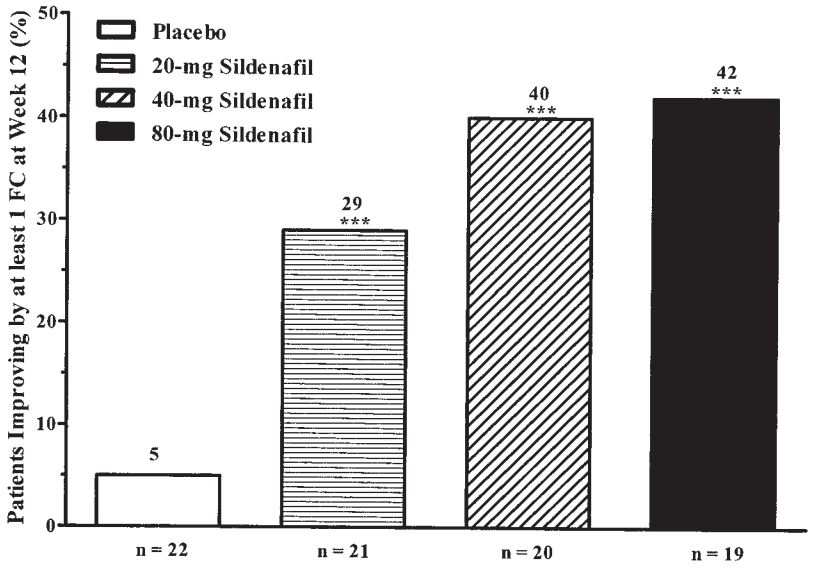

Figure 3. Percentages of patients improving by at least 1 functional class after 12 weeks of sildenafil treatment. ***p < 0.003 vs placebo.

The observed improvement in exercise capacity of 55 m (placebo-corrected) for 6MWD after 12 weeks of sildenafil treatment (20 mg tid) is comparable with that reported for other PAH therapies. Sitaxsentan treatment (pooled 100 mg and 300 mg dose groups) has been found to improve 6MWD by 58 m in PAH-CTD patients[17], while subcutaneous treprostinil (mean dose of 8.4 ng/kg/min at 12 weeks) showed a non-significant improvement of 25 m[18]. In an analysis of a subgroup of patients with scleroderma in the Bosentan Randomized trial of Endothelin Agonist Therapy for PAH (BREATHE-1) study, bosentan therapy (combined 125 mg and 250 mg dose groups at Week 16) prevented deterioration

Table 2. Mean (95% CI) changes in hemodynamic measures from baseline to Week 12.

	Placebo, n = 22†	Sildenafil 20 mg, n = 21†	Sildenafil 40 mg, n = 20†	Sildenafil 80 mg, n = 19†
mPAP, mm Hg	1.4 (–0.8, 3.6)	–4.6** (–8.7, –0.6)	–2.8 (–5.4, –0.1)	–3.2 (–7.9, 1.5)
RAP, mm Hg	0.4 (–1.3, 2.1)	–0.7 (–2.3, 0.9)	0.2 (–1.8, 2.2)	0.03 (–1.9, 2.0)
Cardiac output, l/min	0.08 (–0.3, 0.4)	0.8 (–0.02, 1.5)	0.4 (–0.5, 1.3)	0.2 (–0.4, 0.8)
PVR, dyn.s/cm^5	–19 (–106, 68)	–243* (–408, –77)	–144 (–278, –10)	–156(–267, –46)

* $p < 0.05$ vs placebo; ** $p < 0.01$ vs placebo. p values were not adjusted for multiple testing. † n varied slightly for each measure due to missing assessments.

Table 3. All causality adverse events reported by ≥ 5% of sildenafil-treated patients and more frequently in sildenafil patients than placebo patients.

Adverse Event	Placebo, % n = 22	Sildenfil (all doses), % n = 62
Headache	32	45
Epistaxis	0	13
Nasopharyngitis	9	11
Pain in limb	5	11
Diarrhea	5	10
Insomnia	5	10
Flushing	0	10
Palpitations	5	8
Dyspepsia	5	8
Vomiting	0	8
Muscle cramp	5	8
Pyrexia	5	6
Pruritus	0	6
Any adverse event	86	90

in 6MWD, with an increase of 3 m in the treatment group compared to a decrease of 40 m with placebo[19]. Open-label intravenous epoprostenol therapy (mean dose of 11.2 ng/kg/min at 12 wks) has demonstrated a median increase in 6MWD of 108 m compared to conventional therapy in patients with PAH-CTD[20].

Twelve weeks of sildenafil therapy (20–80 mg tid) resulted in 29%–42% of patients improving by at least 1 WHO FC. This improvement is similar to the improvement in New York Heart Association FC observed for patients treated with epoprostenol (38%)[20] and sitaxsentan (24%)[17]. Treatment with sildenafil for 12 weeks also resulted in hemodynamic benefits in patients with PAH-CTD — mPAP, PVR, and cardiac output improved with therapy in all sildenafil treatment groups, with statistically significant improvements seen in mPAP and PVR in the 20 mg tid dose group. Therapy with intravenous epoprostenol and subcutaneous treprostinil has also been shown to improve mPAP, PVR, and cardiac index in patients with PAH-CTD[18,20].

Sildenafil treatment was generally well tolerated, with the proportion of AE similar to placebo. Further, its safety profile is favorable compared with other agents. Epoprostenol is administered with an intravenous infusion via an implanted central venous catheter, which can result in catheter-associated infections and thromboembolic events[27,28]. The subcutaneous infusion of treprostinil commonly causes pain in the injection area[29], and oral bosentan therapy is associated with hepatic function abnormalities in some patients[19].

Improvements in exercise capacity with sildenafil treatment for these patients with PAH-CTD are similar to those reported for patients with idiopathic PAH, who demonstrated increases in 6MWD of 40–62 m with oral tid dosing[15]. The often poor prognosis of patients with PAH-CTD[3] and the understanding that these patients are less likely to be candidates for lung transplantation due to the systemic nature of CTD[2,34] means that this demonstration of an effective and safe pharmacologic therapy in this subgroup of patients with PAH may be of considerable importance.

Although only one randomized, controlled trial on idiopathic PAH has to date demonstrated a survival advantage compared to placebo[27], most subsequent trials, including this one, have enrolled less ill patients and are, therefore, less likely to detect survival advantages. Nonetheless, FC status is associated with survival in patients with idiopathic (primary) PAH, with FC I/II patients having a better survival rate than those in FC III/IV[35]. If this association is similar in patients with PAH-CTD, then the observed improvements in FC with sildenafil treatment may result in longterm survival benefits for these patients. Similarly, hemodynamic variables are associated with survival in patients with primary PAH[35] and PAH-CTD[7], and the observed hemodynamic benefits with sildenafil therapy could translate into improved survival outcomes in these patients with PAH-CTD. Two limitations of this study were that, first, the duration was short-term, and second, as a post-hoc subgroup analysis, it was not powered to detect statistical significance with corrections for multiple testing. In this context, the apparent greater potency of the 20 mg dose than the 80 mg dose in improving functional capacity and pulmonary hemodynamic variables was not statistically significant and may reflect these limitations rather than any true difference in dose-response. Additional studies on larger numbers of patients would be necessary to further explore this observation.

In patients with PAH-CTD, sildenafil treatment (20 mg tid) improves exercise capacity, hemodynamic measures, and

WHO FC across a range of CTD etiologies. These benefits, combined with the acceptable tolerability profile and oral delivery of the medication, support the use of sildenafil as a therapy for patients with PAH-CTD.

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