Effects of dose and age on adverse events associated with tadalafil in the treatment of pulmonary arterial hypertension

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Abstract: There are limited data on the management of pulmonary arterial hypertension (PAH) in the elderly; therefore, this analysis compared the safety and efficacy of tadalafil between patients ≥ 65 and < 65 years old. This was a post hoc analysis of the randomized, double-blind, placebo-controlled phase 3 Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST-1) study. Patients who completed the 16-week study or who discontinued because of clinical worsening and were not receiving tadalafil 40 mg were eligible for a long-term, open-label extension study. Adverse events (AEs) and efficacy outcomes were assessed in patients ≥ 65 versus < 65 years old, and the dose dependency of common AEs was determined. Twenty-eight percent (112 of 405) of patients were ≥ 65 years of age (mean in this subset, 72 ± 5 years). Compared with younger patients, elderly patients were more likely to be World Health Organization functional class III/IV (75% vs. 65%, respectively) and to have lower exercise capacity as assessed by 6-minute walk distance (6MWD; mean, 299 vs. 366 m). Compared with placebo, tadalafil increased 6MWD by a mean of 35 and 43 m in patients ≥ 65 and < 65 years, respectively. Common AEs (including headache, dyspepsia, and myalgia) were similar in both groups and tended to decrease in incidence with longer treatment duration. No differences in AEs were observed between elderly patients who received tadalafil 20 or 40 mg. In conclusion, the safety and efficacy of tadalafil for treatment of PAH are similar between elderly patients and patients < 65 years old.

Keywords: tadalafil, pulmonary arterial hypertension (PAH), elderly patients.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease characterized by diffuse vascular remodeling of the pulmonary arterial circulation and a variable degree of increased pulmonary vascular tone.^{1,2} These changes increase resistance to blood flow through the lungs and limit right ventricular cardiac output. Symptoms consist primarily of progressive shortness of breath and decreasing functional capacity. As the disease advances, patients develop signs of right heart failure, such as peripheral edema and jugular venous distention. Without treatment, overall survival averages < 3 years from the time of diagnosis.³ Fortunately, recent advances in the understanding of pulmonary vascular biology have led to the development of several PAH-specific classes of medications that delay disease progression and improve survival.

Although the greatest incidence of PAH occurs during midlife, the disease may occur at any age. Increased disease awareness and improved diagnostics have led to an increase in elderly patients diagnosed with PAH.⁴⁻⁶ From 1987 to 2003, the Mayo Clinic registry reported an increase of 16 percentage points in the proportion of patients with idiopathic PAH who were > 65 years old.⁷ The mean age at diagnosis has increased from 36 ± 15 years in the National Institutes of Health registry in 1985 to 50.1 ± 14.4 years in the REVEAL Registry in 2010.^{2,8} Despite these demographic trends, there are very little data on the management of PAH in the elderly.

Elderly patients with PAH can be challenging to treat because they often have a greater number of comorbidities than younger patients and have altered metabolism and

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clearance of a variety of medications. In addition, elderly patients with PAH have decreased survival compared with younger patients with PAH.⁷ Despite these challenges, elderly patients have been generally underrepresented and are often excluded in clinical trials of PAH. Thus, most PAH-specific therapies have not been adequately studied in this population.

Tadalafil (Adcirca; Eli Lilly and Company, Indianapolis, IN) is a long-acting, highly specific phosphodiesterase type 5 (PDE-5) inhibitor that was approved in 2009 for the treatment of World Health Organization (WHO) group 1 PAH. Like other PDE-5 inhibitors, tadalafil slows the metabolism of cyclic guanosine monophosphate, which acts as the second messenger for most of the vasoactive properties of nitric oxide and the natriuretic peptides. Tadalafil may provide a safe and effective treatment option for elderly patients with PAH because it is generally well tolerated and has few drug-drug interactions with frequently used medications, such as digoxin, warfarin, or statins.⁹

In the pivotal phase 3 clinical trial of tadalafil for treatment of PAH (the Pulmonary Arterial Hypertension and Response to Tadalafil [PHIRST-1] trial), a dose-dependent increase in the primary end point (6-minute walk distance [6MWD] at week 16) was observed compared with placebo.¹⁰ Tadalafil also delayed time to clinical worsening and improved health-related quality-of-life scores. Unlike most other clinical trials evaluating novel therapies for PAH, enrollment criteria did not exclude patients with advanced age as long as they met the criteria for group 1 PAH. Four doses of tadalafil were studied: 2.5, 10, 20, and 40 mg given once daily. Subjects were stratified to ensure similar demographic characteristics in each of the dosing groups. The greatest improvements in the primary and secondary end points occurred in the cohort randomized to the 40-mg dose. The 40-mg dose was subsequently approved by the US Food and Drug Administration (FDA) for treatment of PAH, but tadalafil is currently available only as a 20-mg tablet. Treatment is usually initiated as two 20-mg tablets taken together once daily. However, concerns have been raised over precipitating adverse events (AEs), such as headache, dyspepsia, and systemic hypotension, with the use of tadalafil at the approved dose of 40 mg in elderly patients with PAH, prompting many clinicians to initiate treatment in these patients at 20 mg once daily.

This study determined the frequency of AEs in the PHIRST-1 study¹⁰ and the subsequent long-term follow-up study (PHIRST-2)¹¹ between patients assigned to the 40-mg dose and those assigned to lower doses of tadalafil

and compared the tolerability of tadalafil between patients <65 and ≥65 years of age.

METHODS

Patients and study design

The PHIRST-1 study design and methodology have been described in detail elsewhere.¹⁰ Briefly, the inclusion/exclusion criteria were as follows.

Inclusion criteria included age of at least 12 years, body weight of at least 40 kg (~88 pounds), and presence of PAH that was idiopathic, related to collagen vascular disease, related to anorexigen use, or associated with an atrial septal defect or congenital systemic to pulmonary shunt (resting $\text{Sao}_2 \geq 88\%$), with surgical repair, of at least 1 year duration. Patients were allowed to be on bosentan at the time of study entry if they were at the maximal dose of 125 mg twice daily for a minimum of 12 weeks prior to screening and had an aspartate aminotransferase/alanine aminotransferase ratio <3 times normal. History of PAH had to be established by a resting mean pulmonary artery pressure ≥ 25 mmHg, pulmonary artery wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance ≥ 3 Wood units via right heart catheterization with no evidence of significant parenchymal lung disease. Patients had to have WHO functional class I, II, III, or IV status and a 6MWD at screening between 150 and 450 m.

Exclusion criteria included nursing or pregnancy, PAH due to conditions other than noted above in the inclusion criteria, history of left-sided heart disease, history of atrial septostomy within 3 months before study entry, history of angina pectoris or other condition that was treated with long- or short-acting nitrates within 12 weeks before administration of study drug, history of symptomatic coronary disease, and use of a prostacyclin analogue, L-arginine, a phosphodiesterase inhibitor, or an investigational drug within 4 weeks before administration of the study drug.

Patients who completed the 16-week study or who discontinued because of clinical worsening and were not receiving tadalafil 40 mg were eligible for a long-term, open-label extension study (PHIRST-2).¹¹ Patients who received placebo during the PHIRST-1 study were reassigned to tadalafil 40 mg at enrollment into the PHIRST-2 study. However, patients randomized to receive tadalafil 20 mg received this dose throughout both studies.

Clinical efficacy was assessed by measuring 6MWD and clinical worsening through 16 weeks, defined as death, lung or heart-lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of a new approved therapy for PAH, or worsening WHO functional

class. Safety data included AEs that were collected throughout the 16-week randomized study and the 52-week extension study.

This post hoc analysis examined a subgroup of patients who were ≥ 65 years old at study entry. These patients were defined as elderly and were compared with patients < 65 years of age. All patients who received placebo ($n = 82$), tadalafil 20 mg ($n = 82$), or the FDA-approved dose of tadalafil 40 mg ($n = 79$) were included in the analysis.

Statistical methods

Demographic characteristics and baseline information were summarized within age subgroups and treatments using means and SDs for numeric variables and frequencies for categorical variables. Changes from baseline in 6MWD were summarized within age subgroups and treatments using means and SEMs. Differences between treatment groups in the change in 6MWD were summarized using Hodges-Lehmann estimates of the median difference (H-L). Time to clinical worsening is presented as Kaplan-Meier estimates and compared between treatments using the log-rank test. For subjects with missing follow-up data, the last observation carried forward was assigned for calculation of summary statistics.

P values describing the difference between treatments in 6MWD were calculated using the stratified Cochran-Mantel-Haenszel test on the standardized ranks of the changes from baseline, using the same strata as used for randomization. For this analysis, subjects with missing follow-up data were handled as follows: (1) subjects who discontinued the study because of clinical worsening were assigned the worst rank, (2) subjects who discontinued the study because of a treatment-related AE were assigned no change from baseline, and (3) other missing values were assigned the last observation carried forward. Frequencies of AEs were compared between treatments using the Fisher exact test. AEs were categorized by patient age (≥ 65 vs. < 65 years) and by weeks on therapy (week 1, weeks 13–16, weeks 27–52, and weeks 53–68).

RESULTS

Demographic and disease characteristics of elderly and younger patients are shown in Table 1. In general, demographic characteristics of patients who received tadalafil 20 mg were similar to those of patients who received placebo and tadalafil 40 mg. Twenty-eight percent (112 of 405) of PHIRST-1 patients with PAH were ≥ 65 years old at study entry across all dose groups: the mean age was

Table 1. Baseline demographics and characteristics by patient age and treatment assignment

Parameter	≥ 65 years		< 65 years	
	Placebo ($n = 25$)	Tadalafil 40 mg ($n = 19$)	Placebo ($n = 57$)	Tadalafil 40 mg ($n = 60$)
Age, mean $\pm$ SD, years	73 $\pm$ 4	71 $\pm$ 6	46 $\pm$ 11	46 $\pm$ 12
Female sex	16 (64)	12 (63)	49 (86)	47 (78)
PAH etiology				
IPAHA/FPAHA ^a	19 (76)	12 (63)	35 (61)	34 (57)
CVD	6 (24)	6 (32)	10 (18)	13 (22)
Other ^b	0 (0)	1 (5)	12 (22)	13 (21)
Bosentan use	11 (44)	5 (26)	34 (60)	37 (62)
WHO functional class				
I/II	7 (28)	4 (21)	17 (30)	24 (40)
III/IV	18 (72)	15 (79)	40 (70)	36 (60)
6MWD, mean $\pm$ SD, m	301 $\pm$ 76	296 $\pm$ 67	362 $\pm$ 81	370 $\pm$ 73
Borg score, mean $\pm$ SD	4.8 $\pm$ 1.8	4.7 $\pm$ 2.4	3.8 $\pm$ 2.4	3.8 $\pm$ 2.4

Note: Data are no. (%) of patients, unless otherwise indicated. PAH: pulmonary arterial hypertension; IPAHA: idiopathic pulmonary arterial hypertension; FPAHA: familial pulmonary arterial hypertension; CVD: collagen vascular disease; WHO: World Health Organization; 6MWD: 6-minute walk distance.

^a Includes anorexigen use.

^b Includes atrial septal defect and surgical repair of at least 1 year's duration.

72 ± 5 years in the elderly group (range, 65–86 years; Table 2) and 46 ± 12 years in the younger group. Among patients who were <65 years old in the trial, 57 and 60 patients were treated with placebo and tadalafil 40 mg, respectively. Among patients in the older (i.e., ≥65 years old) group, 25 and 19 patients were treated with placebo and tadalafil 40 mg, respectively. Within each age group, there was no significant difference in age between patients treated with placebo and those who received tadalafil. The etiology of PAH was similar in both groups, but a lower proportion of patients were female in the elderly group (64%) than in the younger group (82%). Compared with patients <65 years old, elderly patients were more likely to be in WHO functional class III or IV (65% vs. 75%), more likely to have lower mean 6MWD at baseline (299 vs. 366 m), and less likely to be on background bosentan therapy (61% vs. 36%), although none of these differences were significant.

Clinical efficacy in patients 65 years of age

In patients <65 years old, the mean change from baseline 6MWD at week 16 was greater in those randomized

to tadalafil 40 mg daily than in those receiving placebo (43.1 ± 7.1 vs. 9.7 ± 7.9 m; H-L = 27.0 m; $P = 0.007$; Fig. 1). Similarly, tadalafil 20 mg (mean change from baseline, 34.6 ± 11.2 m; data not shown) and tadalafil 40 mg increased 6MWD at week 16 compared with placebo in elderly patients, although the difference did not quite reach statistical significance (for 20 mg, H-L = 19.8 m, $P = 0.164$; for 40 mg, mean change from baseline was 35.4 ± 8.0 m vs. 8.1 ± 13.2 m in the tadalafil vs. placebo groups; H-L = 25.0 m, $P = 0.054$). In patients who performed a walk test at 1 year during the extension study,¹¹ 6MWD was improved compared with baseline in elderly patients (tadalafil 20 mg, $n = 14$; tadalafil 40 mg, $n = 30$; 26.8 ± 9.3 m; $P < 0.05$) and in patients <65 years old (tadalafil 20 mg, $n = 38$; tadalafil 40 mg, $n = 88$; 42.3 ± 5.9 m; $P < 0.05$; data not shown).

In the PHIRST-1 study, there was a trend toward a lower incidence of clinical worsening with tadalafil compared with placebo in both age groups when combined (5% vs. 16%), but the difference did not reach statistical significance in either age group alone (≥65 years, $P = 0.274$; <65 years, $P = 0.060$; Fig. 2).

Safety and dose dependence of tadalafil in patients 65 years of age

The incidence of AEs in the tadalafil and placebo treatment groups is shown in Table 3. The most common AE in the PHIRST-1 trial was headache. The incidence of headache was most frequent during week 1, but the incidence was no greater in patients treated with tadalafil 40 mg than in those treated with tadalafil 20 mg daily (24% and 29%, respectively; Fig. 3). At weeks 13–16, the percentage of patients reporting headache was similar among those receiving placebo than among both those receiving tadalafil 40 mg and tadalafil 20 mg (40 mg, 9%; 20 mg, 9%; placebo, 7%). The incidence of headache remained at about this level among both those receiving tadalafil 40 mg and those receiving tadalafil 20 mg during weeks 53–68 of the follow-up study (10 [8%] of 126 patients in the group receiving tadalafil 40 mg and 7 [13%] of 55 in the group receiving tadalafil 20 mg). Dyspepsia was more common in patients taking tadalafil 20 mg than in those taking placebo for the first 16 weeks (12% vs. 2%).¹⁰ The incidence of dyspepsia during weeks 13–16 was somewhat lower in patients treated with tadalafil 40 mg than in those treated with tadalafil 20 mg (6% vs. 12%) and was similar between the 40-mg group and the placebo group (6% vs. 3%). No significant difference in the incidence of other clinically relevant AEs was observed between tadalafil 40 and 20 mg over 68 weeks (Table 4).

Table 2. Age distribution of patients >65 years of age by treatment assignment

Age, years	Subjects in treatment assignment, no.	
	Placebo	40 mg
65	0	2
66	3	4
67	0	1
68	3	2
69	0	1
70	1	0
71	3	0
72	2	1
73	0	2
74	2	1
75	2	0
76	3	0
77	4	2
78	1	0
79	0	1
80	0	1
81	1	0
86	0	1

Figure 1. Mean change in 6-minute walk distance (6MWD) at week 16 in elderly (A) and younger (B) patients with pulmonary arterial hypertension. Lowercase letters indicate *n* values as follows: a, *n* = 17; b, *n* = 23; c, *n* = 55; d, *n* = 57; e, *n* = 56.

The most common AE in the elderly treatment group was also headache, and, similar to patients <65 years old, it occurred nearly threefold more often than in patients randomized to placebo. The incidence of headache among elderly patients treated with tadalafil 40 mg was no greater than that among patients <65 years old given the same dose of tadalafil (32% for ≥ 65 years and 45% for <65 years). Peripheral edema was more common in elderly patients than in patients <65 years old, but the percentage of patients with edema did not differ between the tadalafil and placebo groups. The number of other AEs in elderly patients was too small to make comparisons between placebo and tadalafil treatment or between elderly patients and those <65 years old. Likewise, it was difficult to assess the effect of tadalafil dose on the incidence of AEs among the elderly because of the low number of events in each subgroup (Table 3). Although the occurrence of any AE among elderly patients was more frequent in the group receiving tadalafil 40 mg (95%) than in the group receiving tadalafil 20 mg (64%) or in the placebo group (68%), the incidence of any AE among patients receiving tadalafil 40 mg was no greater in the elderly than in patients <65 years of age (95% for both; Table 3). Elderly patients discontinued therapy because of an AE at a rate

similar to that among younger patients (5 [11%] of 44 vs. 15 [13%] of 117 patients).

DISCUSSION

In this study, we report a post hoc analysis that examined the effects of dose and age on the incidence of common AEs in patients treated with tadalafil in the PHIRST-1 and PHIRST-2 studies. We found no meaningful difference in the incidence of clinically relevant AEs between patients treated with tadalafil 20 mg versus 40 mg given as a once-daily dose for up to 68 weeks. Furthermore, we found no evidence that the 40-mg dose of tadalafil was less well tolerated in elderly patients than in patients <65 years of age or that elderly patients tolerated 20 mg of tadalafil better than 40 mg. In both elderly patients and those <65 years of age, most of the increased incidence of headache occurred during the initial week of therapy. By week 16, the incidence of headache was comparable with that in the placebo group. At the same time, elderly patients treated with tadalafil 40 mg daily had a similar increase in 6MWD and decrease in the incidence of clinical worsening over 16 weeks of therapy compared with patients <65 years old.

Figure 2. Percentage of elderly (A) and younger (B) patients with clinical worsening during treatment with placebo or tadalafil 40 mg for 16 weeks. Week 16 comparison between treatment groups of incidence of clinical worsening is as follows: ≥ 65 years of age, $P = 0.274$; <65 years of age, $P = 0.060$.

Table 3. Summary of common adverse events by patient age and treatment assignment

Parameter	≥65 years			<65 years		
	Placebo (n = 25)	Tadalafil 20 mg (n = 22)	Tadalafil 40 mg (n = 19)	Placebo (n = 57)	Tadalafil 20 mg (n = 60)	Tadalafil 40 mg (n = 60)
Any adverse event	17 (68)	14 (64)	18 (95)	48 (84)	55 (92)	57 (95)
Headache	3 (12)	3 (14)	6 (32)	9 (16)	23 (38)	27 (45)
Peripheral edema	4 (16)	1 (5)	3 (16)	3 (5)	6 (10)	2 (3)
Diarrhea	1 (4)	0 (0)	3 (16)	7 (12)	6 (10)	6 (10)
Dizziness	3 (12)	1 (5)	2 (11)	4 (7)	4 (7)	4 (7)
Back pain	2 (8)	2 (9)	1 (5)	3 (5)	8 (13)	7 (12)
Dyspnea	0 (0)	2 (9)	1 (5)	3 (5)	2 (3)	4 (7)
Pulmonary hypertension	2 (8)	0 (0)	2 (11)	5 (9)	7 (12)	4 (7)

Note: Data are no. (%) of patients.

Two PDE-5 inhibitors, sildenafil and tadalafil, have been approved for treatment of PAH.^{9,12} In the pivotal clinical trials of both drugs, several doses were tested on the basis of doses of the drugs commonly used for treatment of erectile dysfunction (ED).^{10,13} However, unlike the intermittent use of PDE-5 inhibitors for ED, treatment of PAH requires daily dosing, raising greater concern about long-term tolerability. This is particularly true with tadalafil, which has a much longer half-life than sildenafil.^{9,12} Tadalafil was approved for the treatment of PAH at 40 mg/d, which is double the highest on-demand dosage (i.e., 20 mg/d) approved to treat ED and four times the highest once-daily dosage (i.e., 5 mg/d) approved to treat ED. By contrast, sildenafil was approved for the treatment of PAH at 20 mg three times daily (60 mg/d), a dosage well below the highest dosage (i.e., 100 mg/d) approved to treat ED. As a result, it would seem prudent to initiate PAH therapy with tadalafil at 20 mg daily and then increase to the FDA-approved 40-mg daily dose if the drug is well tolerated. This approach may be particularly com-

mon in the elderly, who are often considered more susceptible to AEs associated with drugs administered at the full dose.

However, findings from this study suggest that AEs are no more common in patients who are treated initially with tadalafil 40 mg daily than in those treated with 20 mg daily regardless of age. The absence of an association between tadalafil dose and occurrence of AEs is similar to that reported with the use of sildenafil.¹³ However, in contrast to tadalafil, there was no dose-related effect on 6MWD. The findings from the current study, together with the greater efficacy of the 40-mg dose that led to FDA approval of tadalafil at this dose,¹⁰ support the use of 40 mg of tadalafil as the initial treatment dose in most patients with PAH. Use of a lower dose of tadalafil may be justified in patients who are hypotensive or have impaired metabolism of tadalafil because of liver disease or the concomitant use of drugs that inhibit the cytochrome P450 family of hepatic enzymes. For example, patients with HIV-associated PAH who are being treated with ritonavir may have an impaired

Figure 3. Incidence of headache assessed over 68 weeks in patients ≥65 years of age treated with placebo, tadalafil 20 mg, and tadalafil 40 mg. Patients who received placebo during the 16-week study received tadalafil 40 mg during the 52-week extension study.

Table 4. Clinically relevant adverse events with tadalafil over time for all patients (weeks 1–68)

Adverse event	Tadalafil 20 mg				Tadalafil 40 mg			
	Week 1 (n = 82)	Weeks 13–16 (n = 69)	Weeks 27–52 (n = 60)	Weeks 53–68 (n = 55)	Week 1 (n = 154)	Weeks 13–16 (n = 140)	Weeks 27–52 (n = 131)	Weeks 53–68 (n = 126)
Headache	29	9	8	13	24	9	9	8
Myalgia	6	7	5	5	7	4	2	4
Dyspepsia	10	12	5	5	5	6	4	4
Hypotension	2	1	0	5	<1	0	<1	3

Note: Data are percentage of patients.

ability to metabolize tadalafil and should be started on the 20-mg tadalafil dose.⁹

Although the AEs associated with tadalafil use were captured using a prospective placebo-controlled design, the findings of the present study are limited by the post hoc design used to analyze the data and the smaller number of elderly patients relative to the rest of the study population. Differences in the rates of background bosentan use between tadalafil treatment groups may also have confounded interpretation of the results. Although there were no differences in background bosentan use between patients given tadalafil 40 versus 20 mg, background bosentan use was less common in elderly patients than in those <65 years of age. However, the difference in rates of bosentan use between elderly and younger patients was small, and patients on bosentan therapy were required to be on a steady dose for at least 12 weeks before study entry. The effect of tadalafil in elderly patients taking other medications or with liver impairment from other diseases was also not assessed.

Few studies have specifically addressed the use of PAH therapies in geriatric patients despite the growing number of elderly patients diagnosed with this disease. While it is possible that dose- and age-related differences in AEs associated with tadalafil therapy may exist, our findings suggest that such differences are small and unlikely to warrant delay in use of the approved dose of tadalafil (40 mg daily). As the number of elderly patients treated for PAH increases, further studies will be needed to examine the dose effect of other PAH therapies on efficacy and AEs in this population.

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