Efficacy and Safety of Udenafil for the Treatment of Pulmonary Arterial Hypertension: a Placebo-controlled, Double-blind, Phase IIb Clinical Trial

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ABSTRACT

Purpose: Udenafil is an oral phosphodiesterase-5 inhibitor approved for the treatment of erectile dysfunction. In a multicenter, placebo-controlled, randomized Phase IIa study, the reduction of pulmonary vascular resistance index was greater with a 50-mg baseline dose of udenafil than with the 100-mg dose, the cardiac index did not decrease at most points, and the safety was excellent, suggesting that 50-mg udenafil could be used in a Phase IIb trial.

Methods: In this 16-week, double-blind, placebo-controlled study, 63 patients with pulmonary arterial hypertension were randomized to receive 50-mg udenafil or a placebo BID. The primary efficacy end point was the 6-min walking distance. The secondary efficacy end points were the Borg dyspnea score and time to clinical worsening. Patients who completed the 16-week study could participate in a long-term extension study.

Findings: : In terms of the difference between the baseline and 16-week 6-min walking distance in both groups, the mean placebo-corrected treatment effect was 25 (58) m ($P = 0.0873$). Among the patients with a history of endothelin receptor antagonist therapy, the treatment effect at week 16 between the udenafil and placebo groups was 34 (60) m ($P = 0.0460$). However, there were no significant differences in the Borg dyspnea score and time to clinical worsening between groups. The safety profile and adverse effects of udenafil were similar to those of typical phosphodiesterase-5 inhibitors seen in previous studies.

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Implications: Udenafil has a favorable safety profile and improves exercise capacity in patients with pulmonary arterial hypertension. ClinicalTrials.gov identifier: NCT01553721. (*Clin Ther.* 2019;41:1499–1507) © 2019 Published by Elsevier Inc.

Key Words: clinical trial, pulmonary arterial hypertension, udenafil, 6-min walking distance.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease that often causes early death.[1,2] In previous studies, PAH therapies have primarily been based on improvements in exercise capacity.[3] Udenafil is a newly developed, long-lasting phosphodiesterase-5 (PDE-5) inhibitor with an efficacy and safety profile comparable to those of other PDE-5 inhibitors. Similar to other PDE-5 inhibitors, udenafil was also originally developed for erectile dysfunction.[4] Udenafil has a longer half-life than sildenafil and is known to sustain vasodilation for 12 h after administration.[5,6] Clinical application of udenafil has been tried for several major diseases, including left ventricular hypertrophy, heart failure, and portal hypertension.[7–9]

A double-blind, placebo-controlled, Phase IIa study evaluated 2 doses (50 and 100 mg) of udenafil, an oral, once-daily PDE-5 inhibitor. In that study, the mean pulmonary arterial pressure (mPAP) significantly decreased in both the 50- and 100-mg udenafil groups (–11 mm Hg and –8 mm Hg from baseline; $P < 0.01$). This beneficial effect started early, ~1 h after udenafil administration, and persisted for at least 4 h. The cardiac index tended to increase in the 50-mg udenafil group ($P < 0.01$) but was significantly decreased in the 100-mg udenafil group for the first 2 h early after administration of udenafil. The pulmonary vascular resistance index decreased in both groups; however, statistical significance was only achieved in the 50-mg udenafil group compared with the placebo group. This finding implies that 50 mg is considered an appropriate dose of udenafil for treating PAH.[10] Herein, we report the data obtained from the 16-week, placebo-controlled, double-blind, multicenter, prospective Phase IIb study. The primary objective of this study was to evaluate the efficacy and safety of 50-mg udenafil used for treating PAH.

PATIENTS AND METHODS

Study Design and Patient Enrollment

This study was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study of patients with PAH. Phase IIb was performed with udenafil 50 mg, which was found to be appropriate in Phase IIa. Patients older than 18 years with idiopathic PAH, PAH associated with connective tissue disease, or PAH due to congenital heart disease, including Eisenmenger syndrome with symptoms (World Health Organization [WHO] functional classes II–IV), were included in the study. All the patients met the following hemodynamic criteria at the baseline right heart catheterization for inclusion: mPAP ≥25 mm Hg, pulmonary vascular resistance ≥400 dyne s/cm,[5] and pulmonary artery wedge pressure or left ventricular end-diastolic pressure ≤15 mm Hg. The patients included were on a stable dose of endothelin receptor antagonist (ERA) or alternative therapy for ERA (eg, digoxin, anticoagulant, calcium channel blocker, oxygen, diuretics) for at least 12 weeks.

Those who agreed to participate in the clinical trial were evaluated for their suitability. Phase IIa participants could participate in Phase IIb 2 weeks after the end of the Phase IIa study. If they have not undergone pulmonary CT imaging, pulmonary function tests, or echocardiography at the start of the IIb study, we can use the IIa phase results.

Exclusion criteria were as follows: PAH with other causes except for the aforementioned reasons; patients with a life expectancy of <6 months; or patients with a history of myocardial infarction, stroke, or life-threatening arrhythmia within 6 months of the screening test. Patients with atrial septostomy or angina were excluded if they were diagnosed within 12 weeks of screening. Patients with a left ventricular ejection fraction <45%, left ventricular outflow obstruction, uncontrolled hypertension, or blood pressure <90/50 mm Hg were excluded. In addition, patients who were taking prostacyclins, other PDE-5 inhibitor drugs, nitrates, or nitrous oxide donors within 30 days before the screening test and those taking drugs that could affect udenafil metabolism 7 days before the screening test were also excluded.

After screening, 63 patients were enrolled and randomized: 32 to the placebo group, and 31 to the

udenafil group within 4 weeks. The eligible patients were enrolled (N = 63) and received 50 mg of udenafil or a placebo BID for 16 weeks. The protocol was approved by the Ministry of Food and Drug Safety and local institutional review boards, and written informed consent was obtained from all patients. This study was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki).

Outcome Measurement

The primary efficacy end point of the study was a change in the exercise capacity (6-min walking distance [6-MWD]) from baseline (week 0) to week 16. The secondary efficacy end points of the study were the change in Borg dyspnea score from week 0 to week 16, time to clinical worsening (TTCW), N-terminal pro−B-type natriuretic peptide (NT-proBNP) level, and echocardiographic and cardiac magnetic resonance imaging (MRI) parameters.

TTCW was defined as the time to the first of any of the following events: all-cause mortality, hospitalization of >24 h due to aggravation of PAH symptoms, at least 1 stage of deterioration according to the World Health Organization functional class, or a decrease of >15% from baseline in the 6-MWD measured at 2 consecutive visits.

Echocardiography was performed at the time of screening, baseline, 8 weeks, and 16 weeks; mPAP, peak PAP, Doppler-derived cardiac index, right ventricular (RV) area change, right atrial (RA) area, tricuspid annular plane systolic excursion, RV systolic performance (RV S'), pericardial effusion, tricuspid regurgitation (TR), and maximal TR velocity were measured. MRI was performed at baseline at the institution where the trial was conducted, and the RV end-diastolic volume, RV end-systolic volume, RV ejection fraction (RVEF), efficient RVEF, RA volume, cardiac index, maximal TR velocity, TR fraction, and volume parameters were measured.

Safety was evaluated by using adverse events (AEs), results of physical examinations, vital signs, ECG findings, and clinical laboratory data. The clinical laboratory tests that were performed were complete blood cell count (CBC), routine chemistry test, blood coagulation test, and urine test. The per-protocol analysis data set was defined as a subanalysis group of patients who completed the clinical trial without any major deviation in the clinical trial protocol.

Statistical Analysis

This study was an exploratory clinical trial, and thus a formal sample size calculation was not performed. All efficacy end points are summarized with descriptive statistics and 95% CIs. The primary analytical target of the efficacy end points was the full analysis data set, which included those patients who received at least 1 investigational product in the clinical trial after being randomly assigned to the study group and who were evaluated at least once for the primary efficacy variable. The analysis was also performed by using the per-protocol analysis data set. Although this study was designed as an exploratory clinical trial, the primary end point and continuous secondary end points were compared between the treatment groups by using the 2-sample *t* test or Wilcoxon rank-sum test. The paired *t* test or Wilcoxon signed rank test was used to compare changes from baseline to week 16 between both treatment groups. For TTCW, the Kaplan−Meier method and log-rank test were used to compare survival between the treatment groups. The significance tests of the primary and secondary end points were 2-sided with a significance level of 0.05.

For safety end points, AEs were classified according to the Medical Dictionary for Regulatory Activities Terminology. The frequency and percentage of patients who experienced at least 1 AE are presented. Clinical laboratory data were evaluated as normal/abnormal, and the changes before and after the administration of the drug were evaluated by using the McNemar test.

RESULTS

A total of 63 patients were randomized to the placebo or udenafil group and received study medication.

Baseline Patient Characteristics

Baseline patient characteristics were balanced between the 2 groups (Table I). The majority of patients had symptoms in WHO functional class II and had idiopathic PAH; 86% of patients were

Table I. Baseline characteristics of all patients included in the placebo-controlled, double-blind, Phase IIb study. Values are given as mean (SD) unless otherwise indicated.

Characteristic	Udenafil Group (n = 31)	Placebo Group (n = 32)	*P*
Age, y	46 (15)	48 (14)	0.4369*
Female sex	25 (80.6%)	26 (81.2%)	0.9513†
Etiology			
Idiopathic	17 (54.8%)	15 (46.9%)	0.4151†
CTD	7 (22.6%)	5 (15.6%)	
CHD	7 (22.6%)	12 (37.5%)	
6-MWD, m	367.0 (75.9)	378.6 (66.6)	0.5049*
WHO FC			
II	25 (80.7%)	29 (90.6%)	0.3020‡
III	6 (19.3%)	3 (9.4%)	
IV	0	0	
RHC			
mPAP, mm Hg	53.5 (12.3)	52.2 (16.1)	0.1958*
PVR, dyne · s/cm^5	1027.0 (600.5)	936.2 (465.4)	0.7569*
Cardiac output, L/min	3.7 (1.4)	4.1 (1.5)	0.4226*
History of ERA treatment	27 (87.1%)	27 (84.4%)	0.9999‡

6-MWD = 6-min walking distance; CHD = congenital heart disease; CTD = connective tissue disease; ERA = endothelin receptor antagonist; PVR = pulmonary vascular resistance; RHC = right heart catheterization; WHO FC = World Health Organization functional class.
* Wilcoxon rank-sum test.
† The χ^2 test.
‡ Fisher's exact test.

receiving background ERA therapy. No patient was terminated early.

Primary Efficacy End Point: 6-MWD

The 16-week changes in the mean 6-MWD compared with baseline were 46 (66) m in the udenafil group (range, 371−418 m) and 21 (48) m in the placebo group (range, 385−406 m). The difference between the treatment groups (udenafil vs placebo) was 25 (58) m (95% CI, −4 to 56; $P = 0.0873$) (Figure 1).

Subgroup Analysis of the 6-MWD

Subgroup analysis was performed based on ERA administration. Among the patients with a history of ERA therapy, the 16-week changes from baseline were 54 (68) m and 20 (52) m in the udenafil and placebo groups, respectively. The difference between the groups was 34 (60) m (95% CI, 0.6−67), and the increase was higher in the udenafil group than in the placebo group ($P = 0.0460$).

Secondary Efficacy End Points

Borg Dyspnea Score

The baseline values of the Borg dyspnea score were 2.8 (1.9) and 2.6 (1.8) in the udenafil and placebo groups, respectively. The 16-week changes from the baseline value were 0.9 (2.0) and −0.2 (1.5) in the udenafil and placebo groups. The difference between the groups was −0.6 (1.8) (95% CI, −1.5 to 0.3), which was not statistically significant ($P = 0.6628$).

TTCW Assessment

Only 3 events of clinical worsening occurred during the 16-week period. Clinical deterioration occurred in 2 (6.4%) patients in the udenafil group, and 1 patient (3.1%) was hospitalized for >24 h in the placebo

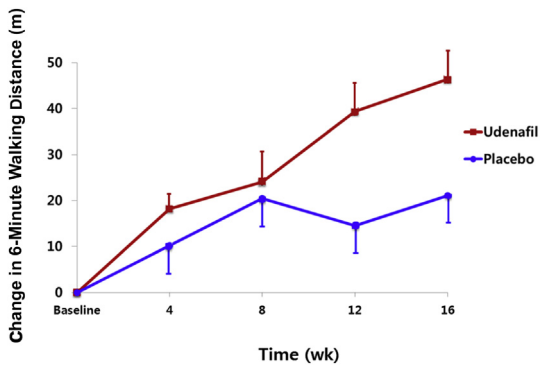

Figure 1. Six-minute walking distance of patients who received 50-mg udenafil or placebo (N = 63).

group. The proportion of patients with no clinical worsening was 100% at week 8 and 93.1% at week 16 in the udenafil group, and 96.9% at week 8 and 96.9% at week 16 in the placebo group. There was no statistically significant difference in survival between the groups (log-rank test, $P = 0.5189$) (Figure 2).

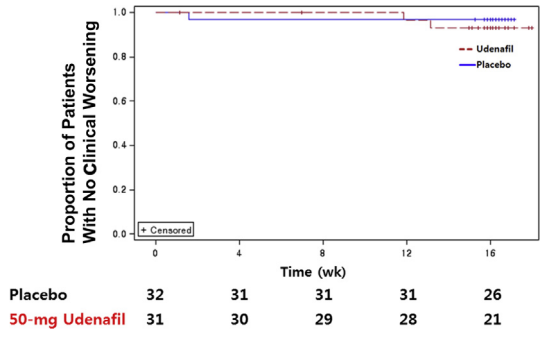

Figure 2. Proportion of patients with no clinical worsening according to the Kaplan–Meier method who received 50-mg udenafil or placebo (N = 63). Deterioration of the World Health Organization functional class was the most frequent cause of clinical worsening.

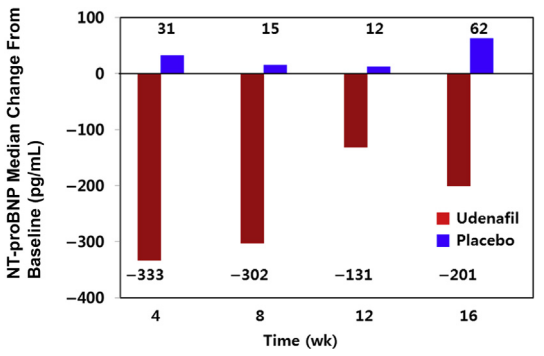

Figure 3. N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of patients who received 50-mg udenafil or placebo.

NT-proBNP Level

The difference between NT-pro BNP level change from baseline to 16 weeks in the udenafil group and NT-pro BNP level change from baseline to 16 weeks in the placebo group was −264 (436) pg/mL (95% CI, −486 to −42); the difference was statistically significant ($P = 0.0314$). Statistically significant differences in the NT-proBNP level were also noted between the groups at weeks 4, 8, and 12 ($P = 0.0036$, $P = 0.0314$, and $P = 0.0337$, respectively) (Figure 3).

Echocardiographic and Cardiac MRI Findings

Among the parameters measured by using echocardiography, only the 16-week changes in the RA area and RV S' were statistically significantly different between the groups. The baseline values of the RA area were 25.56 (14.31) cm^2 and 21.58 (11.36) cm^2 in the udenafil and placebo groups, respectively. The 16-week changes from the baseline values were −1.99 (4.52) cm^2 and −1.43 (11.52) cm^2 in the udenafil and placebo groups. The difference in the 6-week change in the RA area value from baseline in the udenafil group and the value in the placebo group was −0.55 (8.75) cm^2 (95% CI, −5.13 to 4.02). This difference was statistically significant ($P = 0.0384$).

There was a statistically significant difference in the RA area between the udenafil and placebo groups in the 16-week change from baseline, which was −0.55 (8.75) cm^2 (95% CI, −5.13 to 4.02; $P = 0.0384$).

Table II. Change in echocardiographic parameters at baseline and week 16 between the udenafil and placebo groups. Values are given as mean (SD).

Echocardiography Parameter	Udenafil Group (n = 31)		Placebo Group (n = 32)		Difference Between The Udenafil Group and Placebo Group	
	Change From Baseline	*P*	Change From Baseline	*P*	Change From Baseline	*P*
mPAP, mm Hg	−0.95 (6.49)	0.4296*	−2.42 (11.25)	0.0236†	1.47 (9.18)	0.2675‡
Peak PAP, mm Hg	−5.24 (14.59)	0.0501†	−3.31 (12.45)	0.1559*	−1.93 (13.56)	0.6734‡
Doppler-derived cardiac index, L/min/m^2	0.30 (0.87)	0.1592†	−0.16 (0.89)	0.3322*	0.46 (0.88)	0.1630‡
Change in RV area, %	3.24 (7.76)	0.0297*	2.57 (6.14)	0.0294*	0.67 (7.00)	0.7122§
RA area, cm^2	−1.99 (4.52)	0.0226*	−1.43 (11.52)	0.4288†	−0.55 (8.75)	0.0384‡
TAPSE, mm	1.53 (2.99)	0.0088*	0.16 (2.65)	0.7445*	1.37 (2.83)	0.0678§
RV S', cm/s	1.49 (1.94)	0.0002*	−0.43 (2.30)	0.3175*	1.92 (2.13)	0.0010§
TR Vmax, m/s	−0.16 (0.46)	0.0414†	−0.12 (0.42)	0.1151*	−0.04 (0.44)	0.7556‡

mPAP = mean pulmonary arterial pressure; PAP = pulmonary arterial pressure; RA = right atrial; RV = right ventricular; RV S' = right ventricular systolic performance; TAPSE = tricuspid annular plane systolic excursion; TR Vmax = maximal tricuspid regurgitation velocity.
* Paired *t* test.
† Wilcoxon signed rank test.
‡ Wilcoxon rank-sum test.
§ Two-sample *t* test.

The difference in the change of RV S' from baseline to week 16 between the groups was 1.92 (2.13) cm/s, which means that the increase in RV S' in the udenafil group was greater than in the placebo group; this difference was also statistically significant ($P = 0.0010$). No statistical significance was found between the groups for the other echocardiographic parameters (Table II). In addition, RV end-diastolic volume, RV end-systolic volume, RVEF, effective RVEF, RA volume, cardiac index, TR fraction, and TR volume measured by using cardiac MRI showed no statistically significant differences between the groups.

Safety Profile

Udenafil was generally well tolerated, with the most common AEs being headache and chest discomfort (Table III). Of 31 patients in the udenafil group, 23 (74.2% [79 cases]) had AEs, and 4 (12.9% [seven cases]) had serious AEs. In the placebo group (n = 32), 18 (56.3% [34 cases]) had AEs, and 1 (3.1%) among these had a serious AE. Most AEs were reported as mild or moderate (92% in the udenafil group, 82% in the placebo group). Serious AEs of musculoskeletal discomfort, dyspnea, and chest pain were considered not relevant to the investigational product, and other symptoms such as chills, pyrexia, and pain in an extremity were suspected of being relevant to the investigational product. The discontinuation rate was 6.5% in the udenafil group (2 patients [1 with edema, the other with severe chills, febrile sensation, and lower arm and calf pain]). There were no dropouts due to AEs in the placebo group. The clinical laboratory tests were CBC, routine chemistry, blood coagulation, and urine. In terms of CBC, only 4 patients (12.5%) in the placebo group exhibited abnormalities in red blood cells. Regarding blood chemistry tests, 5 patients (15.6%) in the placebo group exhibited abnormal creatinine values. In the udenafil group, no other abnormal laboratory finding was noted. No other findings were observed in any other patients, and there were no clinically meaningful changes in electrocardiographic findings.

Table III. The most common adverse events during the placebo-controlled, double-blind, Phase IIb study.

Adverse Event	Udenafil Group (n = 31)	Placebo Group (n = 32)
Headache	6 (19.4)	1 (3.1)
Chest discomfort	5 (16.1)	1 (3.1)
Nasopharyngitis	3 (9.7)	3 (9.4)
Upper respiratory tract infection	3 (9.7)	1 (3.1)
Face edema	2 (6.5)	2 (6.3)
Cough	2 (6.5)	2 (6.3)
Arthralgia	3 (9.7)	—
Constipation	3 (9.7)	—
Hot flash	3 (9.7)	—
Pruritus	2 (6.5)	1 (3.1)
Dyspepsia	1 (3.2)	2 (6.3)
Peripheral edema	1 (3.2)	2 (6.3)
Ocular hyperemia	2 (6.5)	—
Diarrhea	2 (6.5)	—
Myalgia	2 (6.5)	—
Pain in the extremity	2 (6.5)	—
Generalized edema	2 (6.5)	—
Dyspnea	2 (6.5)	—
Paresthesia	—	2 (6.5)

There was no statistically significant difference in postadministration changes in results of vital signs (ie, systolic and diastolic blood pressures, pulse).

Deaths and Survival

No deaths occurred during this Phase IIb study.

DISCUSSION

The results of this study show that udenafil improved exercise capacity, as assessed by using the 6-MWD, in patients with PAH, especially those with a history of ERA therapy.

In the full analysis data set, the increase in the 6-MWD between baseline and 16 weeks in the udenafil group was 46 (66) m, whereas the increase in the placebo group was 21 (48) m. The difference between the groups was 25 (58) m ($P = 0.0873$), and this tendency was also maintained in the per-protocol analysis data set (difference of 31 [50] m; $P = 0.0370$).

In the subgroup analysis according to ERA administration, the placebo-corrected treatment effect at week 16 was 34 (60) m ($P = 0.0460$) in patients with a history of ERA therapy (changes in the 6-MWD were 54 [68] m and 20 [52] m in the udenafil and placebo groups, respectively).

A Phase III clinical trial of the PDE-5 inhibitor sildenafil (20 mg thrice daily) showed improvement of 45 m in the 6-MWD at 12 weeks (placebo-corrected treatment effect, $P < 0.001$) but only included treatment-naive patients with PAH.[14] The results of the COMPASS-3 (Safety and Efficacy of Bosentan in Combination With Sildenafil in PAH Patients Who Experience Inadequate Clinical Response to Monotherapy) clinical trial showed a 23 m improvement in the 6-MWD when sildenafil (20 mg thrice daily) was added for another 12 weeks after monotherapy with bosentan (125 mg BID) for 16 weeks.[11]

The results of a Phase III trial of 40-mg tadalafil daily showed that the change in 6-MWD at 16 weeks in patients with PAH who were treatment-naive or had a history of bosentan therapy was 33 m (placebo-corrected treatment effect), which was statistically significant ($P < 0.001$); however, the change in 6-MWD was only 23 m ($P = 0.09$) for patients with a history of bosentan therapy.[12]

Among the 63 patients enrolled in the current study, 53 (26 and 27 in the udenafil and placebo groups, respectively) received an ERA, accounting for 84% of the total subjects. In patients on background therapy with an ERA, improvement in the 6-MWD after 16 weeks was 33.86 m higher in the udenafil group than in the placebo group ($P = 0.0460$). The change in the 6-MWD with udenafil and ERA combination therapy was superior to that with sildenafil (COMPASS-3) and tadalafil in previous clinical trials.[12,13] This means that a combination therapy of udenafil and ERA was also effective in improving the 6-MWD.

This finding is consistent with the results of the AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) study,[11] which reported superior efficacy of combined ambrisentan and tadalafil over single treatment.

In this study, there is no statistically or clinically significant improvement in the Borg dyspnea score, which was obseved in other previous studies using PAH drugs although exercised capacity was improved.[14–18] In fact, it is rare to observe treatment effects >0.5 to 1.0 point (of 10). As mentioned in previous studies, this phenomenon is related to the patient's tendency to maximize walking effort at each study visit, and thus similar breathing difficulties may occur regardless of walking.[12]

The incidence of clinical worsening was not significantly different between the patients treated with udenafil and those receiving placebo. However, the overall incidence of clinical worsening in this study was low and may be related to the cohort of patients with PAH of WHO functional class II (84%) and to the short duration of the study (16 weeks). In addition, in the BREATHE-1 (Bosentan Randomized Trial of Endothelin Antagonist Therapy for Pulmonary Hypertension) study, a statistically significant difference in the time to clinical worsening was observed after 16 weeks.[16]

In the safety evaluation, the incidence of AEs was higher with udenafil than with placebo, although the difference was not statistically significant. However, adverse drug reactions were mostly mild and in the predicted range. Udenafil showed a similar or lower incidence of AEs than other PDE-5 inhibitors such as sildenafil and tadalafil.[12,14] In this regard, udenafil is safe and well tolerated, as are other PDE-5 drugs. In the treatment of PAH, udenafil improved the 6-MWD when used in combination with an ERA. In addition, it was safe and well tolerated by the patients.

The limitations of this study were the significant dropouts (namely, 4 patients [12.9%]; two patients due to adverse events [one with edema, the other with severe chills, febrile sensation, and lower arm and calf pain], one patient had no therapeutic effect, and one patient was noncompliant with the clinical trial protocol) in the udenafil group. An additional limitation of this study is that some patients who completed Phase IIa and were registered in Phase IIb could lead to a selection bias. In the placebo group, 27 patients received ERA and the remaining 5 maintained alternative therapies rather than ERA during 16 weeks. These patients were treated but did not receive the optimal treatment recommended by class I.[19]

CONCLUSIONS

The favorable tolerability of udenafil and its positive effects on the 6-MWD and NT-proBNP could potentially translate into improvements in health-related quality of life for patients. The data obtained through the study show the efficacy of udenafil for the treatment of patients with PAH; moreover, udenafil seemed to be safe and well tolerated by patients. Further extended study of udenafil in PAH is warranted.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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