ORIGINAL RESEARCH—ED PHARMACOTHERAPY

The Efficacy and Safety of Udenafil [Zydena] for the Treatment of Erectile Dysfunction in Hypertensive Men Taking Concomitant Antihypertensive Agents

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ABSTRACT

Introduction. Erectile dysfunction (ED) and hypertension are frequent comorbid conditions. The vasodilating properties of type 5 phosphodiesterase inhibitor (PDE5I) are the major concerns for the treatment of ED patients on antihypertensive medications.

Aim. To evaluate the efficacy and safety of Udenafil [Zydena] (Dong-A, Seoul, Korea), a newly developed PDE5I, for the treatment of ED patients on antihypertensive medication.

Methods. It was a multicentered, randomized, double-blind, placebo-controlled, fix-dosed clinical trial among 165 ED patients receiving antihypertensive medications. The subjects treated with placebo, 100 mg or 200 mg of Udenafil for 12 weeks were asked to complete the Sexual Encounter Profile (SEP) diary, the International Index of Erectile Function (IIEF), and the Global Assessment Question (GAQ) during the study period.

Main Outcome Measures. Primary parameter: the change from baseline for IIEF erectile function domain (EFD) score; Secondary parameters: the IIEF Question 3 and 4, SEP Question 2 and 3, the rate of achieving normal erectile function (EFD $\geq$ 26) and the response to GAQ.

Results. Compared to placebo, patients receiving both doses of Udenafil showed significantly improved the IIEF-EFD score. The least squares means for the change from baseline in IIEF-EFD scores were 8.4 and 9.8 for 100 mg and 200 mg Udenafil groups, respectively; those values were significantly higher than that of placebo (2.4, $P < 0.0001$). Similar results were observed in the comparison of Q3 and Q4 of IIEF, SEP diary and GAQ. Headache and flushing were the most common treatment-emergent adverse events, which were transient and mild-to-moderate in nature. No parameters of efficacy and safety were affected among the subsets stratified according to either the number of antihypertensive medication received or the previous experience of PDE5Is treatment.

Conclusion. Udenafil significantly improved erectile function among ED patients with hypertensive symptom treated with concomitant antihypertensive medication. The treatment did not increase the frequency or severity of adverse events. **Paick J-S, Kim SW, Park YK, Hyun JS, Park NC, Lee SW, Park K, Moon KH, and Chung WS. The efficacy and safety of Udenafil [Zydena] for the treatment of erectile dysfunction in hypertensive men taking concomitant antihypertensive agents. J Sex Med 2009;6:3166–3176.**

Key Words. Erectile Dysfunction; Phosphodiesterase 5 Inhibitor; Udenafil; Hypertension

Introduction

Erectile dysfunction (ED) is the inability to attain and/or maintain penile erection sufficient for satisfactory sexual activity, with an overall prevalence of 13.4% among Korean middle-aged men [1].

Successful introduction of sildenafil, tadalafil, and vardenafil, all of which can be classified as type 5 phosphodiesterase inhibitors (PDE5Is), have revolutionized the treatment of ED with high efficacy, good tolerability, and acceptable safety irrespective of the etiology of ED [2]. Currently, PDE5Is are placed as the primary option for ED treatment and expanding their indications for nonerectogenic purposes [3,4].

Udenafil ([Zydena], Dong-A, Seoul, Korea) is another selective PDE5I newly developed for the treatment of ED. Its pharmacokinetic profile includes a T_{max} of 1.0–1.5 hours and $T_{1/2}$ of 11–13 hours, which could confer unique clinical properties of relatively rapid onset and long duration of action [5]. Previous phase 3 study demonstrated the efficacy and safety of this drug in Korean men with ED of broad-spectrum etiologies and severities [6].

ED and hypertension are frequent comorbid conditions and studies indicate that 52–68% men with hypertension also have ED [7,8]. Hypertension causes atherosclerotic involvement of penile vessels and endothelial dysfunction, which could impair penile erection and lower the response to PDE5Is. In addition, many antihypertensive drugs may worsen sexual function as a drug specific side effect [9]. Although some clinical studies have observed similar efficacy of PDE5Is regardless of the number of antihypertensive agents [10–12], it is still probable that significant hypertension and its treatment would cause reduced efficacy of PDE5Is. One of Korean clinical trial indicated relatively lower success rates for restoration of erectile function in those who had four or more antihypertensive agents [13].

Given the known of vasodilatory effect, there has been a concern over the use of PDE5I for ED in patients on antihypertensive medications. Hemodynamic studies with other PDE5Is revealed minor changes, which are not likely to be clinically significant, and modest side effect profiles during the concomitant use of various antihypertensive agents, except in the case of alpha antagonists and nitrate donors [14,15]. Also, recent clinical trials were incomplete to report increased incidence of treatment-emergent adverse events (TEAEs) after the treatment with PDE5Is in those receiving antihypertensive agents [10–13].

The efficacy and safety of Udenafil, previously demonstrated in broad-spectrum population with ED, have not been sufficiently evaluated in hypertensive patients. With this phase 3, double-blind, placebo-controlled, fix-dosed study design, we attempted to clarify whether Udenafil could be used in hypertensive ED patients taking concomitant antihypertensive agents, with acceptable efficacy and safety.

Methods

Study Population

One hundred and sixty-five ED patients were enrolled and randomized. The enrollment took place at eight institutions in Korea, all of which received the approval by Institutional Review Board to carry out the study. The inclusion criteria were 6 months or longer with clinical complaint of ED, arteriogenic hypertension treated with one or more antihypertensive agents in a stable dose, and those who were having stable sexual intercourse with one partner. We excluded the patients with uncontrolled hypertension (>170/110 mm Hg), clinically significant symptomatic postural hypotension (<90/50 mm Hg), chronic heart failure, myocardial infarction, unstable angina, life threatening arrhythmia or atrial tachyarrhythmia with a heart rate more than 100 beats per minutes at screening, stroke or clinically significant cardiovascular disease, and those patients taking drugs containing nitrate agents regularly or intermittently regardless of the type of the drug. Also excluded were patients with mild to severe hepatic dysfunction or liver function abnormalities (ALT or AST over three times higher than upper limits of normal), clinically significant chronic hematological disorder or bleeding disorder, history of significant peptic ulcer disease within the previous year, uncontrolled diabetes mellitus, proliferative diabetic retinopathy, retinitis pigmentosa, and current history of anticancer chemotherapy or serum creatinine above 2.5 mg/dL known at the time of screening. Patients taking anticoagulants (excluding antiplatelet agents), androgen, antiandrogen, trazodone, potent HIV protease inhibitors (ritonavir, indinavir), itraconazole, ketoconazole, and erythromycin were also excluded from the trial. Nonresponders to other PDE5Is were excluded and responders to other PDE5Is exposed within 2 weeks before treatment-free run-in

period were excluded as well. All patients were provided written informed consent before participation.

Study Design

This was a randomized, double-blind, parallel-group, placebo-controlled study evaluating the efficacy and safety of fix dosed of Udenafil in men with arterial hypertension and ED.

On the screening visit (at -4 week), we collected patients' basic demographic data, such as age, duration of ED, smoking and drinking habits, relevant medical history, and performed physical examination including sitting and standing blood pressure and heart rate. General blood test, blood chemistry, and 12-electrode electrocardiogram were screened. Patients were also instructed how to write the diary. Eligible patients had a 4-week treatment-free run-in periods during which subjects made at least four attempts at intercourse. Following this period (at 0 week), we collected basic data on the patients' sexual function with International Index of Erectile Function (IIEF) and diary and entered the 12-week treatment phase. Patients were then randomized to receive placebo, 100 mg or 200 mg Udenafil, the same doses in previous phase 3 clinical trial for Udenafil. Study drug was administrated the 30 minutes to 12 hours time frame prior to attempts at intercourse, based upon the result of phase 3 trial which demonstrated its persistent efficacy up to 12 hours post dosing (unpublished data). The investigators assessed the treatment response and tolerance at 4, 8, and 12 weeks of treatment. For safety analysis, sitting and standing blood pressure and heart rate were taken at every 4 weeks until the completion of the study. In addition, the general blood test, blood chemistry, and 12-electrode electrocardiogram were also performed at the end of clinical trial. No more than a single dose of study drug was permitted per calendar day.

Main Outcome Measures: Efficacy

The primary efficacy parameter was the 12-week change from baseline for IIEF erectile function domain (EFD) score calculated as the sum of the scores from Questions 1 to 5 and 15. The secondary efficacy parameters were the 12 week change from baseline in the IIEF Question 3 (Q3), Question 4 (Q4), and the mean per-patient percentage of "yes" responses to 2 and 3 of Sexual Encounter Profile (SEP) diary, questioning "Were you able to insert your penis into your partner's vagina?" (SEP Q2) and "Did your erection last long enough for you to have a successful intercourse?" (SEP Q3). Both questions were assessed after each attempt at intercourse with Udenafil or placebo therapy. The additional secondary efficacy parameters included the proportion of achieving normal erectile function (EFD $\geq$ 26) assessed by IIEF-EFD score and the response to global assessment question (GAQ), "Has the treatment you have taken over the past 4 weeks improved your erections?" (the answer to which was "yes" or "no"). All efficacy measures were assessed after 4, 8, and 12 weeks of Udenafil or placebo therapy or upon premature discontinuation.

Safety

The adverse events in patients were recorded, and for each adverse event, the investigator judged whether these were mild, moderate, or severe, and whether they were possibly or probably drug-related. The judgment was done without knowledge of which treatment the patient was receiving. Safety analysis was based on blood pressure (sitting and standing), heart rate, electrocardiogram, the results of laboratory tests, and adverse events recorded.

Statistical Analysis

Based on the assumption that the difference between placebo and Udenafil in the mean change from baseline IIEF-EFD scores is 5 and that the common variance is 6.2, sample sizes of at least 40 subjects per treatment group were required to detect the specified difference between the treatment groups, with a power of 95% and a type I error rate of 5%.

All analyses were performed on the intention-to-treat (ITT) principle. The efficacy analyses included all randomized patients who took at least one dose of a study drug and had at least one post-baseline measurement. The last observation carried forward imputation method was used to replace missing values. The safety analyses included patients who received at least one dose of Udenafil or placebo.

The results from IIEF-EFD score, IIEF Q3 and Q4, SEP Q2 and Q3 were analyzed as continuous variables using analysis of variance (ANOVA) models as pre-planned in the protocol. IIEF-EFD score was additionally evaluated using analysis of covariance (ANCOVA) model including terms of treatment group, institution, and baseline ED severity. If the statistically significant difference across means or least-squares means in three groups was

observed, then a multiple comparison method was used to look for specific differences between pairs of groups. In each group, multiple measures over visit for continuous efficacy endpoints were assessed with analysis of variance for repeated measurements (RM-ANOVA). The differences between groups in the assessment of GAQ and the proportion of achieving normal erectile function were compared using the chi-square test. The analyses comparing the incidence of TEAEs across treatment groups were also performed by chi-square test. All tests of statistical significance were 2-tailed at the 0.05 significant level ($\alpha = 0.05$) and all statistical analyses were carried out using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Disposition (Figure 1)

One hundred and ninety-four ED patients were recruited from eight institutions in Korea. One hundred and sixty-five ED patients were enrolled and randomized and 164 ED patients took at least one dose of the study drug and were eligible for safety analysis. Among them, six patients did not have an efficacy evaluation at baseline or post-baseline, leaving 158 patients in the ITT population with 52, 55, and 51 individuals in 100 mg, 200 mg Udenafil, and placebo, respectively.

Patient Demographics and Characteristics

As seen in Table 1, the characteristics of each group were similar except in the case of ED severity. Therefore, the baseline ED severity was considered as covariate using ANCOVA model in efficacy analysis. The mean age for each group was about 56 years and the duration of ED was approximately 4 years. No patients were thought to have pure psychogenic ED. The mean IIEF-EFD scores of placebo, 100 mg, and 200 mg Udenafil group were 16.0, 14.2, and 14.3, respectively. Although the placebo group had a higher baseline mean IIEF-EFD score than Udenafil groups, the mean scores of all groups could be classified as the level of moderate ED. Approximately, half of the patients have had the experience of prior use of PDE5Is. The common concomitant diseases were diabetes (14%) and benign prostatic hyperplasia (11%).

Table 2 describes the number of patients in this study concomitantly receiving antihypertensive agent of different classes, the most common of which was calcium channel blocker (≥60%). The number of antihypertensive agents taken were 1, 2, and 3 or more respectively in 63 (38%), 59 (36%), and 43 (26%) patients. There was no statistical difference in the number of antihypertensive agents taken.

Efficacy

The primary efficacy endpoint was the 12-week change from baseline for IIEF-EFD score in the ITT population. Mean IIEF-EFD scores at baseline (placebo, 16.0; 100 mg Udenafil, 14.2; 200 mg Udenafil, 14.3) were consistent with the diagnosis of moderate ED. After 12 weeks of treatment, the mean IIEF-EFD score in the 100 mg and 200 mg Udenafil groups increased to 22.9 ± 6.2 and 24.3 ± 6.5, respectively, compared to 18.0 ± 7.4 in the placebo group (Figure 2). The least squares means for change from baseline in IIEF-EFD scores were 8.4 and 9.8 for 100 mg and 200 mg Udenafil group, respectively, which are significantly higher than 2.4 for placebo (ANCOVA, treatment effect $P < 0.0001$, baseline ED severity effect, $P = 0.0114$, institution effect, $P = 0.0054$). Meanwhile, no significant difference was observed between the two Udenafil groups. Similarly, significant increases in IIEF-EFD scores was observed in both Udenafil-treated groups compared to placebo when adjusted for the number of antihypertensives. ANCOVA with the number of antihypertensives revealed no statistically significant changes in EFD scores according to the number of antihypertensive drugs ($P = 0.1869$). Udenafil significantly improved all tested secondary efficacy parameters as well. In comparison of mean success rate of ability to penetrate partner (SEP Q2) and to maintain sufficient erection (SEP Q3) with placebo, 100 mg and 200 mg Udenafil treatment significantly increased both parameters at week 12 (Figure 3). Similar improvement was found in the comparison of Q3 and Q4 in IIEF. In Q3, mean change from baseline after 12 weeks of 100 mg and 200 mg Udenafil treatment were 1.3 and 1.4, which contrasted to 0.1 in placebo. In Q4, mean change from baseline after the treatment of 100 mg and 200 mg Udenafil were 2.0 and 2.5, contrasting to 0.7 in placebo. The proportion of achieving normal erectile function (EFD ≥ 26) was 44% and 55% in 100 mg and 200 mg Udenafil group, respectively. These values were significantly higher than that of placebo group (16%) (Figure 4). Likewise, the percentage of patients responding positively to the GAQ was higher in the Udenafil treated groups than placebo (Figure 5).

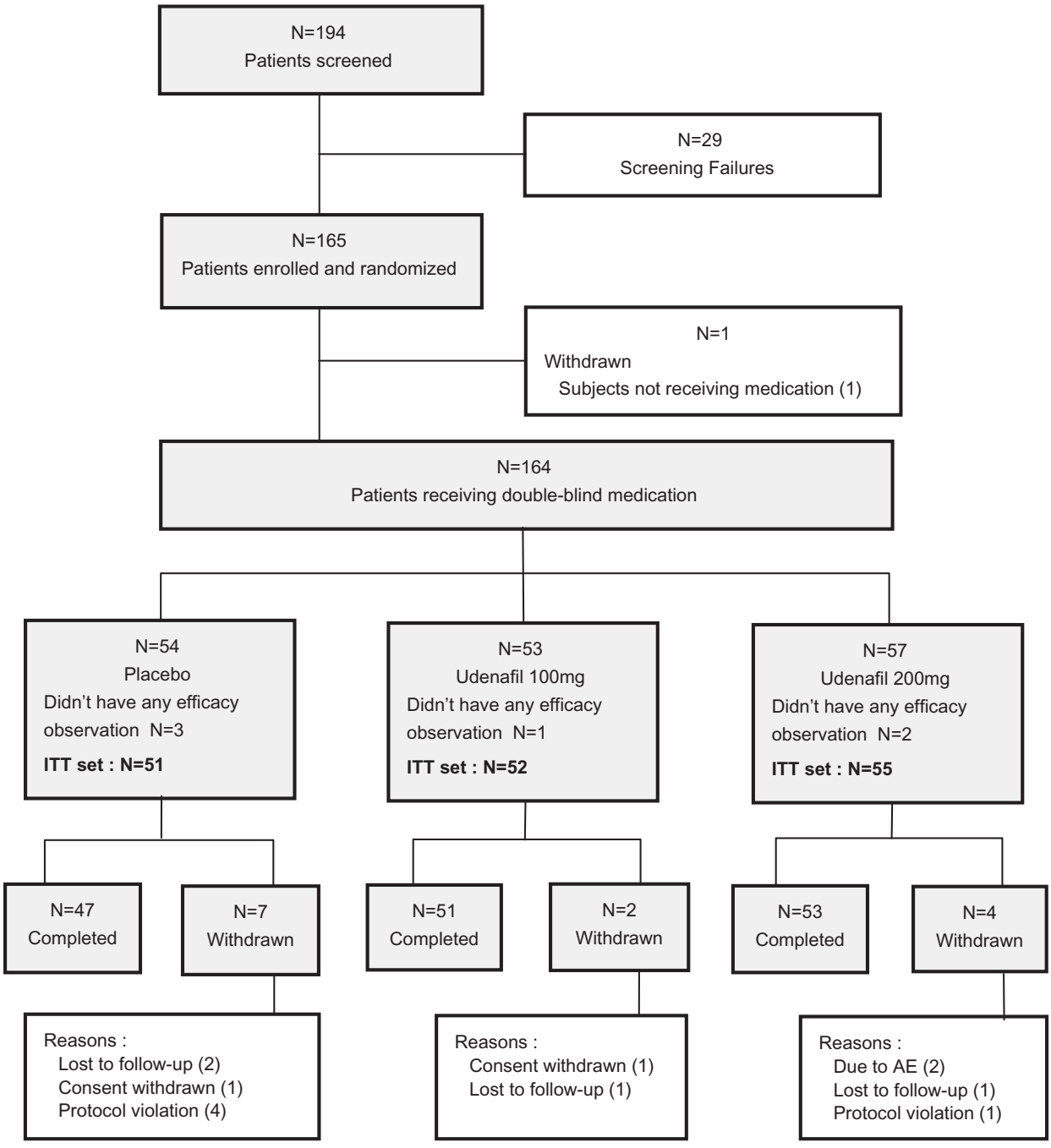

Figure 1 Patient disposition.

The subgroup analyses were performed for baseline ED severity (severe, moderate, or mild to moderate) and the number of antihypertensive agents taken (one drug, two drugs, or three or more drugs). While all subgroups showed improvement of IIEF-EFD score, interestingly the numerically largest increase of the score was observed in subgroups with severe ED or those who took three or more antihypertensive agents. Hence, all subgroups of Udenafil treatment reached the level of mild ED irrespective of baseline ED severity or the number of antihypertensive agents taken. In addition, no difference was noted in improvement of IIEF-EFD score with respect to previous experience of PDE5I (data were not shown).

Table 1 Demographic and erectile dysfunction characteristics of study subjects

		Udenafil			
	Placebo (N = 55)	100 mg (N = 53)	200 mg (N = 57)	Total (N = 165)	*P* value†
Age (year)	55.51 ± 8.25	56.23 ± 8.24	55.89 ± 7.17	55.87 ± 7.85	0.8942
Height (cm)	169.00 ± 4.27	168.68 ± 5.17	168.60 ± 5.12	168.76 ± 4.84	0.8994
Weight (kg)	70.21 ± 7.21	70.94 ± 8.54	72.43 ± 7.60	71.21 ± 7.80	0.3113
ED duration‡ (year)	4.33 ± 3.51	4.06 ± 3.04	3.93 ± 3.53	4.10 ± 3.36	0.8178
≤1 year	9	13	12	34	0.4504
	(16.4)	(24.5)	(21.1)	(20.6)	
2–5 years	33	25	34	92	
	(60.0)	(47.2)	(59.7)	(55.8)	
6–10 years	12	15	9	36	
	(21.8)	(28.3)	(15.8)	(21.8)	
≥11 years	1	0	2	3	
	(1.8)	(0.0)	(3.5)	(1.8)	
ED etiology—no. (%)					
Organic	31	32	33	96	0.9132
	(56.4)	(60.4)	(57.9)	(58.2)	
Psychogenic	0	0	0	0	
	(0.0)	(0.0)	(0.0)	(0.0)	
Mixed	24	21	24	69	
	(43.6)	(39.6)	(42.1)	(41.8)	
Baseline severity (EF domain score of IIEF)—no. (%)					
Severe (≤10)	10	12	9	31	0.0327*
	(18.2)	(22.6)	(15.8)	(18.8)	
Moderate (11–16)	14	22	31	67	
	(25.5)	(41.5)	(54.4)	(40.6)	
Mild-Moderate (17–21)	26	18	16	60	
	(47.3)	(34.0)	(28.1)	(36.4)	
Mild (22–25)	5	1	1	7	
	(9.1)	(1.9)	(1.8)	(4.2)	
Prior use of other PDE5Is—no. (%)	28	29	33	90	0.7589
	(50.9)	(54.7)	(57.9)	(54.6)	

Values are expressed means ± standard deviation.
†*P* values were calculated using chi-square or Fisher's exact tests for comparison of subject numbers and ANOVA for comparison of mean values (**P* < 0.05).
‡ED duration was defined as the number of years from the time of subject's recognition of ED condition to the time of informed consent to this study.
ED = Erectile dysfunction; IIEF = International Index of Erectile Function; -EF = Erectile function.

Safety

Vital Signs and Laboratory Examinations

After 100 mg Udenafil treatment, only the average standing diastolic blood pressure significantly decreased from 85.3 mm Hg to 81.9 mm Hg after 12 weeks of treatment. In those who received 200 mg of Udenafil, both the sitting and standing diastolic blood pressure (DBP) significantly decreased from 83.7 and 85.9 mm Hg to 81.1 and 83.0 mm Hg, respectively. No significant change was noted on systolic blood pressure in the treatment arms. Interestingly, significant reduction of DBP was noted in both sitting and standing position after the treatment of placebo. In comparison of the sitting or standing blood pressure profiles, there were no statistically significant differences between groups (RM-ANOVA). No one experienced any symptoms related to blood pressure change.

Elevated heart rate was only experienced in 100 mg Udenafil group, whose mean heart rate on sitting position significantly changed from 71.6 bpm to 74.5 bpm after 12-week treatment. Likewise, the heart rate profiles did not show significant difference between groups.

The treatment of Udenafil did not exert effect on laboratory examination and electrocardiogram.

Treatment-Emergent Adverse Events

In general, treatment with Udenafil was well tolerated with a low incidence of TEAEs. The most commonly reported adverse events were headache and flushing (Table 3). When compared to the placebo group, higher incidence of TEAEs was noted in treatment arms (100 mg and 200 mg Udenafil), while it was not statistically significant by pairwise comparisons.

During the study duration, two patients discontinued the medication due to adverse events such as moderate conjunctival hyperemia (one case) and mild headache and facial flushing (one case), which were spontaneously resolved after discontinuation of Udenafil.

Table 2 Antihypertensive medications at baseline

	Placebo (N = 55)	Udenafil 100 mg (N = 53)	Udenafil 200 mg (N = 57)	Total (N = 165)	*P* value†
Class of antihypertensive medications					
Angiotensin-converting-enzyme (ACE) inhibitors	8 (14.5)	6 (11.3)	10 (17.5)	24 (14.5)	
α-blocker	0 (0.0)	5 (9.4)	3 (5.3)	8 (4.8)	
Angiotensin II-receptor antagonist	24 (43.6)	22 (41.5)	25 (43.9)	71 (43.0)	
β-blocker	12 (21.8)	12 (22.6)	13 (22.8)	37 (22.4)	—
Calcium channel blocker	41 (74.5)	36 (67.9)	37 (64.9)	114 (69.1)	
Diuretics	19 (34.5)	16 (30.2)	19 (33.3)	54 (32.7)	
Nonselective α/β blocker	1 (1.8)	3 (5.7)	4 (7.0)	8 (4.8)	
Number of antihypertensive medications					
1 drug	19 (34.6)	23 (43.4)	21 (36.8)	63 (38.2)	
2 drugs	24 (43.6)	15 (28.3)	20 (35.1)	59 (35.8)	0.5661
3 or more drugs	12 (21.8)	15 (28.3)	16 (28.1)	43 (26.1)	

†Chi-square test.
No. (%) of subjects.

Discussion

In this study, we have investigated whether Udenafil was well tolerated, effective, and without clinically significant adverse effects on blood pressure, when used in typical hypertensive patients. The results showed that Udenafil significantly improved the erectile function in ED patients on antihypertensive medications. Over the 12 weeks of study, the IIEF-EFD score, the primary outcome variable, improved from one of a moderate level to one of a mild level of ED. The treatment was also beneficial in achieving and maintaining erection during sexual intercourse (SEP Q2, Q3), and restored normal erectile function in approximately half of the patients.

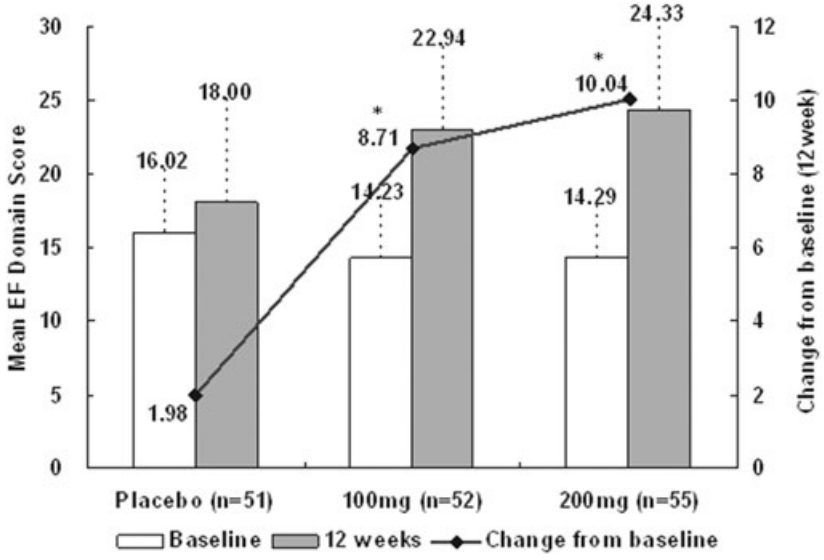

Figure 2 Effect of Udenafil on IIEF-EFD scores at baseline and 12 weeks (*$P < 0.0001$ vs. placebo).

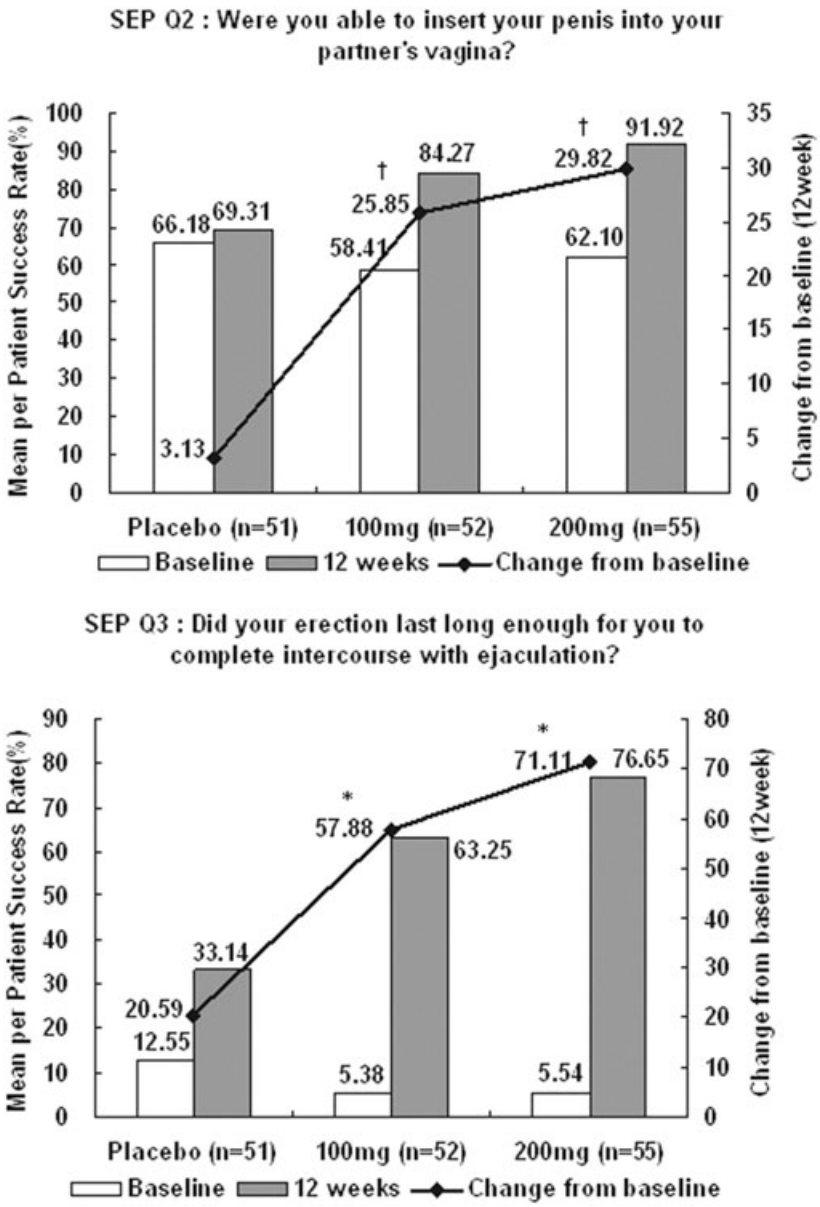

Figure 3 Percentage of successful intercourse attempts: defined as a positive response to SEP questions 2 and 3 (†$P < 0.01$ vs. placebo, *$P < 0.0001$ vs. placebo).

Subjectively, over 70% of the patients approved the beneficial effect of Udenafil on their erectile function. Since previous studies for other PDE5Is have used different primary efficacy parameters or described the post-treatment data only rather than offering data demonstrating the degree of change in IIEF-EFD score, direct comparison is almost impossible or difficult. Only some parameters such as mean changes in success rates of SEP Q2 and SEP Q3 after treatment and the percentages of yes response to GAQ could be compared. Udenafil showed similar or greater changes in the rate of response to SEP Q2 and Q3 compared to other PDE5Is (for SEP Q2 and Q3, Udenafil, 29.8%

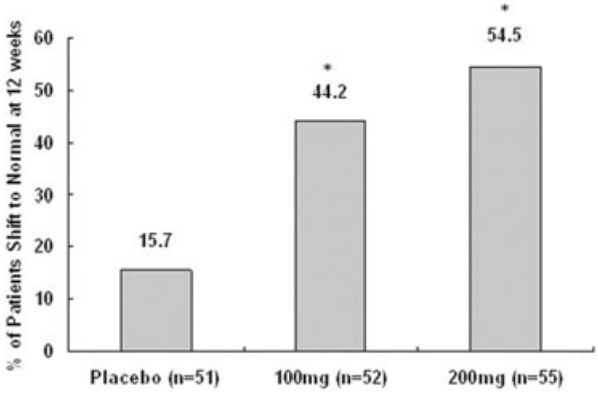

Figure 4 Percentages of achieving normal erectile function (EFD ≥ 26) at 12 weeks (*$P < 0.0001$ vs. placebo).

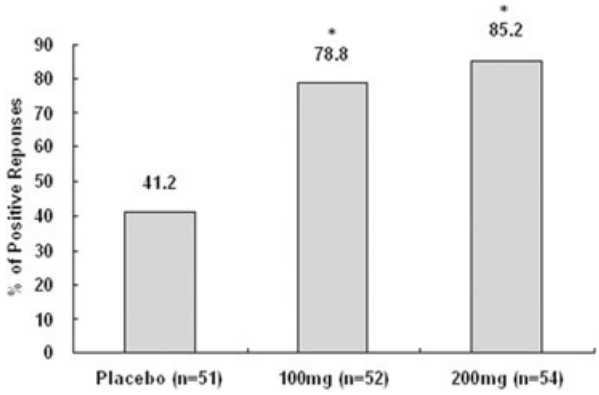

Figure 5 Percentages of positive responses to the global assessment question (GAQ) (*$P < 0.0001$ vs. placebo).

and 71.1%; vardenafil, 33% and 49%; tadalafil, 34% and 45%, respectively). Also Udenafil showed approximately twice higher response to GAQ vs. placebo as other PDE5Is did (Udenafil vs. placebo, 85.2% vs. 41.2; vardenafil vs. placebo, 80% vs. 40%; tadalafil vs. placebo, 87% vs. 33%, respectively) [10,16]. Regarding safety, Udenafil treatment was associated with significant decrease in diastolic blood pressure in both treatment arms. However, patients were neither associated with significant increase in vasodilatory symptoms (headache, flushing) nor the occurrence of significant hypotensive symptoms (dizziness, faintness, vertigo). These efficacy and safety results were similar to previous results from other PDE5Is or the previous trial of Udenafil in broad patient populations [6,17,18]. These results supported the claim that Udenafil could be used in hypertensive men to treat ED.

The subgroup analyses revealed that the greatest improvements in efficacy were observed in the subgroup with severe ED. Also, those who took three or more antihypertensive agents showed the numerically largest change in the IIEF-EFD scores without statistical significance (Udenafil 100 mg, 10.50 ± 5.65; Udenafil 200 mg, 12.56 ± 7.37, respectively) compared to those who were taking one (Udenafil 100 mg, 8.00 ± 7.12; Udenafil 200 mg, 8.21 ± 7.72, respectively) or two antihypertensive agents (Udenafil 100 mg, 8.13 ± 6.75; Udenafil 200 mg, 9.70 ± 5.91, respectively). The efficacy of PDE5I may well be influenced by the severity of ED or the number of antihypertensive agents taken by the patient. One Korean study with sildenafil reported lower efficacy of PDE5Is in those who took more than four antihypertensive drugs [13], while another study with sildenafil have indicated no significant differences in mean responses to drug between patients taking two antihypertensive agents and those taking three or more of these agents [11].

Table 3 Incidence of treatment-emergent adverse drug reactions

		Udenafil	
	Placebo (N = 54)	100 mg (N = 53)	200 mg (N = 57)
Headache		1 (1.9)	5 (8.8)
Flushing	1 (1.9)	3 (5.7)	3 (5.3)
Conjunctival hyperemia		2 (3.8)	3 (5.3)
Dyspepsia		1 (1.9)	3 (5.3)
Chromatopsia			1 (1.8)

No. (%) of subjects.

Although, the number of patients included in the subgroup analysis was not large enough to draw conclusions regarding efficacy, the achievement of comparable IIEF-EFD scores to other groups in patients with severe baseline ED or in patients with three or multiple hypertensive agents highlights the good efficacy of Udenafil in these potential risk groups.

The dose response effects of Udenafil treatments were not observed. The possible explanation for this may be linked to the insufficient power to detect differences between doses, as the estimation of sample number was powered on to detect difference from placebo, not the other tested dose. Future study including larger number of patients will reveal a difference between the doses. Another explanation might be due to the possibility of including only a small number of patients that was exclusively effective in 200 mg Udenafil. As was demonstrated in the previous trial of tadalafil in Japanese patients with severe ED, there is a possibility that the treatment with higher dose of Udenafil may well be more beneficial than the lower doses in some severe ED patients, although this was not the case in our subgroup analysis [19].

One of the interesting observations of our study is the differential effect of Udenafil treatment across the ED severity. The severer the baseline severity, the larger the improvement of IIEF-EFD score (severe, 11.09 ± 6.40; moderate, 7.37 ± 6.58; mild to moderate, 4.84 ± 6.42; mild, 2.88 ± 6.51, respectively, $P = 0.0003$). This needs to be further elucidated, and it is uncertain whether this effect could be found in the treatment of other ED etiologies. Some clinical studies have also indicated that the response to PDE5I may be affected by the baseline ED severity [20,21]. A study with

sildenafil has shown that a low pretreatment EF domain score was the strongest independent prognostic factor for a poor response [21]. However, a study analyzing data from 14 randomized, double-blind, placebo-controlled trials to evaluate the efficacy of tadalafil 20 mg for the treatment of ED in men on thiazides has shown that responses to tadalafil were comparable between thiazide and non-thiazide users regardless of baseline ED severity [16]. Considering that Udenafil belongs to the class of PDE5Is, our results may reflect the sound efficacy of Udenafil in hypertensive ED patients.

The limitation of this study should be also discussed. There is a possibility that different efficacy and safety results might be drawn in other ethnic populations, although previous experience with the three other PDE5Is generated similar results in different ethnic groups.

Conclusions

In hypertensive patients, the treatment of ED with Udenafil has shown effective, safe, and tolerable. The efficacy was maintained irrespective of baseline ED severity, the number of antihypertensive agents, and prior experience with PDE5Is.

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