A Randomised, Double-Blind, Parallel, Placebo-Controlled Study of the Efficacy and Safety of Tadalafil Administered On-Demand to Men with Erectile Dysfunction in Korea

Hyung Ki Choi[1], Je Jong Kim[2], Sae-Chul Kim[3], JunKyu Suh[4], Yoon Kyu Park[5], Seong Choi[6], Woong Hee Lee[7], Ki Hak Moon[8], Hae Young Park[9], Jong Kwan Park[10], Wei Christine Wang[11], Vladimir Kopernicky[12]

From the Department of Urology, [1]Yongdong Severance Hospital, Seoul, [2]Korea University Ansan Hospital, Ansan, [3]Chungang University Hospital, Seoul, [4]Inha University Hospital, Incheon, [5]Kyungpook University Hospital, Daegu, [6]Kosin University Hospital, Busan, [7]Dong Seoul Hospital, Seoul, [8]Yeungnam University Hospital, Daegu, [9]Hanyang University Hospital, Seoul, [10]Chonbuk National University Hospital, Jeonju, Korea, [11]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA, [12]Lilly Area Medical Center, Vienna, Austria

Purpose: Tadalafil is a phosphodiesterase type 5 inhibitor that is used for the treatment of erectile dysfunction (ED). Previous clinical trials have assessed its efficacy and safety in Western populations, but this drug has not been investigated in a large clinical trial involving Korean men with ED. Thus, the aim of this study was to assess the efficacy and safety of 20 mg tadalafil in comparison to placebo when it is taken on demand by Korean men suffering with ED over a study period of 12 weeks.

Materials and Methods: Men more than 18 years of age with mild to severe ED of various etiologies were randomized to receive placebo or tadalafil 20 mg that was taken as needed (maximum once daily). Efficacy assessments included the International Index of Erectile Function (IIEF), the Sexual Encounter Profile (SEP) diary and Global Assessment Questions (GAQ).

Results: Tadalafil significantly improved erectile function, as measured by the erectile function domain of the IIEF, compared to placebo ($p < 0.001$). At the endpoint, the patients receiving tadalafil 20mg reported a greater mean per-patient percentage of successful intercourse attempts (SEP3: 71% compared to 31% for placebo) and a greater proportion of improved erections (GAQ: 80% compared to 44%). The most common treatment emergent adverse events were headache (16.3%), flushing (5%) and eye pain (5%), and most of the adverse events were mild or moderate in severity.

Conclusions: Tadalafil was an effective, well-tolerated therapy for Korean men suffering with ED of broad-spectrum severity and etiology. **(Korean J Urol 2006;47:852-858)**

Key Words: Tadalafil, Erectile dysfunction, Efficacy, Safety, Korea

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[1]영동세브란스병원, [2]고려대학교 안산병원, [3]중앙대학교병원, [4]인하대학교병원, [5]경북대학교병원, [6]고신대학교병원, [7]동서울병원, [8]영남대학교병원, [9]한양대학교병원, [10]전북대학교병원 비뇨기과, [11]Lilly Research Laboratory, Eli Lilly Company, Indiannapolis, Indiana, USA, [12]Lilly Area Medical Center, Vienna, Austria

최형기[1] · 김제종[2] · 김세철[3] · 서준규[4]
박윤규[5] · 최 성[6] · 이웅희[7]
문기학[8] · 박해영[9] · 박종관[10]
Wei Christina Wang[11]
Valdimir Kopernicky[12]

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교신저자: Hyung Ki Choi
Yongdong Severance Hospital, Department of Urology, 146-92, Dogok-dong, Gangnam-gu, Seoul 135-720, Korea
TEL: 82-2-2019-3471
FAX: 82-2-3462-8887
E-mail: ssclinic@yumc.yonsei.ac.kr

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INTRODUCTION

Erectile dysfunction (ED) occurs in approximately 150 million men worldwide.[1] The prevalence and severity of ED increases with age and other medical and psychological conditions including obesity, diabetes mellitus, hypertension, and depression[2,3] ED may lead to anxiety, lower self esteem, and worsen quality of life.[4,5]

Tadalafil is an orally-administered selective inhibitor of

phosphodiesterase type-5 (PDE 5) that enhances erectile function in response to sexual stimulation through the nitric oxide-cyclic guanosine monophosphate (cGMP) pathway.[6,7] Compared with other PDE5 inhibitors, tadalafil has a longer half-life (17.5 hours) and a longer duration of efficacy (up to 36 hours).[8] In several clinical studies, performed mainly in Western populations, tadalafil improved ED of broad spectrum etiology and severity and was well tolerated.[8,9]

Because tadalafil has not been investigated in a large clinical trial in Korean men with ED, we conducted a study in this population. The primary objective of the study was to evaluate the efficacy and safety of 20mg tadalafil compared with placebo when taken on demand in Korean men with ED over 12 weeks. Improvement in erectile function was measured by the erectile function domain of the International Index of Erectile Function (IIEF) and Sexual Encounter Profile (SEP) questions 2 (SEP2) and 3 (SEP3). Efficacy was also assessed with the Global Assessment Questions (GAQ), SEP questions 4, and 5, and additional questions and domains of the IIEF.

MATERIALS AND METHODS

1. Study Design and Patient Population

This study was a multicenter, randomized, double-blind, parallel, placebo-controlled study that evaluated the efficacy and safety of on-demand dosing of orally administered 20mg tadalafil or placebo for 12 weeks to Korean men with erectile dysfunction (ED). The local ethics committees of each medical center reviewed and approved the study protocol. Written informed consent was obtained from each patient prior to randomization.

The study consisted of 2 periods. The first period was a 4-week screening and run-in-period that began once the patient signed an informed consent document. The second period was a 12-week double-blind treatment period of three 4-week visits. The patients were randomly assigned to receive placebo or tadalafil 20mg in a 1:2 ratio according to a computer-generated randomization table. The patients were instructed to take study medication as needed prior to expected sexual activity, but not more than once daily. Food intake and timing thereof were unrestricted.

The patients eligible for inclusion in the study were men at least 18 years of age who were in a monogamous relationship with a female partner and who had at least a 3 month history of ED of psychogenic, organic or mixed etiologies. Erectile dysfunction was defined as an inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance.[4] For purposes of this study, ED severity was classified based on baseline IIEF Erectile Function Domain score into mild ($\geq$ 17), moderate (11-16) and severe (0-10). Severity groups defined by Cappelleri et al[11] as mild to moderate, mild and no ED were combined in this study to form the mild ED severity group.

The etiology of ED was determined by the study investigator based on the patient history, physical and laboratory examination findings, and any previous diagnostic testing.

Exclusions to study participation included history of radical prostatectomy (with the exception of bilateral nerve-sparing prostatectomy) or other pelvic surgery with subsequent failure to achieve erection; clinically significant renal insufficiency within the last 6 months; clinically significant hepatobiliary disease; angina occurring during sexual intercourse in the last 6 months; unstable angina within 6 months prior to the first visit; history of myocardial infarction or coronary artery bypass graft surgery or percutaneous coronary intervention (e.g. angioplasty or stent placement) within 90 days prior to the first visit; history of HIV infection or current infection with any sexually transmitted disease; or current treatment with nitrates, cancer chemotherapy, or antiandrogens.

2. Assessment of Efficacy

The efficacy of tadalafil was assessed using the self-administered IIEF questionnaire that assesses five domains of male sexual function, including erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction,[10] SEP diary and Global Assessment Questions (GAQ). The patients completed the IIEF at the conclusion of the run-in period (baseline) and after 4, 8, 12 weeks of double-blind therapy. They completed the SEP diary after each sexual encounter and reviewed the diary with the physician at each visit. The patients completed the GAQ at the final visit (study end or early discontinuation).

The primary efficacy endpoints were changes from baseline to endpoint in the IIEF EF domain and changes from baseline to postbaseline on SEP2 and SEP3. The IIEF erectile function domain is the sum of Questions 1-5 and 15, with a maximum score of 30. The mean per patient percentage of 'yes' responses were determined for SEP2 (Were you able to insert your penis

into your partner's vagina?) and SEP3 (Did your erection last long enough for you to have successful intercourse?). The baseline and endpoint score for each SEP question was the patient's percentages of 'yes' responses to that question during the run-in period and post baseline period, respectively.

The secondary efficacy endpoints included the change from baseline in intercourse satisfaction domain score of the IIEF; overall satisfaction domain score of the IIEF; Questions 3 and 4 of the IIEF; SEP4 and SEP5 of the patient SEP diary; and the percentage of 'yes' responses to two Global Assessment Questions [GAQ 1 ("Has the treatment you have been taking during this study improved your erections?"), and GAQ 2 ("If yes, has the treatment improved your ability to engage in sexual activity?") asked of the patients at the end of the treatment period or at the discontinuation visit. The IIEF Intercourse Satisfaction was defined as the sum of Questions 6, 7, and 8 (possible total score 0 through 15), IIEF Overall Satisfaction was defined as the sum of Questions 13 and 14 (possible total score 2 through 10) and for Question 3 [penetration ability: "Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?"] and Question 4 [erection maintenance: "Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?"] of the IIEF questionnaire scores were graded on scale of 1 to 5.

3. Assessment of Safety

A complete medical history and a 12- lead ECG of the patients was performed at the first visit. A physical examination was conducted at both the first and the final visits. During the study, adverse events were collected at each visit. In addition, concomitant medication use was recorded and blood pressure and heart rate were measured at each visit. The clinical laboratory tests were performed at the screening visit and the end of the treatment.

4. Statistical Analysis

Patient baseline characteristics were summarized for each treatment group using descriptive statistics. All efficacy analysis was performed on an intent-to-treat basis and included all patients with baseline and post baseline observations. Last observation carried forward (LOCF) was used to impute missing IIEF EF Domain data. The baseline and endpoint score for each SEP question was the patient's percentages of 'yes' responses to the question during the run-in period and the treatment period respectively. The percentage of 'yes' responses to each SEP question was treated as a continuous variable.

Analysis of covariance (ANCOVA) models for the change from baseline in the IIEF domains and the SEP variables included terms for the baseline value of the efficacy variable, treatment group, pooled investigator site, and baseline-by-treatment group interaction (if significant at $p < 0.10$). Logistic regression models were used to evaluate the GAQ at endpoint and to evaluate the percentage of patients who attained normal erectile function at the endpoint. The logistic regression models included the same covariate terms as in the ANCOVA models, but the baseline IIEF erectile function domain score was used as the baseline efficacy value.

Safety analyses included all randomized patients. Safety was assessed by evaluating all reported adverse events and the change in vital signs, clinical laboratory values and physical examination findings. Adverse events entered by the investigators were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 5) preferred terms. The investigator recorded the severity of the adverse events and their relationship to the study drug. Change in continuous laboratory analytes and vital signs were evaluated by a ranked ANOVA model with a term for treatment group. The statistical analyses were conducted using Statistical Analysis Software version 8.1 (SAS®, SAS Institute Inc., Cary, USA).

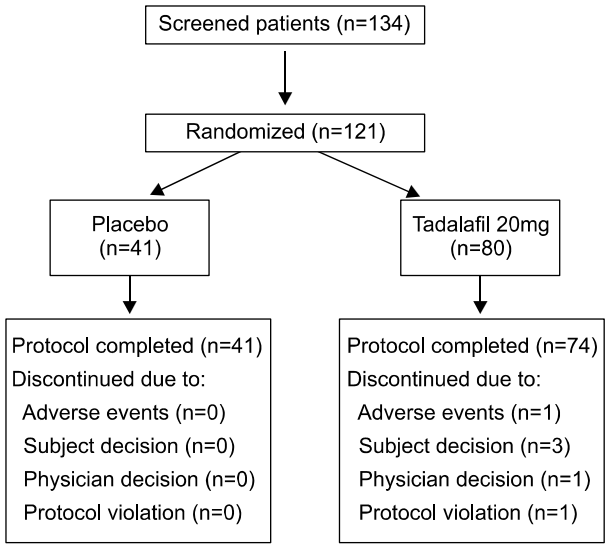

Fig. 1. Patient disposition.

RESULTS

Of the 134 patients screened for the study, 121 were randomly assigned to a treatment group (placebo, n=41 and tadalafil 20mg, n=80). Of these 121, 115 (95.0%) completed the study (Fig. 1).

Baseline characteristics were largely balanced across the treatment groups (Table 1). A difference in distribution of patients diagnosed with Diabetes Mellitus was noted with 12.2% enrolled in the placebo group and 20.0% in the tadalafil group. Approximately 91% of the patients had ED for at least a year; the most common etiology was organic. Common comorbid conditions were prostatic disorder (predominantly benign prostatic hyperplasia), hypertension, diabetes mellitus and hyperlipidemia. The IIEF Erectile Function domain score determined the patient's ED severity at baseline; 41% had mild ED, 41% had moderate ED, 18% had severe ED.

Table 1. Patients' demographics and baseline characteristics

Variable	Placebo (n=41)	Tadalafil 20mg (n=80)
Mean age, years (range)	51.7 (33.5-74.4)	51.0 (24.7-71.9)
Mean weight (kg)	70.6	70.8
Mean height (cm)	168.5	169.9
Duration of ED≥12 months, n (%)	39 (95.1)	71 (88.8)
ED etiology, n (%)		
Psychogenic	10 (24.4)	15 (18.8)
Organic	27 (65.9)	56 (70.0)
Mixed	4 (9.8)	9 (11.3)
IIEF erectile function severity n (%)		
Mild (≥17)*	17 (41.5)	33 (41.3)
Moderate (11-16)	16 (39.0)	33 (41.3)
Severe (1-10)	8 (19.5)	14 (17.5)
Medical history, n (%)		
Benign prostatic hyperplasia	9 (22.0)	16 (20.0)
Diabetes mellitus	5 (12.2)	16 (20.0)
Hypertension	5 (12.2)	12 (15.0)
Hyperlipidemia	4 (9.8)	5 (6.3)

*Patients were included based on a history of ED (defined as a consistent change in the quality of erection that adversely affects the patient's satisfaction); the diagnosis of ED was not based on IIEF scores. Subsequent assessment of erectile function by the IIEF at baseline revealed that 1 patient from each treatment arm (1.7% of all the patients) had a baseline EF domain score ≥26. ED: erectile dysfunction, n: number of patients, IIEF: International Index of Erectile Function. The cause of erectile dysfunction was determined by the investigators based on the patient history, the physical examination findings and any previous diagnostic testing.

During the on-demand treatment period, patients randomized to 20mg tadalafil took an average of 3.3 doses per week and patients on placebo took an average of 3.1 doses per week.

1. Primary Efficacy Measures

Tadalafil 20mg was superior to placebo on all primary efficacy measures (Table 2). The mean change from baseline in the IIEF EF domain score for the tadalafil group was 7.8 vs. 0.1 for the placebo group ($p<0.001$).

Similarly, improvement from 17.7% at baseline to 71.2% at endpoint in the mean per-patient success rate for intercourse attempts (SEP3) for the tadalafil group, were significantly greater than the 10.1% mean change, for the placebo group ($p<0.001$).

Patients of all ED severities (mild, moderate or severe at baseline) demonstrated significantly greater mean changes (baseline to endpoint) in the IIEF EF domain score in the tadalafil 20mg group compared with placebo (Fig. 2). Additionally, 44.2% of patients treated with tadalafil 20mg had IIEF EF Domain score ≥26 ("return to normal") compared to 5.0% treated with placebo ($p<0.001$).

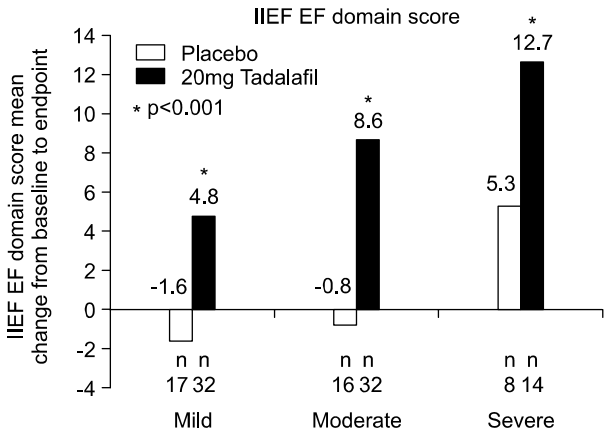

Fig. 2. Change from baseline in the IIEF EF domain score by the ED severity. The population summarized consists of those patients having both baseline and endpoint scores on the IIEF Erectile Function domain. n: number of patients with mild, moderate and severe ED based on the IIEF Erectile Function Domain scores measured at the end of the 4-week baseline period. IIEF: International Index of Erectile Function, EF: erectile function

Table 2. Summary of primary and secondary efficacy variables

Efficacy variables	Placebo (n=41)			Tadalafil 20mg (n=80)			
	Baseline	Endpoint	Change	Baseline	Endpoint	Change	p-value
Primary							
IIEF erectile function domain (mean)	15.3	15.4	0.1	15.4	23.2	7.8	<0.001
Mean per-patient percent "yes" response to SEP questions (%)							
SEP2. successful penetration	67.2	67.7	0.5	68.3	85.4	17.1	<0.001
SEP3. successful intercourse	21.4	31.4	10.1	17.7	71.2	53.6	<0.001
Secondary							
IIEF Questions (mean)							
IIEF Q3. Penetration ability	3.1	2.9	-0.2	3.1	4.1	0.9	<0.001
IIEF Q4. Maintenance ability	2.0	2.2	0.2	2.1	3.8	1.6	<0.001
IIEF domains (mean)							
IIEF intercourse satisfaction	7.0	8.4	1.5	6.9	11.2	4.4	<0.001
IIEF overall satisfaction	4.1	4.9	0.7	4.4	7.1	2.6	<0.001
Mean per-patient percent "yes" response to SEP questions (%)							
SEP4. satisfaction with hardness	11.0	24.8	13.8	11.0	66.0	55.0	<0.001
SEP5. overall satisfaction	10.2	20.9	10.7	6.9	64.3	57.3	<0.001
Global Assessment Questions (%)							
GAQ 1		43.9			80.0		<0.001
GAQ 2		43.9			80.0		<0.001

IIEF: International Index of Erectile Function, SEP: Sexual Encounter Profile, GAQ: Global Assessment Question, n: number of patients randomized per treatment group. p-values are for comparison of the mean change from the baseline to the endpoint, and tadalafil versus placebo.

2. Secondary Efficacy Measures

The secondary endpoint efficacy variables are also summarized in Table 2. Tadalafil therapy significantly improved erectile function and patient satisfaction compared with placebo in all secondary efficacy variables ($p<0.001$). In addition, a significantly greater proportion of patients treated with tadalafil (80%) reported improved erections at endpoint than those treated with placebo (44%; GAQ, $p<0.001$).

3. Safety

Tadalafil was generally well-tolerated. No deaths or serious adverse events were reported. Headache (tadalafil 16.3%, placebo 4.9 %, p=0.086), flushing (tadalafil 5%, placebo 4.9%, p=1.00) and eye pain (tadalafil 5%, placebo 0 %, p=0.298) were the 3 most commonly reported adverse events in the tadalafil group (Table 3). Four patients reported Eye Pain, 3 of them mild and transient and 1 as moderate. One patient in the

Table 3. Summary of treatment-emergency adverse events that occurred in ≥2% of patients in any treatment group

Adverse events*	Placebo (n=41)		Tadalafil 20mg (n=80)	
	n	%	n	%
Headache	2	4.9	13	16.3
Flushing	2	4.9	4	5.0
Eye pain	0	0	4	5.0
Arthralgia	1	2.4	3	3.8
Palpitations	1	2.4	3	3.8
Myalgia	0	0	3	3.8
Pharyngitis	2	4.9	2	2.5
Nasopharyngitis	1	2.4	2	2.5
Gastritis	1	2.4	2	2.5
Somnolence	1	2.4	2	2.5

*Events are ordered by the overall decreasing frequency. n: number of patients, %: percent of patients reporting treatment emergency adverse events by the MedDRA preferred term.

tadalafil treatment group reported a severe adverse event (intervertebral disc herniation) which was not considered to be related to study drug. One patient in the tadalafil group discontinued from the study because of an adverse event (headache). There were no statistically significant differences between treatment groups in the mean change from baseline to endpoint in any laboratory parameter. No clinically relevant changes occurred in vital signs.

DISCUSSION

Among this sample of Korean men with ED, tadalafil 20mg was superior to placebo on all primary and secondary efficacy measures. The efficacy measures used to assess erectile function: the IIEF, the SEP diary and the GAQ have been widely used in clinical studies to assess ED therapy. The IIEF has been shown to be valid cross-culturally[10] and its adaptation to Asian languages has not been associated with problems of comprehension.[11,12]

The endpoint and change from baseline scores for placebo and tadalafil 20mg on the IIEF and SEP were comparable to those reported previously,[9,13,14] although a smaller change could have been expected with the predominantly mild to moderate ED patient sample enrolled in our study. For example, men randomized to 20mg tadalafil had an increase of 7.8 points in the IIEF erectile function domain in the present study compared with 7.9[13], 8.0[14] and 8.6 points[9] in other studies. An analysis of efficacy by baseline IIEF EF Domain score showed the efficacy of tadalafil regardless of ED severity in Korean men. While a difference in proportion of patients with Diabetes Mellitus was observed between the treatment groups, this has not affected the balance in distribution of ED severities across treatments.

The results of the secondary efficacy measures also demonstrated significant increases in patient satisfaction with erections and with sexual experience overall in patients receiving tadalafil compared with placebo. Thus, significant improvements in the IIEF intercourse and overall satisfaction domain scores, in SEP questions 4 and 5 (satisfaction with erection hardness and overall satisfaction) and in erections (GAQ response rates) at the end of the study was observed in men taking tadalafil compared with placebo. Similar results were obtained in other studies, including studies of PDE5 inhibitors enrolling Asian men.[15,16] This suggests that tadalafil has similar efficacy in treating Korean men with various ED etiologies (organic, psychogenic or mixed) and comorbid conditions, as in treating Taiwanese[14] or Western populations.[9,13]

Safety results from our study demonstrated that tadalafil 20mg was well tolerated in Korean men, confirming the tolerability results from previous studies of tadalafil[9,13,14] Of note, while in studies with sildenafil citrate the most common adverse event reported by Korean men was flushing followed by headache.[17,18] in this study the incidence of facial flushing on tadalafil was relatively low and similar to placebo.

CONCLUSIONS

Tadalafil therapy, when taken as needed by Korean men with a broad-spectrum of erectile dysfunction, significantly improved their erectile function, satisfaction with erection hardness or intercourse satisfaction. It allowed almost half of patients to achieve IIEF EF Domain scores within the normal range ($\geq$ 26). Tadalafil was well tolerated in this clinical trial population of men with ED from Korea.

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