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Efficacy of Tadalafil Add-on Treatment for Men with Lower Urinary Tract Symptoms Refractory to Alpha-1 Adrenoceptor Blockers

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SUMMARY

Introduction : To evaluate the efficacy and safety of once daily phosphodiesterase type 5 inhibitor (PDE5i) tadalafil as an add-on treatment for men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS) refractory to an alpha 1-blocker (α1-blocker).

Materials and Methods : This study enrolled men aged >50 years with BPH/LUTS and erectile dysfunction (ED) that were refractory to >3 months of α1-blocker. We defined "refractory" as an international prostate symptoms score (IPSS) of >8 and a maximum flow rate (Qmax) <15 despite in no space take of an α1-blocker. Patients with contraindications to phosphodiesterase-5 inhibitors ; those with symptoms of other diseases that were difficult to differentiate from BPH/LUTS ; and those with postvoid residual of >100 ml were excluded. Eligible patients received added-on treatment with tadalafil 5 mg/day for 12 weeks.

Results : Tadalafil add-on treatment significantly improved the IPSS parameters in terms of total score ($P<0.001$), subscore for storage ($P=0.001$), subscore for voiding ($P<0.001$), and quality of life ($P=0.002$). The 3-day frequency volume chart showed significant improvements in mean number of daily nocturnal micturations ($P=0.002$), nocturnal polyuria index ($P=0.001$), and hours of undisturbed sleep ($P=0.006$). Five patients dropped out because of an adverse event : two with a headache, two with dizziness and one with dyspepsia. There were no serious adverse events.

Conclusion : Tadalafil add-on treatment was effective for patients with BPH/LUTS and ED that were resistant to α1-blockers.

Keywords : tadalafil, benign prostatic hyperplasia, lower urinary tract symptoms, refractory to alpha-1 adrenoceptor blockers

INTRODUCTION

An alpha 1-adrenoceptor blocker (α1 blocker) has been widely used for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH/LUTS)[1]. As improvement of symptoms occurs relatively early after administration, α1-blockers are considered to be extremely beneficial. However, some patients respond poorly to these drugs need additional medications. In recent years, a combination of an α1-blocker and a 5-alpha reductase inhibitor has been shown to relieve BPH/LUTS better than monotherapy with each compound, especially in patients with a large prostate[2]. Furthermore, some trials have demonstrated the efficacy and safety of a combination of an α1-blocker and an anticholinergic

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agent for BPH/LUTS patients with significant symptoms of urinary retention and overactive bladder (OAB)[3,4].

There had been basic scientific evidence that BPH/LUTS and erectile dysfunction (ED) share the same pathophysiology[5~7]. Oger et al. demonstrated *in vitro* that a combination of an α1-blocker and a phosphodiesterase-5 inhibitor (PDE5i) was more efficient than each compound alone in relaxing the adrenergic tone or enhancing the nitrergic relaxation of the human corpus cavernosum[8]. However, existing clinical trials of a combination of an α1-blocker and a PDE5i reported a variety of outcomes with inconsistent findings[9~10]. Furthermore, other data suggested that a combination of an α1-blocker and a PDE5i might worsen hemodynamic changes[10].

To clarify the efficacy and safety of a combination of an α1-blocker and a PDE5i, we performed a single-center prospective study of once daily PDE5i tadalafil add-on treatment in patients with BPH/LUTS and ED that were resistant to α1-blockers.

MATERIALS AND METHODS

This open label study was designed as a prospective investigation. The study protocol was approved by the Ethics Committee of Dokkyo Medical University Koshigaya Hospital (#1406), and was conducted in compliance with the Helsinki Declaration. We obtained written informed consent from all participants after thoroughly explaining the efficacy and possible adverse reactions of a combination of an α1-blocker and tadalafil.

The inclusion criteria were men aged >50 years ; a total International Prostate Symptom Score (IPSS) of ≥8 points despite treatment with α1-blockers for at least 3 months ; bladder outlet obstruction as indicated by a maximum urinary flow rate (Qmax) of ≤15 ml/s ; and self-reported ED as indicated by an International Index of Erectile Function of Erectile Function Domain (IIEF5) of ≤11 points. Exclusion criteria were history of specified contraindications to PDE5i ; prostate-specific antigen (PSA) >10 ng/ml or >4 ng/ml if prostate cancer could not be ruled out ; post void residual urine volume (PVR) of >100 ml ; and the presence of other diseases that caused symptoms that were difficult to differentiate from those of BPH/LUTS.

Patients had been receiving an α1-blocker (either tamsulosin 0.2 mg/day or naftopidil 50 mg/day) until the day of study enrollment (day 0). After enrollment, once daily tadalafil 5 mg was prescribed in addition to an α1-blocker for 12 weeks. During the study period, patients were asked to refrain from using other medications that influenced urinary frequency and incontinence, as well as drugs that produce nitric oxide.

The efficacy of treatment was assessed using the data collected from a questionnaire and 3-day frequency volume chart (FVC) before and after the treatment period. IPSS and IIEF5 were determined by a physician (HY) who was blinded on the clinical background of the patients. Other efficiency variables included Qmax, PVR and serum testosterone. As a marker of oxidative stress, urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels were evaluated using an ICR-001 device (Techno Medica, Yokohama, Japan) according to the manufacturer's recommendations.

The primary end-point was change in the mean IPSS scores. The secondary end-points were changes in the mean values of the following parameters : (1) Qmax and PVR, (2) number of micturations per night and hours of undisturbed sleep (HUS), (3) IIEF5 score and serum testosterone, and (4) urinary 8-OHdG level. The patient's QOL was assessed on the basis of the IPSS-QOL. HUS was designated as the time between falling asleep and first waking to void.

Safety of treatment was assessed in terms of the number and severity of adverse events, results of laboratory tests, and values of vital parameters. Adverse events were investigated throughout the treatment period. Laboratory tests and measurement of vital signs were conducted before and the end of the 12-week period (or at discontinuation). Further, complete blood count was obtained, and blood chemistry tests were performed for the following parameters : serum levels of albumin, lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, total bilirubin, creatinine, urea nitrogen, sodium, potassium, and chlorine. Urinalysis was performed at every visit.

Data were reported as mean ± SD and were analyzed using SPSS software version 12.0 (IBM, Chicago,

IL USA). Wilcoxon signed-rank test was used to evaluate the effects of treatment. $P<0.05$ was considered significant.

RESULTS

Baseline patient profile

The total number of patients enrolled in the study was 30. Of these, 25 patients (83.3%) completed the study and 5 patients (16.7%) dropped out because of adverse events. The baseline clinical characteristics of the patients are shown in Table 1.

Efficacy

After the 12-week treatment periods, there were significant improvements in lower urinary tract symptoms, as indicated by change in the mean IPSS scores in terms of total score ($P<0.001$), storage subscore ($P=0.001$), voiding subscore ($P<0.001$), and QOL ($P=0.002$) ; the mean Qmax and PVR did not significantly change (Table 2). The FVC showed significant improvements in HUS ($P=0.006$), nocturnal polyuria index (NPI, $P=0.001$), and mean number of micturations per night ($P=0.012$), not in the mean number of micturitions per day.

There were no significant improvements in sexual function, as indicated by the change in the mean IIEF5 score and serum testosterone level. Likewise, oxidative stress, which was assessed by the urine 8-OHdG levels, showed no improvement.

Safety

Among the 30 patients exposed to the study drug, 5 (16.7%) dropped out because of adverse events : 2 had a headache, 2 had dizziness and 1 had dyspepsia. There was no serious adverse event reported during the study and there was no evidence of hypotension or syncope during the treatment period. The results of blood biochemistry and urinalysis remained unchanged after 12 weeks (data not shown).

DISCUSSION

This study showed significant improvement in the mean number of nocturia per night in FVC. The aim of our study was to evaluate whether tadalafil add-on treatment was effective for patients with BPH/LUTS and ED that showed resistance to α1-blockers.

Table 1 Baseline clinical characteristics of patients with BPH/LUTS and ED (N=30)

Age (years)	Mean (SD)	71.3±8.5
	Range	58-80
Weight (kg)	Mean (SD)	57.3±10.2
	Range	49.2-88.3
Alpha-1 blockers, n (%)	Tamsulosin	19 (63.3)
	Naftopidil	11 (26.7)
IPSS	Total score	15.6±5.7
	Storage subscore	6.9±3.2
	Voiding subscore	8.7±4.3
	QOL	4.3±1.3
IIEF5		5.5±6.5
UFM	PVR (ml)	27±18
	Qmax (ml/s)	9.0±5.8
	Voided volume (ml)	154±101
Serum Testosterone (ng/ml)		5.5±2.1
Urinary 8-OHdG (ng/ml CRE)		23.5±12.9

BPH/LUTS, lower urinary tract symptoms suggestive of benign prostatic hyperplasia ;
CRE, creatinine ;
ED, erectile dysfunction ;
IPSS, International Prostate Symptom Score ;
IIEF5, International Index of Erectile Function of Erectile Function Domain ;
UFM, uroflowmetry ;
PVR, post-void residual urine ;
Qmax, maximum urinary flow rate ;
QOL, quality of life ;
SD, standard deviation ;
8-OHdG, 8-hydroxy-2′-deoxyguanosine

Tadalafil, a selective cyclic guanosine monophosphate PDE5i, was approved by the US Food and Drug Administration for ED in 2003 for on demand use at 10-20 mg and, in 2008 for once daily use at 2.5 to 5.0 mg ; in 2011, it was approved for once daily use at 5 mg for BPH/LUTS[11]. Improvement in BPH/LUTS was evident from in 4 pivotal randomized, double-blind, placebo controlled studies that reported a significantly greater mean change in total IPSS from baseline to week 12[10,12~14].

The rationale for using a combination of an α1-blocker and a PDE5i was based on the following findings. First, it is well established that BPH/LUTS and ED are highly prevalent in aging men and are strongly linked independent of age and cardiovascular comorbidities ; this link has biologic plausibility[15,16]. Also, a combination of an α1-blocker and a PDE5i

Table 2 Change in parameters after add-on treatment with tadalafil

		Baseline	12 Weeks	P-value
IPSS	Total score	15.6±5.7	9.3±4.7	<0.001
	Storage subscore	6.9±3.2	4.5±2.9	0.001
	Voiding subscore	8.7±4.3	4.8±2.7	<0.001
	QOL	4.3±1.3	7.1±6.5	0.002
IIEF5		5.5±6.5	7.1±6.5	0.191
UFM	voided volume (ml)	154±101	191±93	0.257
	PVR (ml)	27±18	39±35	0.180
	Qmax (ml/s)	9.0±5.8	10.4±7.3	0.330
FVC				
	Number of micturitions per day	11.1±4.0	9.9±3.1	0.154
	Number of nocturia per night	2.9±1.5	2.1±1.2	0.024
	NPI	0.39±0.14	0.29±0.12	0.002
	HUS (hours)	2.5±1.1	3.4±1.7	0.026
Serum testosterone (ng/ml)		5.5±2.1	5.8±2.3	0.130
Urinary 8-OHdG (ng/ml CRE)		23.5±12.9	23.2±12.7	0.129

IPSS, International Prostate Symptom Score ;
IIEF5, International Index of Erectile Function of Erectile Function Domain ;
UFM, uroflowmetry ;
PVR, post-void residual urine ;
Qmax, maximum urinary flow rate ;
FVC, frequency volume chart ;
NPI, nocturnal polyuria index ;
(ratio of nocturnal urine volume to 24 hour urine volume) ;
HUS, hours of undisturbed sleep ;
(time between falling asleep and first waking to void) ;
8-OHdG, 8-hydroxy-2′-deoxyguanosine

acts on common urogenital target organs by two different mechanisms of action. Blockage of α-adrenergic receptors and reduction of penile smooth muscle and prostate/bladder neck sympathetic tone could enhance the nitric oxide-mediated relaxant influence of PDE5i on the same smooth muscle targets[17]. A potentiating action of these two drugs is supported by preclinical and clinical findings. Indeed, in spontaneously hypertensive rats, α1-blocker alfuzosin showed no pro-erectile effect in itself, but enhanced the number and amplitude of erections induced by PDE5i apomorphine[18]. In a randomized study of ED patients who failed to respond to PDE5i, addition of an α1-blocker was associated with a significant improvement in IIEF5 in a majority (78.4%), compared with those who received a placebo[19]. Similarly, in a retrospective analysis of men with ED and who were considered non-responders to PDE5i, addition of an α1-blocker was shown to improve ED in 71% of patients[20]. However, efficacy of PDE5i tadalafil as an add-on treatment for men with BPH/LUTS refractory to an α1-blocker has been not reported to date.

Frequent nighttime voiding episodes have been associated with increased risk of falls, fractures, sleep deprivation, and chronic fatigue, especially in older patients[21]. Nocturia is common in patients with heart, lung, kidney, bladder, or prostate problems, as well as in many other diseases, both urologic and non-urologic in origin. Polydipsia, use of diuretics in the evening, and fluid overload before sleeping are other reasons for nocturia[22]. Though nocturia is frequently reported by patients with BPH/LUTS, treatment with α1-blockers generally has low efficacy[21]. On the other hand, a statistically significant improvement in nocturnal frequency was seen with tadalafil over placebo ; however, the treatment difference was small and not considered clinically meaningful[23]. Limitations of our study to assess nocturia were not to exclude

certain co-morbidities such as nocturnal polyuria. Whether tadalafil might show a greater effect on nighttime voiding frequency in studies specifically designed to assess nocturia remains unknown. If the impact of tadalafil on nocturia is to be assessed specifically in future studies, they should incorporate detailed patient history and frequency-volume charts.

HUS is considered as an important indicator of sleep quality and is a useful parameter for evaluating sleep disorders due to nocturia[24]. Sleep has two main phases : rapid eye movement (REM) sleep and non-REM sleep[24]. Non-REM sleep normally comprises deep and shallow sleep phase and deep one is important for growth hormone secretion and functional restoration[25]. Slow-wave sleep is a deep and restorative non-REM sleep that occurs within approximately 3 to 4 hours of falling asleep, after which REM sleep and other shallow sleep stages become more prominent[25,26]. Interruption of this restorative non-REM sleep can significantly impair sleep quality, causing general fatigue and discomfort. Djavan et al. reported that prolonging early undisturbed sleep may be effective for improving sleep quality[27]. The results of the present study showed that HUS was prolonged by an average of 54 minutes, which meant that early sleep was also significantly prolonged. Prolongation of early sleep is thought to have a positive influence on sleep quality and may have contributed to the improvement of IPSS-QOL.

Oxidative stress was reported to result in pathophysiologic conditions of the urinary bladder due to damage to the urothelium and the sensitizing bladder afferent signals[28]. Previous studies have shown that oxidative stress mediated capsaicin-sensitive C-fibers to induce bladder hyperactivity[29]. Several investigators have shown that PDE5i enhanced the antioxidant system and scavenged free radicals[30]. Therefore, we hypothesized that PDE5i might ameliorate the pathophysiologic conditions in the urinary bladder because of its anti-oxidant activity and could be a supplementary therapy for patients with BPH/LUTS and ED that are unresponsive to α1-blockers. However, in the present study, no significant improvement was observed in the urine 8-OHdG level.

The major drawbacks of this study are the small number of patients, the lack of a placebo controlled group, and the absence of urodynamic data. In LUTS conditions that have a strong placebo component, the possibility of a placebo effect might be high. Therefore, the value of once daily add-on tadalafil as a potential therapeutic alternative in patients with α1-blocker resistant BPH/LUTS and ED needs to be evaluated prospectively in the future.

CONCLUSIONS

Once daily add-on administration of tadalafil in patients with BPH/LUTS and ED that are resistant to α1-blocker alleviated lower urinary tract symptoms and prolonged HUS, which is an indicator of sleep quality. Therefore, we recommend the use of tadalafil in patients with BPH/LUTS and ED that are resistant to α1-blockers and associated sleep disturbances.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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