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Efficacy of Combination Treatment with Tadalafil and Mirabegron in Patients with Benign Prostatic Hyperplasia Who Presented with Persistent Storage Symptoms After Tadalafil Monotreatment: A Prospective, Multicenter, Open-Labeled Study

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ABSTRACT

Background The aim of this study is to evaluate the efficacy and safety of tadalafil, a phosphodiesterase type 5 inhibitor, plus mirabegron, a β_3-adrenoreceptor agonist, in patients with benign prostatic hyperplasia who presented with persistent storage symptoms after tadalafil monotreatment.

Methods The registration of this study started in August 2016 and ended in July 2019. The inclusion criteria included patients aged ≥ 50 years who were diagnosed with benign prostatic hyperplasia and who presented with overactive bladder symptoms. Patients were treated with oral tadalafil 5 mg once daily for 4 weeks. Then, its efficacy was evaluated. Patients who responded to the treatment received oral tadalafil 5 mg once daily for 4 more weeks (monotreatment group). Meanwhile, those who did not respond received oral tadalafil 5 mg and mirabegron 50 mg, which is an add-on treatment, once daily for 4 more weeks (combination therapy group).

Results After 8 weeks, the monotreatment group (n = 19) and the combination group (n = 56) had significantly better total Overactive Bladder Symptom Score and International Prostate Symptom Score and International Prostate Symptom Score voiding and storage subscale scores. Moreover, the two groups experienced significant improvements in the total Overactive Bladder Questionnaire and Nocturia Quality of Life Questionnaire scores, and Nocturia Quality of Life Questionnaire Bother/Concern subscale score after 8 weeks. However, there were no cases of urinary retention or serious adverse events.

Conclusion Combination treatment with tadalafil and mirabegron is effective and safe for patients with benign prostatic hyperplasia who presented with persistent storage symptoms after tadalafil monotreatment. Hence, tadalafil plus mirabegron is a promising therapeutic option, and it can improve overactive bladder related-quality of life.

Key words benign prostatic hyperplasia; combination treatment; phosphodiesterase type 5 inhibitor; storage symptoms; β3-adrenoreceptor agonist

Lower urinary tract symptoms (LUTS) are commonly correlated with benign prostatic hyperplasia (BPH) and overactive bladder (OAB), and their prevalence increases with advancing age.[1] A recent worldwide prevalence estimation model showed that by 2018, approximately 2.3 billion individuals will be affected by at least 1 LUTS, 546 million by OAB, and 1.1 billion by LUTS secondary to BPH (LUTS/BPH).[2] Moreover, Asia, followed by Europe, Africa, North America, and South America, had the highest regional burden caused by these conditions.[2] LUTS significantly affects the quality of life (QOL) of patients with BPH.[3] Among the LUTS, OAB, which is defined as urinary urgency with urinary frequency, nocturia, and sometimes urgency incontinence, is the most troublesome symptom experienced by patients daily.[4]

Phosphodiesterase type 5 inhibitors (PDE5-Is) are used as the first-line treatment for BPH. The use of tadalafil, which is a PDE5-I, for the treatment of LUTS/BPH has been approved in several countries, and previous randomized studies have shown that its efficacy is similar to that of α_1-blocker.[5, 6] However, in some men with BPH, PDE5-I treatment is not effective against LUTS. Therefore, other treatment strategies must be considered. These include combination or add-on treatment with other agents, such as anticholinergics and β_3-adrenoreceptor agonists. Several reports revealed that concomitant anticholinergics were effective in patients with BPH who presented with storage symptoms unresponsive to α_1-blocker monotherapy.[7, 8] By contrast, in patients with BPH, treatment with anticholinergics is

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Abbreviations: AE, Adverse Event; BMI, Body Mass Index; BPH, Benign Prostatic Hyperplasia; IPSS, International Prostate Symptom Score; LUTS, Lower Urinary Tract Symptoms; N-QOL, Nocturia-Quality of Life Questionnaire; OAB, Overactive Bladder; OAB-q, Overactive Bladder-Questionnaire; OABSS, Overactive Bladder Symptom Score; PDE5-I, Phosphodiesterase type 5 Inhibitor; PSA, Prostate-Specific Antigen; PVR, Post-Void Residual; QOL, Quality Of Life; RCT, Randomized Clinical Trial

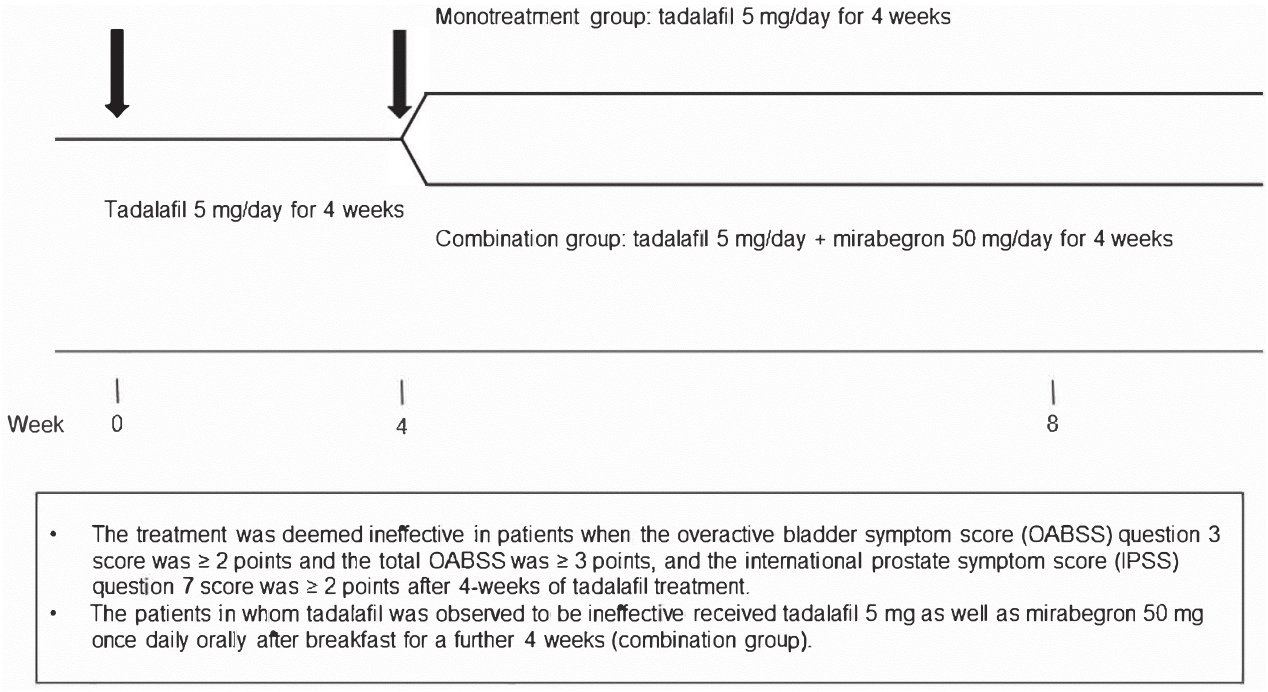

Fig. 1. Study design.

associated with an increased risk of developing urinary retention,[7, 8] with an incidence of 6.8 per 1000 person-years in men. Urinary retention is painful, and it significantly reduces QOL.[9]

Recent studies about OAB have identified three β-adrenoreceptor subtypes (β_1, β_2, and β_3) in the detrusor muscle and urothelium.[10] The β_3-adrenoreceptor is the predominant subtype in the human urinary bladder.[11] β_3-adrenoreceptor agonists facilitate the relaxation of the detrusor smooth muscle during the bladder storage phase and increase bladder capacity without negatively affecting voiding parameters, including maximum urinary flow rate, detrusor pressure at maximum urinary flow rate, and post-void residual (PVR) volume.[12] Moreover, combination treatment with PDE5-Is and β_3-adrenoreceptor agonists for BPH has not been comprehensively evaluated. Therefore, the current study aimed to examine the safety and efficacy of tadalafil, a PDE5-I, plus mirabegron, a β_3-adrenoreceptor agonist, in patients with BPH who presented with persistent storage symptoms after tadalafil monotreatment.

MATERIALS AND METHODS

Patient inclusion criteria and study design

This was a prospective, multicenter, open-labeled study conducted at eight sites. The registration started in August 2016 and ended in June 2018. The research was carried out in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies (revised July 2008). This study was registered (UMIN000030560) and was reviewed and approved by the ethics committee of Tottori University Hospital (approval number 1607B027). Moreover, a written informed consent was obtained from each patient.

The total study duration was 8 weeks. Participants were recruited from the regular outpatient department of each study site. The inclusion criteria were as follows: age ≥ 50 years, BPH diagnosis made by an urologist, presence of OAB symptoms with urinary urgency (Overactive Bladder Symptom Score [OABSS] question 3, score of ≥ 2 and a total OABSS of ≥ 3), and an International Prostate Symptom Score (IPSS) of ≥ 2 for question 7. The exclusion criteria were as follows: PVR volume ≥ 100 mL, history of urinary retention, neurogenic bladder, diseases other than OAB that might affect voiding, malignant tumors, radiation therapy that might cause urinary tract function, long QT syndrome, serious heart disease, or liver and renal dysfunction. The criteria for withdrawal from the current research were patient's decision to drop-out, no clinic visit, need to change the treatment regimen, and decision of the investigator.

Figure 1 depicts the study design. Patients were treated with oral tadalafil 5 mg once daily after breakfast for 4 weeks, and its effect was evaluated. The treatment was considered ineffective if patients had

Table 1. Demographic and other baseline characteristics of the patients (*n* = 75)

Age (years), mean (range)	72.6 (54–87)
BMI (kg/m^2), mean (range)	22.9 (16.6–31.7)
Prostate volume, *n* (%)	
< 20 mL	22 (29.3)
20–50 mL	35 (46.7)
> 50 mL	14 (18.7)
Total IPSS, *n* (%)	
Mild	6 (8.0)
Moderate	43 (57.3)
Severe	25 (33.3)
PVR volume (mL), mean (range)	26.7 (0–90)
PSA (ng/mL), mean (range)	2.70 (0.39–11.99)

BMI, body mass index; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; PVR, post-void residual.

an OABSS question 3 score of ≥ 2, total OABSS of ≥ 3, and IPSS question 7 score of ≥ 2 after 4 weeks of tadalafil treatment. Patients who responded to tadalafil continually received oral tadalafil 5 mg once daily after breakfast for 4 more weeks (monotreatment group). Meanwhile, those who did not respond were treated with oral tadalafil 5 mg and mirabegron 50 mg once daily after breakfast for 4 more weeks (combination group). The efficacy endpoints were changes in OABSS, IPSS, OAB Questionnaire (OAB-q), and Nocturia Quality of Life Questionnaire (N-QOL) scores. Patients were instructed to complete the OABSS, IPSS, OAB-q, and N-QOL questionnaires at weeks 0, 4, and 8. Throughout the study, treatment compliance was closely monitored and recorded by two urologists, and treatment safety was assessed based on the presence of adverse events (AEs).

Statistical analysis

A sample size of 14 patients per group was required to demonstrate the efficacy of tadalafil with mirabegron add-on treatment at a 2-sided significance level of 5% with a power of 75%. The two treatment groups were compared using the unpaired *t* test. Differences in baseline characteristics were evaluated using the paired *t* test. All statistical tests were two-sided, and a *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 13.0 (SPSS Inc., Chicago, IL) and GraphPad Prism (GraphPad Software, Inc., San Diego, CA).

Table 2. Baseline characteristics of the monotreatment and combination groups

Baseline characteristics	Monotreatment group *n* = 19	Combination group *n* = 56	*P* value
Age (years), mean	70.2	73.4	0.053
BMI (kg/m^2), mean	23.6	22.7	0.355
Prostate volume, *n*			0.339
< 20 mL	8	14	
20–50 mL	9	26	
> 50 mL	2	12	
Total IPSS, mean	15.6	17.8	0.252
IPSS question 7, mean	2.9	3.4	0.122
PSA (ng/mL), mean	2.6	2.7	0.879
Smoking history, *n*	2	17	0.082
Diabetes mellitus, *n*	2	11	0.278
Hypertension, *n*	6	19	0.504
Hyperlipidemia, *n*	3	9	0.582

BMI, body mass index; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.

RESULTS

Efficacy

In total, 2 (2.6%) patients discontinued tadalafil monotreatment due to AEs. The mean patient age was 72.6 years; the mean prostate-specific antigen (PSA), 2.70 ng/mL; and the mean PVR volume, 26.7 mL (Table 1). Between-group differences in terms of baseline characteristics were not significant (Table 2). After 4 weeks, the total IPSS, IPSS voiding and storage subscale scores, total OABSS and N-QOL scores, N-QOL sleep/energy and bother/concern subscale scores, and total OAB-q score significantly decreased (Table 3). Table 4 depicts the mean changes in the total OABSS and IPSS, IPSS voiding and storage subscale score, total OAB-q and N-QOL scores, and N-QOL bother/concern subscale score from baseline to 8 weeks between the two groups. After 8 weeks, the two groups experienced significant improvements in the total OABSS and IPSS, IPSS voiding and storage subscale scores, total OAB-q and N-QOL scores, and N-QOL bother/concern subscale score. The mean changes from baseline to 8 weeks between the two groups were as follows: the total OABSS ranged from −1.8 to −2.3; the total IPSS, from −5.4 to −6.3; the IPSS voiding subscale score, from −2.1 to −2.4; the IPSS storage subscale score, from −3.3 to −3.6; and the total OAB-q, from −13.5 to −22.0. Moreover, the mean N-QOL bother/concern subscale score from baseline to 8 weeks of the combination

Table 3. Changes in the IPSS, OABSS, OAB-q scores, and N-QOL score at 4 weeks (n = 75)

	Pretreatment	4 weeks	P value
Total IPSS, mean ± SD	17.1 ± 7.0	13.6 ± 7.3	< 0.001
IPSS voiding score, mean ± SD	8.0 ± 5.1	6.6 ± 5.3	0.010
IPSS storage score, mean ± SD	8.9 ± 2.9	6.9 ± 3.3	< 0.001
IPSS question 7, mean ± SD	3.2 ± 1.1	2.6 ± 1.2	< 0.001
Total OABSS, mean ± SD	7.6 ± 2.8	6.3 ± 3.0	< 0.001
Total OAB-q score, mean ± SD	87.4 ± 30.9	74.0 ± 31.3	< 0.001
Total N-QOL score, mean ± SD	39.6 ± 21.6	30.3 ± 20.3	< 0.001
N-QOL sleep/energy subscale score, mean ± SD	34.9 ± 24.0	28.9 ± 21.3	0.002
N-QOL bother/concern subscale score, mean ± SD	43.4 ± 21.4	21.2 ± 21.4	< 0.001

IPSS, International Prostate Symptom Score; N-QOL, Nocturia Quality of Life Questionnaire; OAB-q, Overactive Bladder Questionnaire; OABSS, Overactive Bladder Symptom Score.

Table 4. Differences in mean changes in the IPSS, OABSS, OAB-q scores, N-QOL score, and PVR volume from baseline to 8 weeks between the two treatment groups

	Monotreatment group	Combination group	P value
	n = 19	n = 56	
Total IPSS, mean ± SD	−5.4 ± 4.8	−6.3 ± 7.0	0.629
IPSS voiding score, mean ± SD	−2.1 ± 2.7	−2.4 ± 5.2	0.844
IPSS storage score, mean ± SD	−3.3 ± 3.1	−3.6 ± 3.2	0.696
IPSS question 7, mean ± SD	−1.0 ± 1.2	−0.9 ± 1.3	0.790
Total OABSS, mean ± SD	−1.8 ± 3.8	−2.3 ± 3.0	0.552
Total OAB-q score, mean ± SD	−13.5 ± 22.5	−22.0 ± 25.9	0.229
Total N-QOL score, mean ± SD	−8.6 ± 16.2	−17.2 ± 15.7	0.056
N-QOL sleep/energy subscale score, mean ± SD	−6.6 ± 13.5	−13.4 ± 17.0	0.140
N-QOL bother/concern subscale score, mean ± SD	−10.1 ± 19.8	−20.8 ± 18.5	0.046
PVR volume (mL), mean ± SD	−7.6 ± 47.0	11.4 ± 50.5	0.201

IPSS, International Prostate Symptom Score; N-QOL, Nocturia Quality of Life Questionnaire; OAB-q, Overactive Bladder Questionnaire; OABSS, Overactive Bladder Symptom Score; PVR, post-void residual.

therapy group significantly increased.

Safety

Four patients in the monotreatment group (n = 2, palpebral edema and n = 2, dyspepsia) and one (voiding difficulty) in the combination therapy group presented with AEs. In two patients, tadalafil monotreatment was discontinued due to palpebral edema. The mean changes in PVR volume from baseline to 8 weeks in the combination therapy and monotreatment groups were 11.4 ± 50.5 and −7.6 ± 47.0 mL, respectively (Table 4). The changes did not significantly differ between the groups (P = 0.201), and there were no cases of urinary retention or serious AEs.

DISCUSSION

The current study aimed to evaluate the safety and efficacy of mirabegron in patients with BPH who had persistent storage symptoms after tadalafil monotreatment. BPH is the histological terminology. The condition itself does not require treatment and is not the target of therapeutic intervention. Although we could not validate whether the term LUTS/BPH is scientifically correct, its usage has been accepted in the treatment of LUTS among male patients according to the American Urological Association. For the treatment of LUTS/BPH, α_1-blockers and/or PDE5-Is have been used as the first-line treatment. These drugs may improve voiding and storage symptoms, including OAB.[5, 6, 13, 14] However, OAB symptoms may remain

despite treatment with these drugs.[15] In these patients, several combination treatment or add-on therapies have been found to be effective.[7, 8, 15, 16] The most frequently used combination was α_1-blockers and anticholinergics, and treatment with these drugs can be effective for OAB symptoms caused by BPH.[8, 15] However, the addition of anticholinergics may cause several adverse effects, such as constipation, dry mouth, blurred vision, and cognitive function decline. Although rarely, this combination treatment may increase PVR volume, and urinary retention may occur in about 1%–3% of patients.[15, 17] The use of mirabegron, a β_3-adrenoreceptor agonist, for the treatment of OAB has been approved in several countries. Nevertheless, data about the efficacy and safety of combination treatment or add-on therapy with PDE5-Is plus β_3-adrenoreceptor agonists are insufficient. Therefore, the current study aimed to evaluate whether combination treatment with tadalafil and mirabegron is effective in men with remaining storage symptoms after tadalafil monotreatment.

In this study, the total OABSS, total IPSS, IPSS for voiding, and IPSS for storage decreased significantly in the two groups after 8 weeks. PDE5-I is the gold standard for the treatment of erectile dysfunction. Moreover, the drug can be effective for the management of LUTS in several preclinical and clinical trials since it can increase oxygenation and blood supply, reduce intraprostatic inflammation, and reduce the smooth muscle tone of the lower urinary tract.[18–20] Indeed, PDE5 was highly expressed not only in the penile corpora cavernosa but also in the male bladder, urethra, and prostate.[21, 22] Noteworthy, the use of tadalafil 5 mg once daily has been approved, and the prescription of this drug, which is a valuable treatment option for patients with LUTS with or without erectile dysfunction, has increased in recent years.[18, 20] Porst et al. performed a randomized clinical trial (RCT) comparing tadalafil 5 mg and placebo. In total, 325 men with LUTS were evaluated. Tadalafil was found to significantly improve total IPSS compared with placebo. Further, the tadalafil group experienced improvements in IPSS voiding, storage, frequency (question 2), and urgency (question 4) subscale scores. The most common AEs were headache and back pain.[23] In 2014, Takeda et al. compared tadalafil 5 mg (n = 306) and placebo (n = 304) in Japanese and Korean men with LUTS/BPH. The IPSS storage and voiding subscale scores significantly improved in the treatment group compared with the placebo group. The most common AEs were nasopharyngitis (tadalafil and placebo: 4.2 vs. 3.3%), dyspepsia (3.9 vs. 0.7%), and headache (2.9 vs. 2%).[24] In this study, the total OABSS, total IPSS, and IPSS voiding and storage subscale scores decreased significantly in the monotreatment group after 8 weeks. The American Urological Association guidelines recommend the use of oral anticholinergics or β_3-adrenoreceptor agonists as the first-line pharmacologic treatment for OAB.[25] Mirabegron can promote relaxation of the detrusor smooth muscle, which increases bladder capacity without changing micturition pressure or PVR volume.[12] Moreover, it can act as a competitive antagonist of α_1-adrenoceptors in the urethra, causing relaxation of the urethral smooth muscles.[26] Several RCTs have evaluated the efficacy and safety of mirabegron in men.[27] Shin et al. performed a randomized, double-blind, placebo controlled, multicenter trial. They aimed to evaluate the efficacy and safety of mirabegron in men with OAB symptoms. In total, 464 Korean men were randomized to the mirabegron 50 mg group (n = 310) or the placebo group (n = 154). At the end of the initial 12-week follow-up period, men randomized to the mirabegron group had significant improvements in total OABSS. Changes in the maximum urinary flow rate, voided volume, and PVR volume did not significantly differ between the two groups. When mirabegron was administered to both groups for 14 more weeks, the investigated parameters from week 12 to week 26 did not significantly differ between the two groups. Moreover, there were no significant differences in terms of the incidence of AEs.[28] Since the mechanism of action of mirabegron differs from that of anticholinergics, it might be useful in treating patients with intolerable AEs associated with anticholinergics. Recently, in the CONTACT study, Yamanishi et al. evaluated the efficacy and safety of combination treatment with tadalafil and mirabegron for OAB/BPH. In total, 176 patients were randomized to either the monotherapy group (n = 87) or the combination therapy group (n = 89). The total OABSS of patients who received combination therapy significantly decreased compared with that of patients who received monotherapy. The OAB nighttime voiding score, urgency score, and IPSS storage subscale score significantly decreased after combination therapy. Moreover, one moderate AE (pain in the hip joint) with presumed causal relationship with therapy and seven mild AEs were noted in the monotherapy and combination therapy groups, respectively.[29] The effects of the combination therapy on the total OABSS and IPSS storage subscale scores in this study were similar to those in our study. On the other hand, we also evaluated the effects of combination therapy on QOL using the OAB-q and N-QOL. After 8 weeks, the total OAB-q and N-QOL scores and N-QOL Bother/Concern subscale score in the combination therapy group were significantly improved, similar to those in the monotherapy

group. Improvement in patient-rated measures strongly indicates that combination treatment with tadalafil and mirabegron might improve OAB related QOL by improving urinary urgency with urinary frequency and nocturia due to OAB.

The current study had several limitations. First, this study was conducted to examine the safety and efficacy of mirabegron as an add-on treatment for persistent storage symptoms despite tadalafil treatment for 4 weeks in patients with BPH. However, comparison with a placebo group or cross over trial was not performed. Second, this study might not be sufficiently large enough to show small differences in outcomes. Therefore, a randomized controlled trial with a sufficient number of samples would be necessary to elucidate the true efficacy profile of mirabegron as an add-on treatment. Third, safety evaluation was not performed by electrocardiogram measurement or blood pressure monitoring. Since β_3-adrenoreceptors are expressed in cardiovascular tissues, there are concerns that β_3-adrenoreceptor agonists may affect the heart and vasculature. However, a recent review has shown that cardiovascular safety of mirabegron appears to be acceptable at therapeutic doses and comparable with that of anticholinergics.[30]

Combination treatment with tadalafil and mirabegron was effective, and its safety was comparable to that of tadalafil monotreatment in patients with BPH who presented with persistent storage symptoms. Hence, tadalafil plus mirabegron is promising therapeutic option, and it can improve QOL. Moreover, it is associated with a lower incidence of LUTS in patients with OAB caused by BPH.

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