#140 SAFETY AND EFFICACY OF MIRABEGRON AS ADD-ON TREATMENT FOR PERSISTENT STORAGE SYMPTOMS DESPITE TADALAFIL TREATMENT IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

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Introduction

- Lower urinary tract symptoms (LUTS) are a common occurrence in benign prostatic hyperplasia (BPH), and their prevalence increases with advancing age.
- LUTS significantly affect the quality of life (QOL) of patients with BPH.
- Among the LUTS, overactive bladder (OAB), which is defined as urinary urgency with urinary frequency, nocturia, and sometimes urgency incontinence, is the most troublesome symptom in the daily life of patients.
- Phosphodiesterase type 5 inhibitors (PDE5-Is) are used as first-line treatment for BPH [1].
- However, some men with BPH experience inadequate improvement in LUTS after PDE5-Is treatment.
- Therefore, we sought to identify further treatment strategies for these patients, including combination or add-on treatment with other agents that can control the LUTS, such as anticholinergics and β3-adrenoreceptor agonists.
- However, treatment of BPH with anticholinergics increases the risk of developing urinary retention.
- Moreover, combination treatment for BPH with PDE5-Is and β3-adrenoreceptor agonists has not been extensively studied.
- Therefore, we conducted a study to examine the safety and efficacy of the β3-adrenoreceptor agonist mirabegron as an add-on treatment for persistent storage symptoms despite PDE5-I tadalafil treatment in patients with BPH.

Methods and Materials

- This was a prospective, multicentre, open-labeled study conducted at 12 sites.
- Registration started in August 2016 and ended in April 2019.
- The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice and the Declaration of Helsinki.
- The study was conducted in accordance with a protocol approved by the institutional ethics committee for clinical trials, and written informed consent was obtained from all patients.
- The total duration of the study was 8 weeks. Participants were recruited from the regular out-patients at each study site.
- Patients meeting the following criteria were included in this study: aged ≥50 years, diagnosed as having BPH by a urologist, presence of OAB symptoms with urinary urgency (OAB symptom score [OABSS] question 3 score ≥2 points and a total OABSS of ≥3 points), and an international prostate symptom score (IPSS) question 7 score ≥2 points.
- The exclusion criteria were as follows: post void residual (PVR) ≥100 mL, a history of urinary retention, neurogenic bladder, any disease other than OAB that might affect voiding, malignant tumours, radiation therapy that might affect urinary tract function, long QT syndrome, serious heart disease, or insufficient liver and renal function.
- Criteria for withdrawal from this study were as follows: request for withdrawal from the patient, no clinic visit, necessity to change the study treatment regimen, or decision of the investigator.
- Tadalafil (5 mg once daily orally after breakfast) was administered to the patients for 4 weeks and its effect was evaluated. The treatment was deemed ineffective in patients when the OABSS question 3 score was ≥2 points and the total OABSS was ≥3 points, and the IPSS question 7 score was ≥2 points after 4-weeks of tadalafil treatment. The patients in whom tadalafil was observed to be effective received tadalafil 5 mg once daily orally after breakfast for a further 4 weeks (monotreatment group) . The patients in whom tadalafil was observed to be ineffective received tadalafil 5 mg as well as mirabegron 50 mg once daily orally after breakfast for a further 4 weeks (combination group) (**Figure 1**).
- Efficacy endpoints were changes from baseline in the OABSS, IPSS, OAB questionnaire (OAB-q), and nocturia-QOL (N-QOL).
- Patients were instructed to complete the OABSS sheets, IPSS sheets, OAB-q sheets, and N-QOL sheets at weeks 0, 4, and 8.
- Throughout the study, treatment compliance was closely monitored and recorded by two urologists, and treatment safety was assessed from the reporting of adverse events (AEs).
- The data were compared using the paired and unpaired *t* test and Fisher's exact test. All statistical tests were two sided with a significance level set at P <0.05.

Figure 1. Study design.

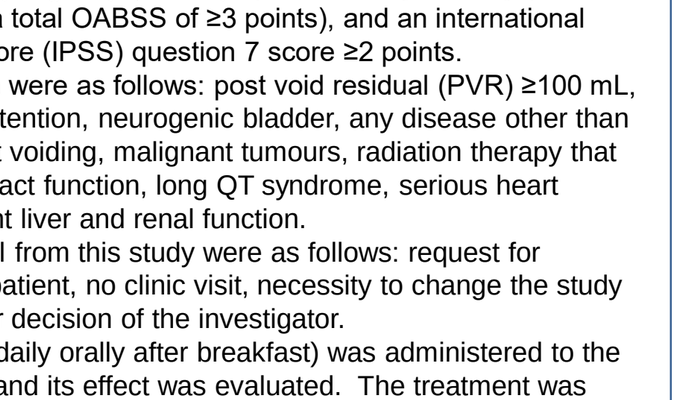


Table 1. Patient demographic and other baseline characteristics.

		n = 61
Age, yr, mean (range)		72.8 (54−87)
BMI, kg/m^2, mean (range)		22.8 (12.7−37.8)
Prostate volume, *n* (%)	< 20 mL 20−50 mL > 50 mL	20 (32.8%) 26 (42.6%) 11 (18.0%)
IPSS total score, *n* (%)	mild moderate severe	5 (8.2%) 37 (60.7%) 19 (31.1%)
PVR volume, mL, mean (range)		30.6 (0−90)
PSA, ng/mL, mean (range)		2.76 (0.40−11.99)

		Monotreatment	Combination	*P*
		n = 18	*n* = 43	
Age, yr, mean		70.2	73.8	0.048
BMI, kg/m^2, mean		23.4	22.6	0.500
Prostate volume, *n*	< 20 mL 20−50 mL > 50 mL	8 8 2	12 18 9	0.454
IPSS total score, mean		15.9	17.5	0.211
PSA, ng/mL, mean		2.7	2.8	0.832

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

Results

- Of the 61 patients (18 patients in the monotreatment group and 43 patients in the combination group) enrolled in the study (**Table 1**).
- Overall, the mean patient age was 72.6 ± 6.5 years, the mean prostate volume was 36.7 ± 13.2 mL, and the mean PVR was 30.6 ± 15.1 mL (**Table 1**).
- No significant differences between the two groups were observed in the baseline characteristics, including the efficacy endpoints OABSS, IPSS, OAB-q, and N-QOL (**Figure 2**).
- Significant improvements from the baseline were seen in the OABSS total score, IPSS total score, IPSS voiding score, IPSS storage score, OAB-q total score, N-QOL total score, and N-QOL bother/concern subscale score in the two groups at week 8 (**Figure 2**).
- The mean changes from baseline to week 8 ranged from −5.9 to −6.6 for the two groups; the IPSS voiding score ranged from −2.2 to −2.5, the IPSS storage score ranged from −3.3 to −3.7, and the OAB-q total score ranged from −12.8 to −24.9 (**Figure 2**).
- Moreover, the mean changes in the N-QOL total score and N-QOL bother/concern subscale score from baseline to week 8 in the combination group significantly increased compared with the scores in the monotreatment group (**Figure 2**).
- No significant changes from the baseline were seen in PVR volume in the two groups at week 4 and 8 (**Figure 3**).
- AEs were reported in 4 patients in the monotreatment group and 1 patient in the combination group.
- The events reported were palpebral edema in 2 patients and dyspepsia in 2 patients in the monotreatment group, and voiding difficulty in 1 patient in the combination group.
- No cases of urinary retention or serious AEs were reported in the two groups.

Figure 2. Mean change from baseline in International Prostate Symptom Score (IPSS), Overactive Bladder questionnaire (OAB-q), Nocturia-Quality of Life (N-QOL) during the treatment period. **P*<0.05. monotreatment, combination.

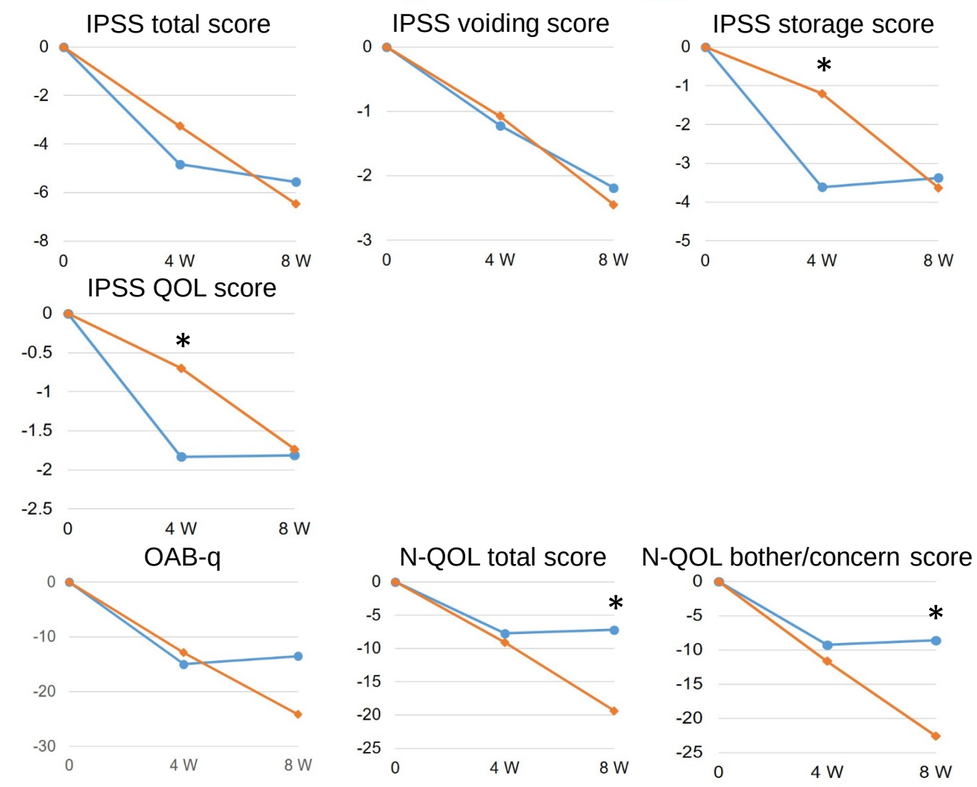
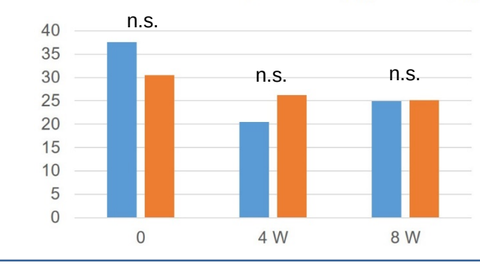


Figure 3. Mean post void residual (PVR) volume in the two groups during the treatment period.
monotreatment, combination.



Discussion

- The present study was conducted to evaluate the safety and efficacy of add-on treatment with mirabegron (50 mg/day) in patients with BPH who had persistent storage symptoms after treatment with tadalafil (5 mg/day). The PDE5-I tadalafil has been approved in many countries for the treatment of BPH, and previous randomised studies have demonstrated that its efficacy is similar to that of the α1-blockers [2]. Nevertheless, currently there is insufficient data on the efficacy and safety of add-on treatment involving a PDE5-I plus a β3-adrenoreceptor agonist. β3-adrenoreceptor agonists relax detrusor smooth muscle during the bladder storage phase and increase bladder capacity without negatively affecting voiding parameters, including maximum flow rate, detrusor pressure at maximum flow rate and PVR [3]. Mirabegron was the first β3-adrenoreceptor agonist to be used in clinical practice. Since the mechanism of action of mirabegron is different from that of anticholinergics, it might prove useful in treating patients experiencing intolerable AEs to anticholinergics.
- A limitation of the present study was that efficacy endpoints were based on changes from the baseline. In addition, this study might not be sufficiently large enough to show small differences in outcomes. A placebo-controlled study would be necessary to elucidate the true efficacy profile of mirabegron as an add-on treatment.

Conclusions

- Combination treatment of tadalafil (5 mg/day) with mirabegron (50 mg/day) add-on showed improved efficacy with comparable safety in BPH patients with persistent storage symptoms after initial tadalafil monotreatment.
- This study indicated that combined treatment with tadalafil and mirabegron add-on is an attractive therapeutic option and contributes to improvements in the QOL, as well as decreases the impact of LUTS in patients with OAB caused by BPH.

References

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7 (Open Discussion ePoster) - ePoster 1, ePoster Station 8, Wednesday 4th September 2019