A Randomized Controlled Study of the Efficacy of Tamsulosin Monotherapy and its Combination with Mirabegron for Overactive Bladder Induced by Benign Prostatic Obstruction

Koji Ichihara, Naoya Masumori,*,† Fumimasa Fukuta, Taiji Tsukamoto, Akihiko Iwasawa and Yoshinori Tanaka

From the Department of Urology, Sapporo Medical University School of Medicine (KI, NM, FF, TT), Iwasawa Clinic (AI), and Department of Urology, Hokkaido Prefectural Esashi Hospital (YT), Hokkaido, Japan

Purpose: We evaluated the efficacy and safety of add-on treatment with a β_3-adrenoceptor agonist (mirabegron) for overactive bladder symptoms remaining after α_1-blocker (tamsulosin) treatment in men with benign prostatic obstruction.

Materials and Methods: Patients with benign prostatic obstruction with urinary urgency at least once per week and a total OABSS of 3 or more points after 8 or more weeks of treatment with tamsulosin were enrolled in the study. They were randomly allocated to receive 0.2 mg tamsulosin daily or 0.2 mg tamsulosin and 50 mg mirabegron daily for 8 weeks. The primary end point was change in total OABSS. Safety assessments included change in post-void residual urine volume and adverse events.

Results: From January 2012 through September 2013 a total of 94 patients were randomized. Of these patients 76 completed the protocol treatment. In the full analysis set the change in total OABSS during the treatment period was significantly greater in the combination group than in the monotherapy group (−2.21 vs −0.87, p=0.012). The changes in scores for urinary urgency, daytime frequency, International Prostate Symptom Score storage symptom subscore and quality of life index at 8 weeks were significantly greater in the combination group. The change in post-void residual urine volume was significantly greater in the combination group. Although 6 patients experienced adverse events in the combination group, urinary retention was observed in only 1 patient.

Conclusions: Combined tamsulosin and mirabegron treatment is effective and safe for patients with benign prostatic obstruction who have overactive bladder symptoms after tamsulosin monotherapy.

Key Words: prostatic hyperplasia; adrenergic alpha-antagonists; urinary bladder, overactive; adrenergic beta-agonists

Abbreviations and Acronyms

AEs = adverse events
BPO = benign prostatic obstruction
I-PSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
OAB = overactive bladder
OABSS = OAB symptom score
PV = prostate volume
PVR = post-void residual urine volume
Qmax = maximum flow rate
QOL = quality of life

Accepted for publication September 12, 2014.
Study received institutional review board approval.

* Correspondence: Department of Urology, Sapporo Medical University School of Medicine, S1, W16, Chuo-ku, Sapporo 060-8543 Japan (telephone: +81-11-611-2111, ext. 3474; FAX: +81-11-612-2709; e-mail: masumori@sapmed.ac.jp).

† Financial interest and/or other relationship with Astellas Pharma, Inc. and Daiichi Sankyo Company.

In the 2013 European Association of Urology guideline for nonneurogenic male LUTS including benign BPO,[1] patients with BPO with OAB symptoms and those with BPO still having OAB symptoms after α-blocker administration were recommended to use anticholinergic agents simultaneously or in the add-on setting. The effectiveness of anticholinergic agents was demonstrated by large scale, well designed, randomized,

0022-5347/15/1933-0921/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2014.09.091
Vol. 193, 921-926, March 2015
Printed in U.S.A.

controlled clinical trials.[2–8] In real-life clinical practice we had revealed the efficacy of combination therapy using an anticholinergic agent and an α-blocker in patients with BPO and remaining OAB symptoms.[9] However, anticholinergic agents involve several adverse effects such as urinary retention, dry mouth, blurred vision and constipation. Moreover these adverse effects make it difficult for patients with OAB to continue on the medication.[10,11]

Beta-adrenoceptors have a role in mediating the relaxation of bladder smooth muscle. An important role has been proposed for the β_3-adrenoceptor subtype in promoting urine storage in the bladder.[12] Mirabegron, a β_3-adrenoceptor agonist first developed in Japan and launched in 2011, can now be used for the treatment of OAB symptoms. The rate of adverse effects such as dry mouth and constipation with mirabegron is lower than that with anticholinergic drugs.[13] However, there are no randomized controlled study data to our knowledge about its efficacy and safety in men who received initial α-blocker treatment for BPO and have remaining OAB symptoms. Therefore, we examined the efficacy of add-on treatment with mirabegron compared to monotherapy with the α-blocker tamsulosin. Moreover we evaluated the safety for these patients after mirabegron induction.

MATERIAL AND METHODS

Patient Inclusion Criteria and Study Design

This 8-week, multicenter, randomized, open label, controlled trial was conducted at 21 urological clinics in Hokkaido, Japan. From January 2012 through September 2013 men 50 years old or older with LUTS most likely secondary to BPO were included in the study. All participants had persistent OAB symptoms after 0.2 mg α-blocker tamsulosin monotherapy daily for at least 8 weeks. The definition of persistent OAB symptoms is a total OABSS of 3 points or more with urinary urgency at least once per week.[14] This study was approved by the institutional review board of each study site and was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The clinical study design is posted at https://upload.umin.ac.jp (UMIN 000007269). All participants provided written informed consent. Study exclusion criteria were PVR greater than 100 ml, Qmax less than 5 ml per second, history of urinary retention, prior diagnosis of neurogenic bladder or performance of clean intermittent catheterization, severe bladder diverticulum or urethral stricture, planning to have a child, suspected malignant disease, previous intrapelvic irradiation, suspected urinary infection, renal or hepatic impairment, taking medicine contraindicated to combination with mirabegron, or considered unsuitable for the trial by doctors.

Patients were randomized to a monotherapy group, which continuously received 0.2 mg tamsulosin daily, or an add-on group, which received 0.2 mg tamsulosin and 50 mg mirabegron daily. The approved dose of tamsulosin is 0.2 mg per day and the upper limit dose of mirabegron is 50 mg per day in Japan. Randomization was performed through central registration using an allocation table.

Before randomization the OABSS, I-PSS and I-PSS-QOL were evaluated, and PV was measured by transabdominal or rectal ultrasonography together with uroflowmetry and PVR. Eight weeks later the changes from baseline were determined for the OABSS, I-PSS, QOL, uroflowmetry and PVR. We set the treatment duration to 8 weeks since this amount of time is considered sufficient for the effectiveness of mirabegron to reach a plateau.

The primary end point was change in total OABSS. Secondary end points were changes in each index of the OABSS and total I-PSS, and in each index of the I-PSS, QOL and Qmax. Safety assessments included change in PVR and AEs. All AEs were closely monitored and details were reported throughout the study period.

Statistical Analysis

To detect a 2-point difference in the change in OABSS between the 2 groups with a significance level of 5% and a power of 99%, at least 38 patients were required in each group. Since 20% of the enrolled patients were considered withdrawn during the 8 weeks because of self-discontinuation or withdrawal of consent, 50 patients in each group were required to evaluate the primary end point.

The differences in the changes in parameters from baseline to 8 weeks in each group were examined using the paired t-test. The difference in parameters between the 2 groups was examined with the unpaired t-test. Safety analysis was performed for all treated patients and treatment efficacy was evaluated in the full analysis set (with $p < 0.05$ considered statistically significant).

RESULTS

Patient Population

A total of 94 men were enrolled in the study. Although the number of enrolled patients was insufficient, the study was closed because of the lower number of withdrawals than expected. Analysis for safety was done using 81 patients because 9 were excluded due to protocol violation and 4 never came back to the hospital after the randomization. Of these men 76 (tamsulosin alone group 38 and mirabegron add-on group 38) completed the protocol treatment and served as a full analysis set. Five patients withdrew from the study because of adverse events (fig. 1).

In the full analysis set mean patient age was 74.5 ± 8.2 years, mean duration of prior tamsulosin treatment was 779 ± 1,183 days and mean PV was 34.2 ± 16.2 ml. Of the 76 patients 46.1% had comorbidity, including hypertension (20), diabetes mellitus (8), ischemic heart disease (5), a history of cerebral infarction (2) and others (11). Patient demographic data and other baseline