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# A RANDOMIZED CONTROLLED STUDY TO EVALUATE THE EFFICACY OF TAMSULOSIN MONOTHERAPY AND ITS COMBINATION WITH MIRABEGRON ON PATIENTS WITH OVERACTIVE BLADDER INDUCED BY BENIGN PROSTATIC HYPERPLASIA

Hypothesis / aims of study

This study was conducted to evaluate the efficacy and safety of add-on treatment with a beta 3-adrenoceptor agonist (mirabegron) for overactive bladder (OAB) symptoms remaining after alpha 1-blocker (tamsulosin) treatment in male patients with benign prostatic hyperplasia (BPH).

Study design, materials and methods

Patients with BPH having urinary urgency at least once per week and a total OAB symptom score (OABSS) ≥ 3 points after ≥ 8 weeks treatment with tamsulosin were enrolled in a multicenter, open-label study. Patients were randomly allocated to receive tamsulosin (0.2 mg/day) monotherapy or tamsulosin (0.2 mg/day) and mirabegron (50 mg/day) for 8 weeks. The primary endpoint was the change in the total OABSS. To detect a 2-point difference in the change in the OABSS between the two groups with a significance level of 5% and a power 99%, 38 patients in each group were required. Since it was considered that 20% of the enrolled patients would withdraw during the 8 weeks because of self-discontinuation or withdrawal of consent, 50 patients in each group were required to evaluate the primary endpoint. Secondary endpoints were the changes in each category of the OABSS and the International Prostate Symptom Score (IPSS), quality of life (IPSS-QOL) and maximum flow rate (Qmax). Safety assessments included the change in post-void residual urine volume (PVR) and adverse events (AEs).

Results

From January 2012 through September 2013, a total of 94 men were randomized to the tamsulosin-alone group (n = 47) or mirabegron add-on group (n = 47). Although the number of enrolled patients was initially considered insufficient, the study was closed because of a smaller number of withdrawals than expected. In all, 76 men (n=38 in the tamsulosin-alone group and n=38 in the mirabegron add-on group) completed the protocol treatment and provided a full analysis set.

In the full analysis set, the change from baseline to 8 weeks in the total OABSS was significantly greater in the mirabegron add-on group than in the tamsulosin-alone group (p = 0.012). The changes in the score of urinary urgency (OABSS Q3) (p = 0.006), daytime frequency (IPSS Q2) (p = 0.025), IPSS storage symptom subscore (p = 0.006) and IPSS-QOL (p = 0.020) from baseline to 8 weeks were significantly greater in the mirabegron add-on group. Although the change in Qmax was not significantly different between the two groups, the change in PVR was significantly greater in the mirabegron add-on group (p = 0.020). Six patients in the mirabegron add-on group had AEs (constipation in 1, acute urinary retention in 1, increased voiding difficulty in 1, dizziness in 1, heartburn in 1, and elevation of hepatic enzymes in 1). Of the 6, 5 patients quit mirabegron due to the AEs. No patients in the tamsulosin-alone group reported AEs.

| | Tamsulosin monotherapy (n = 38) | | | Tamsulosin + Mirabegron combination (n = 38) | | | difference in the change from baseline |
|---|---|---|---|---|---|---|---|
| variables | Mean ± SD | | Mean change from baseline | Mean ± SD | | Mean change from baseline | p value |
| | baseline | 8w | | baseline | 8w | | unpaired t-test |
| **OABSS** | | | | | | | |
| total score | 7.34±2.67 | 6.47±2.84 | −0.87 | 7.81±2.48 | 5.60±2.83 | −2.21 | 0.012 |
| Q1 daytime urination | 0.68±0.57 | 0.76±0.63 | 0.08 | 0.68±0.52 | 0.65±0.53 | −0.03 | 0.377 |
| Q2 nighttime urination | 2.26±0.79 | 2.05±0.76 | −0.21 | 2.34±0.74 | 2.05±0.83 | −0.29 | 0.591 |
| Q3 urgency | 2.97±0.88 | 2.42±1.38 | −0.55 | 3.42±1.00 | 2.07±1.56 | −1.34 | 0.006 |
| Q4 urgency incontinence | 1.44±1.40 | 1.23±1.21 | −0.21 | 1.39±1.44 | 0.81±1.22 | −0.58 | 0.195 |
| **IPSS** | | | | | | | |
| total score | 12.94±6.09 | 12.68±8.13 | −0.26 | 13.97±5.52 | 11.63±5.91 | −2.34 | 0.099 |
| Q1 incomplete emptying | 1.39±1.51 | 1.44±1.63 | 0.05 | 1.28±1.29 | 1.18±1.37 | −0.11 | 0.610 |
| Q2 day frequency | 2.18±1.55 | 2.13±1.69 | −0.05 | 2.63±1.34 | 1.86±1.33 | −0.76 | 0.025 |
| Q3 intermittency | 1.10±1.37 | 1.36±1.74 | 0.26 | 1.34±1.38 | 1.34±1.54 | 0.00 | 0.466 |
| Q4 urgency | 2.34±1.59 | 2.13±1.49 | −0.21 | 2.57±1.53 | 1.78±1.49 | −0.79 | 0.069 |
| Q5 weak stream | 2.34±1.58 | 2.00±1.72 | −0.34 | 2.26±1.68 | 2.31±1.64 | 0.05 | 0.222 |
| Q6 straining | 1.07±1.26 | 1.28±1.59 | 0.21 | 1.13±1.49 | 0.89±1.22 | −0.24 | 0.254 |
| Q7 nocturia | 2.47±1.10 | 2.31±1.14 | −0.16 | 2.73±1.13 | 2.26±1.00 | −0.47 | 0.093 |
| voiding symptom subscore | 4.52±3.39 | 4.65±4.14 | 0.13 | 4.84±3.34 | 4.63±2.69 | −0.21 | 0.647 |
| storage symptom subscore | 7.00±3.30 | 6.57±3.57 | −0.42 | 7.84±2.73 | 5.81±2.93 | −2.03 | 0.006 |
| QOL index | 3.34±1.32 | 3.28±1.39 | −0.05 | 3.97±1.32 | 3.21±1.33 | −0.76 | 0.020 |
| **UFM** | | | | | | | |
| Qmax | 15.4±7.2 | 14.1±7.0 | −1.4 | 13.3±7.6 | 13.0±6.5 | −0.4 | 0.564 |
| PVR | 34.7±28.7 | 38.5±40.8 | 3.9 | 37.8±28.1 | 75.1±74.1 | 37.3 | 0.020 |

Interpretation of results

There is solid evidence supporting the efficacy and safety of add-on treatment with anti-muscarinic agents such as propiverine hydrochloride, solifenacin and imidafenacin. The present study demonstrated that add-on treatment with the beta 3-adrenoceptor agonist mirabegron was effective for the patients with BPH whose OAB symptoms were not controled by alpha 1-blocker monotherapy, similarly to anti-muscarinic agents. However, attention should be paid to whether voiding difficulty, acute urinary retention and an increased amount of PVR develop.

Concluding message

Combined tamsulosin and mirabegron treatment is effective and safe in patients with BPH having remaining OAB symptoms after tamsulosin monotherapy.

Disclosures

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