Randomized Controlled Trial to Treat Benign Prostatic Hyperplasia with Overactive Bladder Using an Alpha-blocker Combined with Anticholinergics

Osamu NISHIZAWA,1* Osamu YAMAGUCHI,2 Masayuki TAKEDA,3 and Osamu YOKOYAMA4 for the TAABO Study Group†

1Department of Urology, Shinshu University School of Medicine, Matsumoto, Japan, 2Department of Urology, Fukushima Medical University School of Medicine, Fukushima, Japan, 3Department of Urology, Interdisciplinary Graduate School of Medicine & Engineering, University of Yamanashi, Koufu, Japan, and 4Department of Urology, University of Fukui, Fukui, Japan

Objectives: TAABO was a randomized, controlled trial to evaluate the efficacy and safety of combination therapy of tamsulosin (TAM) with propiverine (PROP) in men with both benign prostatic hyperplasia and overactive bladder.

Methods: It enrolled men 50 years or older who had an international prostate symptom score (IPSS) of 8 or higher, an urgency item score of 1 or higher, and a quality of life (QOL) score of 2 or higher. After 8 weeks of TAM 0.2 mg/day, patients who met the inclusion criteria (8 micturitions per 24 h and 1 urgency per 24 h, evaluated by bladder diary) and were eligible for 12-weeks of continued Treatment II. Five hundred and fifteen patients were enrolled. Thereafter, 214 patients were assigned randomly to receive either TAM alone (n = 67), TAM plus PROP 10 mg (n = 72), or TAM plus PROP 20 mg (n = 75) in Treatment II. The primary efficacy end point was a change in micturitions per 24 h documented in the bladder diary. The change from baseline in urgency episodes per 24 h, IPSS, IPSS/QOL subscore, urinary flow rate and postvoid residual volume were assessed as secondary efficacy measures.

Results: A total of 141 men (47 TAM, 49 TAM plus PROP 10 mg, and 45 TAM plus PROP 20 mg patients) were assessed by week 12. Compared with the TAM, TAM plus PROP 10 mg patients experienced significantly fewer micturitions (P = 0.0261), urgencies (P = 0.0093) per 24 h, lower IPSS storage (P = 0.0465), and IPSS urgency (P = 0.0252) subscores.

Conclusions: These results suggest that combining TAM and 10 mg of PROP for 12 weeks provides added benefit for men with both benign prostatic hyperplasia and overactive bladder.

Key words benign prostatic hyperplasia, overactive bladder, propiverine, tamsulosin

1. INTRODUCTION

Lower urinary tract symptoms (LUTS) greatly affect the quality of life (QOL) of patients with benign prostatic hyperplasia (BPH). Among LUTS, overactive bladder (OAB) symptoms are most troublesome in patients with BPH. In Japan, anticholinergics have been administered with α1-blocker empirically to treat OAB symptoms of BPH with a caution regarding urinary retention related to anticholinergics.1,2 BPH patients who have both an OAB and bladder outlet obstruction symptoms are treated with a combination of α1-blocker and anticholinergics with increasing evidence of efficacy.3 Treatment with the α1-blocker tamsulosin (TAM) plus the anticholinergic tolterodine extended release for 12 weeks has been suggested to benefit men with BPH and moderate-to-severe LUTS, including OAB.4 Twelve weeks of therapy with the α1-blocker TAM plus the anticholinergic solifenacin decreased daily micturitions and urgency episodes, but only the reduced urgency achieved statistical significance versus TAM plus placebo.5

We sought to clarify the role of combination treatment of LUTS of BPH with an α1-blocker with anticholinergics, and the appropriate dose of anticholinergics. We compared the efficacy and safety in three clinical treatment groups: (i) α1-blocker TAM alone; (ii) combined treatment of TAM with 10 mg of the anticholinergic

*Correspondence: Osamu Nishizawa, MD, PhD, Professor of Urology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan. Tel: 81-263-37-2661; Fax: 81-263-37-3082. Email: onishiz@shinshu-u.ac.jp

†TAABO Study Group: List of hospitals involved in study group appears in Appendix.

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propiverine (PROP); (iii) and combined treatment of TAM with 20 mg of the anticholinergic PROP in men with both BPH and OAB.

2. METHODS

2.1. Patients

Patients were recruited at 74 urology offices and clinics in Japan. Those eligible were men at least 50 year old with clinically significant bladder outlet obstruction (BOO). The inclusion criteria were a total international prostate symptom score (IPSS) of 8 or more with urgency item score of 1 or higher, and an IPSS/QOL item score of 2 or greater and maximum urinary flow rate less than 15 mL/sec in a total voided volume more than 150 mL.

Each investigator obtained prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents from the appropriate institutional review board or independent ethics committee. All correspondence with the institutional review board or independent ethics committee was retained by the investigator. Written, informed consent was obtained from each patient. After the initial evaluation, all patients were registered at a web site (http://www.evidence.jp/taabo/) and included in the Treatment I period of the α1-blocker TAM at 0.2 mg daily in the morning with breakfast for 8 weeks.

At the end of 8 weeks for Treatment I, therapeutic effect was assessed using the IPSS, voiding diary, urine flow rate and postvoid residual volume. Men with clinically significant BOO were excluded (defined as a postvoid residual volume > 100 mL and maximum urinary flow rate < 5 mL/sec in a total voided volume > 150 mL).

The patients who met the inclusion criteria (8 micturitions per 24 h and 1 urgency per 24 h by bladder diary), and otherwise eligible to enter the 12 week Treatment II, were assigned randomly to one of three treatment groups (TAM, TAM plus PROP 10 mg, or TAM plus PROP 20 mg) at the web site.

Other exclusion criteria were: treatment with an α1-receptor antagonist; taking antimuscarinics, antispasmodics, saw palmetto to influence voiding function; prostate cancer; some neurologic bladder conditions (e.g. multiple sclerosis, spinal cord injury, Parkinson disease); urethral stricture; previous treatment for BPH; prostate surgery; irradiation to the pelvis; urinary tract infection or stones; interstitial cystitis; prostatitis; use of an indwelling catheter or self catheterization program; significant hepatic or renal or heart disease; history of postural hypotension or syncope; obstruction of the gastric pylorus, duodenum, or intestine; atony of the stomach and intestine; or any condition (e.g. glaucoma, myasthenia gravis) for which use of antimuscarinics was contraindicated.

2.2. Clinical efficacy assessments

Treatment efficacy for micturitions and urgency per 24 h was assessed using data from bladder diaries. The primary efficacy end point was micturitions per 24 h at week 12.

Micturitions per 24 h was assessed by bladder diaries after 4, 8, and 12 weeks of treatment. At each visit patients were instructed to complete bladder diaries for the 3 day preceding a visit at baseline and weeks 4, 8, and 12. Secondary efficacy measures were assessed as: change from baseline in urgency episodes per 24 h, IPSS, IPSS/QOL subscore, urinary flow rate and postvoid residual volume. Patients were instructed to complete bladder diaries for the 3 day preceding visits at baseline and week 4, 8, and 12.

IPSS was completed by patients at baseline and at week 4, 8, and 12, and was assessed as the change from baseline. Postvoid residual volume was measured using ultrasound, and urinary flow rate was measured using a flowmeter. Both were assessed at baseline and week 4, 8, and 12 of treatment. All adverse events were recorded.

2.3. Statistical analyses

Efficacy was assessed on the full analysis set, defined as those patients who received at least one dose of the study medication, and who had a baseline assessment and at least one post baseline assessment. Differences between treatment groups were evaluated by t-test. Assessments of safety and tolerability were based on all patients who received at least one dose of study medication. A two-sided significance level of 5% was applied for all statistical tests. All analyses were performed using SAS 9.1.3 (SAS Institute Inc, Cary, NC).

3. RESULTS

3.1. Patients

Patients were recruited between October 2004 and September 2008. The study was completed in March 2009. Patient disposition is summarized in Figure 1. A total of 515 patients were enrolled in Treatment I. For Treatment II, 214 patients were assigned randomly to one of three treatment groups (67 for TAM, 72 for TAM plus PROP 10 mg, and 75 for TAM plus PROP 20 mg). Twenty patients (29.9%) in the TAM group, 23 (31.9%) in TAM plus PROP 10 mg, and 30 (40%) in TAM plus PROP 20 mg discontinued for various reasons. Respective discontinuation for lack of efficacy and adverse event were four and zero patients in the TAM group, two and four in TAM plus PROP 10 mg, and two and seven in TAM plus PROP 20 mg. Demographic and baseline clinical characteristics are summarized in Table 1. Baseline demographic characteristics were similar across groups.

3.2. Efficacy end points

At week 12, the primary efficacy analysis a total of 141 patients (47 TAM, 49 TAM plus PROP 10 mg, and 45 TAM plus PROP 20 mg) were assessed. Only patients who received TAM plus PROP 10 mg had significant reductions in micturitions per 24 h compared with TAM in the full analysis and per-protocol sets (Table 2). And significant reductions from baseline in micturitions per 24 h were demonstrated in all three treatment groups (Fig. 2a).

Urgency per 24 h was reduced significantly from baseline in the TAM plus PROP 10/20 mg groups. Compared
with the TAM group, significant reductions were demonstrated in the TAM plus PROP 10 mg group (Fig. 2b).

Total IPSS was significantly lower than baseline in all three treatment groups; however, no significant difference was found between treatment groups. Significant reductions from baseline in IPSS storage subscores were demonstrated in all three treatment groups, and there were significant improvements among patients who received the TAM plus PROP 10 mg versus TAM (Fig. 2c). Patients in the TAM and TAM plus PROP 10 mg groups had significantly lower IPSS voiding subscore from baseline; we found no significant differences between treatment groups. Significant reductions from baseline in IPSS incomplete emptying subscore were found in the TAM and TAM plus PROP 10 mg groups, with no significant differences between treatment groups. IPSS
frequency subscore was significantly below baseline in all three treatment groups. Again, there were no significant differences between groups. No significant reduction in IPSS dribbling subscore from baseline within groups nor differences between groups was demonstrated. IPSS urgency subscore was reduced significantly from baseline in all three groups. Compared with the TAM group, significant reductions in IPSS urgency subscore were demonstrated in the TAM plus PROP 10 mg group at week 12 (Fig. 2d). A significant reduction in IPSS weak stream subscore relative to baseline occurred in the TAM plus PROP 10 mg group without any significant differences between treatment groups. No significant reductions from baseline in IPSS straining subscore were demonstrated in any treatment group, and there were no significant differences between groups. Nocturia was significantly lower than baseline in both the TAM plus PROP (10, 20 mg) groups; there were no significant differences between all the treatment groups. There were significant reductions from baseline in the IPSS/QOL subscore for all groups and no significant differences between groups. No reductions from baseline or between groups in Qmax and Qave were found in any treatment groups. However, postvoid residual volume was significantly above baseline in all three treatment groups at the same time point, combined with significant differences among patients who...
received TAM plus PROP 20 mg versus TAM (Fig. 2c). Four out of 47 patients in the TAM group, 12 out of 49 patients in the TAM plus PROP10 mg group and 11 out of 45 patients in the TAM plus PROP 20 mg group had more than 100 mL of postvoid residual volume at 12 week.

Compared with the TAM group, patients in TAM plus PROP 10 mg experienced significant reductions in micturitions per 24 h \( (P = 0.0261) \), urgency episodes per 24 h \( (P = 0.0093) \), IPSS storage subscore \( (P = 0.0465) \), and IPSS urgency subscore \( (P = 0.0252) \). Compared with the TAM group, TAM plus PROP 20 mg patients had significantly increased postvoid residual volume \( (P = 0.0325) \).

### 3.3. Safety and tolerability

Adverse events that were reported in 14 out of 515 patients during Treatment I included: liver dysfunction, ejaculation failure, dizziness, orthostatic hypotension, gastric discomfort, diarrhea, urticaria, fever elevation, drug eruption, dry mouth, and constipation. Diarrhea was reported by three patients, the most frequent adverse event. In the Treatment II period, adverse events were reported by 16 of the 214 patients (Table 3). No patients in the TAM group reported adverse events. Five patients in TAM plus PROP 10 mg each reported different events: dry mouth, increased postvoid residual volume, blurred vision, constipation, or dizziness. Eleven patients in the TAM plus PROP 20 mg group reported dry mouth \( (n = 3) \), constipation \( (n = 2) \), urinary retention \( (n = 1) \), voiding difficulty \( (n = 1) \), blurred vision \( (n = 1) \), and loss of consciousness \( (n = 1) \).

### 4. DISCUSSION

BPH patients who have concurrent symptoms of BOO and OAB recently have been recommended to treatment that combines an \( \alpha \)-blocker with anticholinergics. Results from previous studies support this combination treatment in men with both BPH and OAB. Athanassopoulos et al.\(^6\) reported that TAM combined with tolterodine significantly improved symptoms of storage without compromising urine outflow compared to TAM alone in

### TABLE 1. Demographics and baseline clinical characteristics

<table>
<thead>
<tr>
<th>Age group</th>
<th>T (n = 60)</th>
<th>T + P10 (n = 60)</th>
<th>T + P20 (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>70.0 (8.1)</td>
<td>70.9 (8.7)</td>
<td>69.8 (7.6)</td>
</tr>
<tr>
<td>Range</td>
<td>51–85</td>
<td>52–85</td>
<td>57–90</td>
</tr>
<tr>
<td>50–64</td>
<td>16 (26.7)</td>
<td>14 (23.3)</td>
<td>18 (29.0)</td>
</tr>
<tr>
<td>65–74</td>
<td>26 (43.3)</td>
<td>24 (40.0)</td>
<td>25 (40.3)</td>
</tr>
<tr>
<td>≥75</td>
<td>18 (30.0)</td>
<td>22 (36.7)</td>
<td>19 (30.6)</td>
</tr>
</tbody>
</table>

### TABLE 2. The change in micturitions per 24 hours at week 12

<table>
<thead>
<tr>
<th>Change in micturitions per 24 h†</th>
<th>T (n = 60)</th>
<th>T + P10 (n = 60)</th>
<th>T + P20 (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>−0.82 (1.84)</td>
<td>−1.89 (2.13)</td>
<td>−1.20 (2.86)</td>
</tr>
</tbody>
</table>

### TABLE 3. Adverse events (safety population)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>T (n = 60)</th>
<th>T + P10 (n = 60)</th>
<th>T + P20 (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blurred vision</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Increased postvoid residual volume</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Voiding difficulty</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

\( ^{†} \)Average for at least 2 days. SD, standard deviation; T, tamsulosin 0.2 mg; T + P, tamsulosin 0.2 mg propiverine 10 mg; T + P20, tamsulosin 0.2 mg propiverine 20 mg.
patients with BOO+ detrusor overactivity (DO) confirmed urodynamically. Moreover, the symptomatic improvement substantially raised QOL scores.

Lee et al.\(^7\) reported that 24 (35%) of 68 men with BOO + DO confirmed urodynamically had improved symptoms on doxazosin alone, while 44 (65%) did not improve. Thirty-two (73%) of these 44 men with BOO + DO, who did not respond to treatment with doxazosin alone, experienced symptomatic improvements (>3-point reduction in total IPSS) after 3 months of treatment with doxazosin and tolterodine. In our TAABO study 214 (41.6%) of 515 men with BPH + OAB had no symptomatic improvement on TAM alone in the Treatment I period. This no response rate of 41.6% on TAM alone was inconsistent with the no response rate of 65% in the study by Lee.\(^7\) Key differences between the studies were inclusion of patients based on symptomatic and urodynamic criteria. Lee et al.\(^8\) studied a further 211 patients with symptoms of BOO + OAB confirmed urodynamically. Sixty-nine patients were treated by doxazosin alone and 142 by doxazosin and PROP for 2 months. The combination therapy improved voiding frequency, voided volume, symptoms of IPSS storage and patient satisfaction versus doxazosin monotherapy. Yokoyama, et al.\(^9\) studied the efficacy and safety of \(\alpha_1\)-blocker naftopidil monotherapy, PROP monotherapy, and combination therapy of naftopidil with PROP for 4 weeks in 66 patients who had male LUTS that suggested BPH and concomitant OAB. Combination therapy was the most effective treatment.

TAABO was designed to evaluate the safety and efficacy of combination therapy of the \(\alpha_1\)-blocker TAM and the anticholinergic PROP in men suffering LUTS from both BPH and OAB. In TAABO, PROP with combined anticholinergic and calcium antagonistic actions\(^10\) was used because it was available as the most commonly prescribed drug with anticholinergic action in Japan in 2004. This was a randomized, controlled study to compare efficacy and safety in the three treatment groups using a bladder diary to document OAB symptoms. Randomization was conducted through a website.

Overall, Treatments I and II were found to be safe and well tolerated. During Treatment II, most adverse events were mild or moderate, and considered associated with PROP. The most frequently reported adverse event was dry mouth, reported by one patient in the TAM plus PROP 10 mg group and by three in the TAM plus PROP 20 mg group. Constipation and increased postvoid residual volume were reported by one patient in the TAM plus PROP 10 mg group and by two in the TAM plus PROP 20 mg group. There was one case of urinary retention among TAM plus PROP 20 mg patients that required an indwelling catheter. One patient treated with TAM plus PROP 10 mg experienced dizziness that was classified as an adverse event associated with TAM.

There has been concern that the inhibitory effect of antimuscarinic agents on detrusor muscle contraction could aggravate difficulty voiding, increase postvoid residual volume or cause urinary retention. In TAABO, postvoid residual volume was significantly increased from baseline in all three treatment groups at week 12. Postvoid residual volume increased, respectively, by 11.9, 29.7, and 31.9 mL in all three treatment groups. A significant increase was found between the TAM and TAM plus PROP 20 mg groups. Careful management for patients with more than 100 mL of postvoid residual volume during combination therapy of an \(\alpha_1\) blocker plus PROP is clinically important.

In TIMES\(^4\) a combination of TAM and tolterodine was more effective than TAM monotherapy, and was similarly tolerated in men with BPH and OAB. The combination arm found significant improvements against PBO in how patients perceived the benefits of treatment, in micturitions and urgency per 24 h, but was not significant versus TAM monotherapy. In the VICTOR study,\(^5\) TAM was combined with solifenacin and therapy decreased micturitions and urgency per 24 h, with a significant improvement relative to TAM monotherapy in urgency only at week 12. In TAABO, two combination groups were compared with the \(\alpha\)-blocker TAM alone. Compared with the TAM group, patients who received TAM plus PROP 10 mg had significantly fewer micturitions (\(P = 0.0261\)) and urgency per 24 h (\(P = 0.093\)), and lower IPSS storage (\(P = 0.0465\)) and IPSS urgency subscores (\(P = 0.0252\)) by week 12. Exact reasons of no significant results on micturitions per 24 h, urgency episodes per 24 h, IPSS storage subscores and IPSS urgency subscore at 12 week in TAM plus PROP 20 mg group remains to be unknown. One possible explanation would be that PROP 20 mg inhibits actions of acetylcholine released from postganglionic parasympathetic axons innervating the bladder, suppresses detrusor activity with increased postvoid residual volume and produces no significant results. While PROP 10 mg may inhibit predominantly actions of non-neuronal ACh released from urothelium contributing to the pathophysiology of OAB\(^11\) and produce significant results.

The safety and efficacy of TAM plus PROP 10 mg may not be comparable with real clinical practice treating patients with large postvoid residual volume, detrusor underactivity, and aging bladder. A previous study has suggested that combination therapy of an \(\alpha_1\) blocker plus PROP may be more useful in patients with a maximum flow rate of 10 mL/sec or more or patients with a residual urinary volume of 50 mL or below.\(^2\) Important inclusion criteria of TAABO in Treatment II were postvoid residual volume less than 100 mL and maximum urinary flow rate more than 5 mL/sec in a total voided volume greater than 150 mL. In conclusion, the primary objective of the TAABO study was to assess the effectiveness and safety of therapy when the \(\alpha_1\)-blocker TAM was combined with the anticholinergic PROP in men suffering from LUTS with both BPH and OAB. The results demonstrated that combination therapy of TAM and 10 mg of PROP might provide more benefit for men with both BPH and OAB than TAM monotherapy.

**Disclosure**

There are no financial or commercial interests for the authors of the present paper.
REFERENCES


APPENDIX

The TAABO Study Group:
Akita City Hospital, Ashiya Medical Community
Sakamoto Urology, Bange Kousei General Hospital, Boku Urology Clinic, Daigakumae Clinic Sasagawa In, Dokkyo Medical University, Dokkyo Medical University Koshi-
gaya Hospital, Ehime Rosai Hospital, Fujita General Hos-
pital, Fujita Health University Hospital, Fukuda Urological
and Dermatological Clinic, Fukui Red Cross Hospital,
Fukushima Medical University Hospital, Fukushima Red
Cross Hospital, Furuya Hospital, Hamamatsu Uni-
versity School of Medicine University Hospital, Hanawa
Kousei Hospital, Hokkaido Prefecture Esashi Hospital,
Hokkaido University Graduate School of Medicine/School
of Medicine, Hokushin General Hospital, Hyogo Reha-
bilitation Center, Ibara Urology and Nephrology Clinic,
Ina Central Hospital, Ishii Clinic, JA Shizuoka Kohseiren
Enshu Hospital, Japanese Red Cross Kyoto Daini Hospital,
Japanese Red Cross Medical Center, Juntendo Univer-
sity Urayasu Hospital, Jyuzen General Hospital, Kaetsu
Hospital, Kagawa University Hospital, Kawahara Urolo-
ic Clinic, Kawahara Urology and Nephrology Clinic,
Kawasaki Medical School Hospital, Kawasaki Rinko Gen-
eral Hospital, Kitano Urological Clinic, Kiyota Urological
Clinic, Kosei General Hospital, Kumamoto University
Hospital, Kurosu Hospital, Maruyama Hospital, Masuko
Memorial Hospital, Nagano Matsushiro General Hospital,
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Medicine, Naka Clinic, Nara Prefectural Nara Hospital,
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National Hospital Organization Kobe Medical Center,
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Hospital, Okayama University Hospital, Saku Hospital,
Shinshu University Hospital, Shio Urological Clinic, Suna-
gawa City Medical Center, Tohoku Kosai Hospital, Tokai
University Oiso Hospital, Tonan Hospital, Toshima Hospi-
tal, Tsujino Clinic, University Hospital Kyoto Prefectural
University of Medicine, University of Fukui Hospital, Uro-
logic Clinic Imari, Usuda Clinic, Yamanashi Prefectural
Central Hospital, Yamanashi University Information Pro-
cessing Center, Yasuda Urological Clinic, Yonezawa City
Hospital.