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UROLOGY - ORIGINAL PAPER

β3-Adrenoceptor agonist mirabegron is effective for overactive bladder that is unresponsive to antimuscarinic treatment or is related to benign prostatic hyperplasia in men

Hideo Otsuki · Takeo Kosaka · Kenzo Nakamura · Junnji Mishima · Yoshitaka Kuwahara · Takuji Tsukamoto

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Abstract
Purpose To investigate the safety and efficacy of mirabegron for patients with overactive bladder (OAB) that is unresponsive to antimuscarinic agents or is related to benign prostatic hyperplasia (BPH).
Methods Fifty-two newly diagnosed OAB patients (M group) and 45 patients with OAB that was unresponsive to antimuscarinics (S group) received mirabegron 50 mg once daily and were evaluated by OAB symptom score (OABSS), IPSS-QOL index, and IPSS at the time of baseline, 4 and 8 weeks. Newly diagnosed OAB patients treated with antimuscarinic agents were compared as controls.
Results Mirabegron was effective for 85.2 % in M group. Significant improvements were seen in each domain of OABSS, and there was no significant difference with antimuscarinic therapy. Mirabegron was efficacious for 61.6 % of S group, and significant decreases of OABSS and IPSS-QOL index were observed. Significant improvements were also seen in voiding symptoms in men. Post-void residual urine volumes before and after treatment were 32.1 and 34.8 ml, and 26.2 and 31.3 ml in M and S group, respectively, and there was no significant difference. The incidence of adverse events was 8.4 %, although none were serious, and the patients recovered spontaneously after mirabegron was discontinued.
Conclusion The present study suggests mirabegron is as effective as antimuscarinics for OAB. It improves OAB symptoms in patients with OAB for which antimuscarinic agents are insufficient. This study revealed that mirabegron improves not only OAB symptoms related to BPH, but also voiding symptoms in men. Low and mild incidences of side effects support the safe utility of mirabegron.

Keywords Overactive bladder · β3-Adrenoceptor · Mirabegron · Male OAB · Antimuscarinics

H. Otsuki (✉) · T. Kosaka · K. Nakamura · Y. Kuwahara · T. Tsukamoto
Department of Urology, Nagakubo Hospital, 6907-1, Yaho, Kunitachi, Tokyo 186-0011, Japan
e-mail: hideotsuki2004@hotmail.com

T. Kosaka
Department of Urology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

J. Mishima
Mishima Hinyokika Clinic, 3-3-1, Shinmachi, Ome, Tokyo 198-0024, Japan

Background

Overactive bladder (OAB) is a symptom syndrome presented with urinary urgency with or without urinary frequency or urgency incontinence and causes a deterioration in the quality of life of a patient [1]. Antimuscarinic agents are currently the first-line pharmacotherapy for OAB; however, antimuscarinics

are contraindicated for patients with angle-closure glaucoma, gastrointestinal obstruction, paralytic ileus, myasthenia gravis, severe heart disease, etc. Adverse events resulting from muscarine receptor blockade, that is, dry mouth, constipation or visual disorder, are inevitable in some patients. It was reported that 64–89 % of patients discontinued one or more OAB medication because the therapy did not produce the treatment benefit expected [2, 3]. Moreover, suppressing detrusor activity with antimuscarinic effects might cause urinary retention [4], especially in men with a benign prostatic hyperplasia (BPH). Therefore, a new drug without the adverse events above has been desired.

Since it was revealed that β3-adrenoceptor acts as a subtype of relaxation of detrusor, β3-adrenoceptor is considered to be one of the targets of OAB pharmacotherapy [5–7]. Another action of β3-adrenoceptor agonist is to enhance the storage function of the bladder with less effect on detrusor pressure during micturition and post-void residual urine volume [8, 9]. As a result, mirabegron improves urinary urgency, frequency, and urgency incontinence. The usefulness of β3-adrenoceptor agonist was verified both in vitro and in vivo [10, 11]. Mirabegron appeared on the Japanese market in September 2011, and it provides a new treatment option for OAB.

Women have been the main objects of most OAB studies so far. Although it is clear that mirabegron is effective for OAB symptoms according to the results of the phase 3 trial, the main objects of the study were females. No data are available on the efficacy of mirabegron for OAB males, especially with BPH.

Here, we report the safety of mirabegron and its efficacy for treating OAB compared to antimuscarinic agents. We investigated the effectiveness of mirabegron for patients with OAB that cannot be managed with antimuscarinics and for men with OAB related to BPH.

Methods

Inclusion criteria were patients aged 50 years or older having OAB symptoms, who had a sudden desire to urinate, which was difficult to defer, once a week or more and scored two points or more for urinary urgency according to the Overactive bladder symptom score (OABSS) [12]. This prospective study enrolled newly diagnosed OAB patients in the mirabegron group (M group), with those having no contraindications for antimuscarinics as the control group, and OAB patients already treated with antimuscarinic agents having poor therapeutic effects, who converted to mirabegron, as the switching group (S group). Because mirabegron is a new drug, medication more than once every 14 days was not permitted until the end of September 2012 based on Notification No. 107 of the Ministry of Health, Labour and Welfare in Japan. Mirabegron 50 mg once daily was prescribed for those who agreed to the above and came to hospital every 2 weeks. Antimuscarinics (tolterodine, solifenacin, propiverin, or imidafenacin) were prescribed every 4 weeks for the control group ($n = 27$). Men who had OAB symptoms with BPH being treated with an alpha 1-adrenergic receptor antagonist (α1-blocker) were included in this study, but the α1-blocker did not change during this period. Exclusion criteria were patients who had stress urinary incontinence, prostate cancer, bladder cancer, vesical stone, urinary tract infection, interstitial cystitis, polyuria (more than 3 l of urine a day), or post-void residual urine over 100 ml.

The period of this study was 8 weeks. Evaluation was performed at the time of baseline, 4 and 8 weeks of medication. Adverse events were recorded throughout the period. In the control group, only patients who were evaluated at 8 weeks not to have side effects were registered and data were used for comparing effectiveness with the M group.

The OABSS is a 4-item questionnaire that collectively expresses OAB symptoms with a single score [12]. The main subjective symptoms evaluated in this study were OABSS, IPSS-QOL index, and IPSS in men. Post-void residual (PVR) urine volume was measured using transabdominal ultrasound before and 4 weeks after starting medication. Prostate volume was measured by transrectal ultrasound in men. Those who switched from mirabegron to another medicine or discontinued follow-up before 8 weeks were only included in the safety evaluation. The ethics committees of both Nagakubo Hospital and Mishima Hinyokika Clinic approved this clinical study.

Statistic analysis was performed using Wilcoxon signed-rank test or Student's t-test with $p < 0.05$ considered statistically significant.

Results

Patients

One hundred and forty-three patients were enrolled for mirabegron treatment (M and S group). Sixty-four cases were enrolled in the M group, but 6 and 3 patients stopped treatment due to the lack of treatment benefits and adverse events, respectively, and 3 cases were lost for follow-up; therefore, 52 patients were evaluated in the M group. Seventy-nine cases having a history of OAB treatment with antimuscarinics were enrolled in the S group, but 20 and 8 cases ceased treatment due to the lack of treatment benefits and adverse events, and 6 were lost for follow-up; therefore, 45 cases were registered and evaluated in the S group. Eleven patients stopped mirabegron treatment due to side effects. Twenty-seven patients with newly diagnosed OAB were enrolled in the control group. The characteristics of patients are listed in Table 1.

Table 1 Characteristics of the groups and the patients

	M group	S group	Control
N	52	45	27
Female	16	9	9
Male	36	36	18
Age (years)	70.9	74.1	70.0
OABSS at baseline	8.22	8.56	8.14
OABSS at 8 weeks	5.11	6.76	4.18
Mean prostate volume (ml)	28.1	24.0	30.2
Use of α-blocker	20	15	7
Tamsulosin	9	5	3
Naftopidil	7	7	3
Silodosin	4	3	1
Use of antimuscarinics			
Solifenacin		21[a]	15[b]
Imidafenacin		12[a]	6[b]
Tolterodine		10[a]	4[b]
Propiverine		2[a]	2[b]
Oxybutynin		0	0

OABSS overactive bladder symptom score

[a] Used before the study

[b] Used during the study

Mirabegron is as effective as antimuscarinics for newly diagnosed OAB (Fig. 1)

Mirabegron for newly diagnosed OAB showed significant decreases in the scores for total OABSS, OABSS daytime and nighttime frequency, urinary urgency, urgency incontinence score, and IPSS-QOL index at 4 and 8 weeks ($p < 0.05$). We compared the efficacy of mirabegron for patients with newly diagnosed OAB with antimuscarinic agents (control). No significant differences were seen at 4 and 8 weeks in OABSS total score and each domain between M group and control.

PVR before and after medication in M group was 32.1 and 34.8 ml, respectively, and the difference was not significant ($p = 0.51$). No significant difference in efficacy between men and women was seen at each point.

Mirabegron is effective for OAB that is resistant to antimuscarinics (Fig. 2)

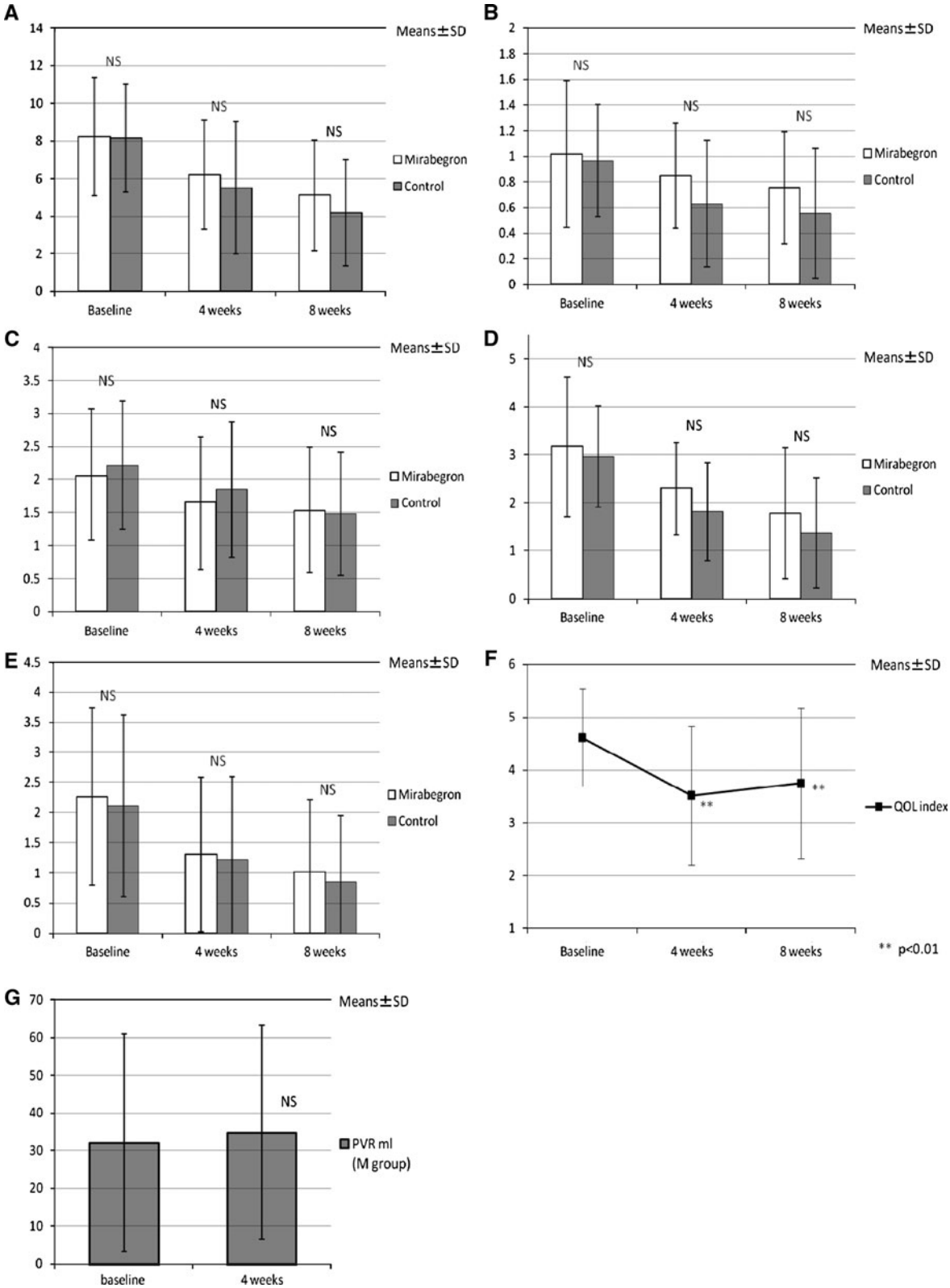
Forty-five patients with OAB that did not respond sufficiently to antimuscarinic agents were switched into mirabegron and evaluated. Scores of total OABSS, OABSS daytime and nighttime frequency, urinary urgency, urgency incontinence score, and IPSS-QOL index significantly decreased at each point. PVR increased slightly from 26.2 to 31.3 ml after medication, but this was not a significant difference ($p = 0.14$). No significant difference for the reduced scores of OABSS between men and women was seen at 8 weeks ($p = 0.47$).

Mirabegron is effective for males with BPH (Fig. 3)

Scores of total OABSS, OABSS 4 items, and IPSS-QOL index decreased significantly in 72 male patients. A comparison between the M group ($n = 36$) and the S group ($n = 36$) showed that nighttime frequency scores were significantly higher in the S group than in the M group. Other evaluations indicated no significant difference at any point.

Investigations on those with prostate size of 30 ml or more and of less than 30 ml denoted no significant differences in OABSS 4 items and IPSS-QOL index.

We compared efficacy with ($n = 35$) and without ($n = 37$) treatment using α1-blocker for BPH. The score for urgency incontinence was lower in patients using α1-blocker, but was not significant ($p = 0.12$).


A
Means±SD
NS
NS
NS
Mirabegron
Control
Baseline
4 weeks
8 weeks
B
Means±SD
NS
NS
NS
Mirabegron
Control
Baseline
4 weeks
8 weeks
C
Means±SD
NS
NS
NS
Mirabegron
Control
Baseline
4 weeks
8 weeks
D
Means±SD
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NS
Mirabegron
Control
Baseline
4 weeks
8 weeks
E
Means±SD
NS
NS
NS
Mirabegron
Control
Baseline
4 weeks
8 weeks
F
Means±SD
**
**
QOL index
Baseline
4 weeks
8 weeks
** p<0.01
G
Means±SD
NS
PVR ml
(M group)
baseline
4 weeks

◀ **Fig. 1** Comparison of OABSS between mirabegron group and control group. Decrease of OABSS total score (**a**) was significant between baseline and evaluations at 4 and 8 weeks in both groups. Comparisons of daytime frequency score (**b**), nighttime frequency score (**c**), urinary urgency score (**d**), and urgency incontinence score (**e**) at each point between mirabegron and control group showed no significant difference according to Student's *t*-test. IPSS-QOL index in the M group (**f**) decreased significantly at each point in the mirabegron group. Post-void residual urine volumes were 32.1 and 34.8 ml before and after treatment in the M group (**g**), and it was not significant difference

IPSS-QOL index showed a significant decrease in patients not treated with α1-blocker at 8 weeks. No significant difference was observed in other items.

IPSS voiding symptom score is the sum of intermittency, weak stream, and straining score, and it declined significantly and gradually at 4 and 8 weeks. It showed no significant difference with or without previous OAB treatment, prostate size, or use of α1-blocker.

Adverse drug events with mirabegron

We experienced 12 cases of side effects deemed to be related to mirabegron during the study: 2 cases of dry mouth and 1 case of palpitation, vertigo, headache, insomnia, dysuria, increased PVR, cystitis, constipation, paresis of the left leg, and erectile dysfunction (ED), and the incidence was 8.4 %. The extent of side effects with the exception of ED was grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0. Because the patient with ED preferred to continue mirabegron in spite of our recommendation to suspend, PDE-5 inhibitor was used, thus ED was grade 2. The other 11 patients recovered spontaneously after mirabegron was discontinued.

Discussion

We showed similar efficacy with β3-adrenoceptor agonist mirabegron for OAB treatment as antimuscarinic agents. We indicated that mirabegron is effective for those whose OAB is not controlled with antimuscarinics in this study. Overall, mirabegron was efficacious for 72.4 % (97/134 cases) of OAB patients. Furthermore, we verified the efficacy for male OAB with or without BPH and improvement of voiding symptoms. The incidence of adverse events was relatively low (8.4 %) and none were serious; therefore, it can be used safely and has good tolerability.

Mirabegron was effective for all of urinary urgency, urgency incontinence, daytime frequency, and nighttime frequency in newly diagnosed OAB patients (M group). In particular, urgency score decreased significantly from 3.2 to 1.5, which means the frequency of urge of once a day dropped to less than once a week. In the present study, the efficacy of mirabegron was not significantly different from that of antimuscarinics; however, each score of OAB symptoms was slightly higher in M group. If a study was conducted on a larger scale, there might be a significant difference between the efficacy of mirabegron and antimuscarinics. Mirabegron did not increase PVR, suggesting that it has almost no negative effect on detrusor contraction or micturition. Mirabegron was effective for 85.2 % (52/61) of patients in our study for newly diagnosed OAB, and this seems to be higher than when treated with antimuscarinic agents.

Mirabegron also improved the symptoms of patients with OAB that were not sufficiently improved with antimuscarinic therapy (S group). However, the reduction of OABSS total score at 8 weeks in the S group was 1.8 and less than 3.3 in the M group, and the effectiveness of mirabegron was less in patients with OAB which is unresponsive to antimuscarinic drugs. Mirabegron might be insufficient for severe overactivity of the bladder; however, mirabegron was 61.6 % effective for patients with OAB who were not being managed with antimuscarinics in our study. The fact that it can be used for patients with contraindications to antimuscarinics provides immeasurable benefits for those patients with OAB and a great impact on the treatment options for OAB. On the other hand, our study revealed that 38.4 % of OAB patients do not respond to mirabegron as well as to antimuscarinics. This subject requires further elucidation.

Mirabegron ameliorates OAB symptoms in men. There is no significant difference in effectiveness for OAB that was unresponsive to antimuscarinic medication with the exception of efficacy for nocturia. Severe nighttime frequency might not be managed with mirabegron as well as with antimuscarinics. We speculate that another cause of mirabegron insufficiency might be an expression change or degeneration of mechanical sensor, chemical receptor, or nerve fibers resulting from a previous antimuscarinic blockade.

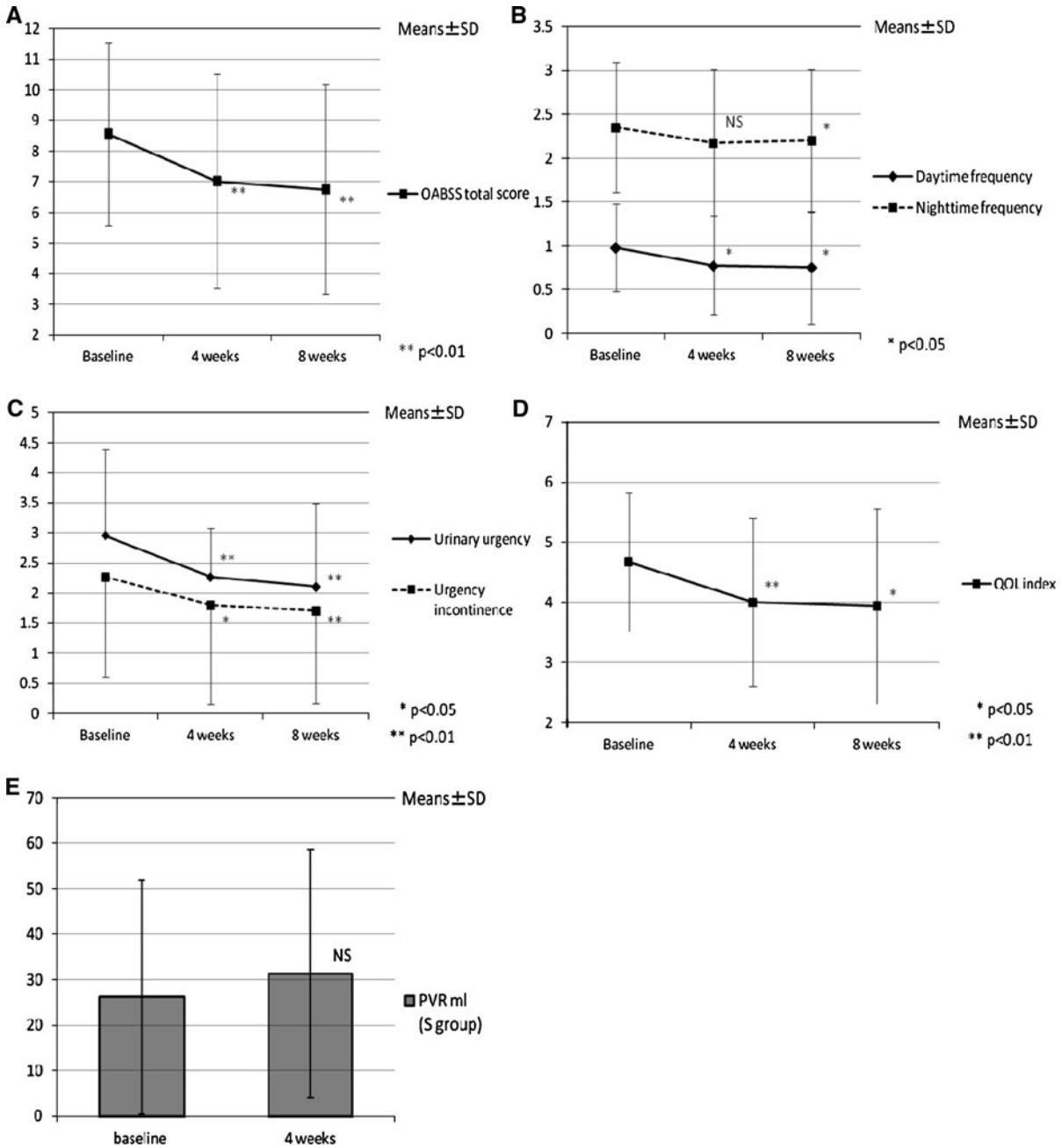

Fig. 2 Change of OABSS and IPSS-QOL index in the switching (S) group. Decrease of OABSS total score (**a**), daytime and nighttime frequency score (**b**) and urinary urgency and urgency incontinence score (**c**) was significant between baseline and evaluations at 4 and 8 weeks in the S group. IPSS-QOL index in the S group (**d**) decreased significantly at each point. Post-void residual urine volumes were 26.2 and 31.3 ml before and after treatment in the S group (**e**). It did not increase significantly with mirabegron

Those treated with α1-blocker for BPH had better urgency incontinence than those not treated with α1-blocker. Combining mirabegron with α1-blocker might be effective for male wet OAB. Similar benefit of combination therapy of doxazosin with tolterodine in men with BPH and OAB was reported [13]. Adding mirabegron to α1-blocker for treating lower urinary tract symptoms might contribute to a deterioration of

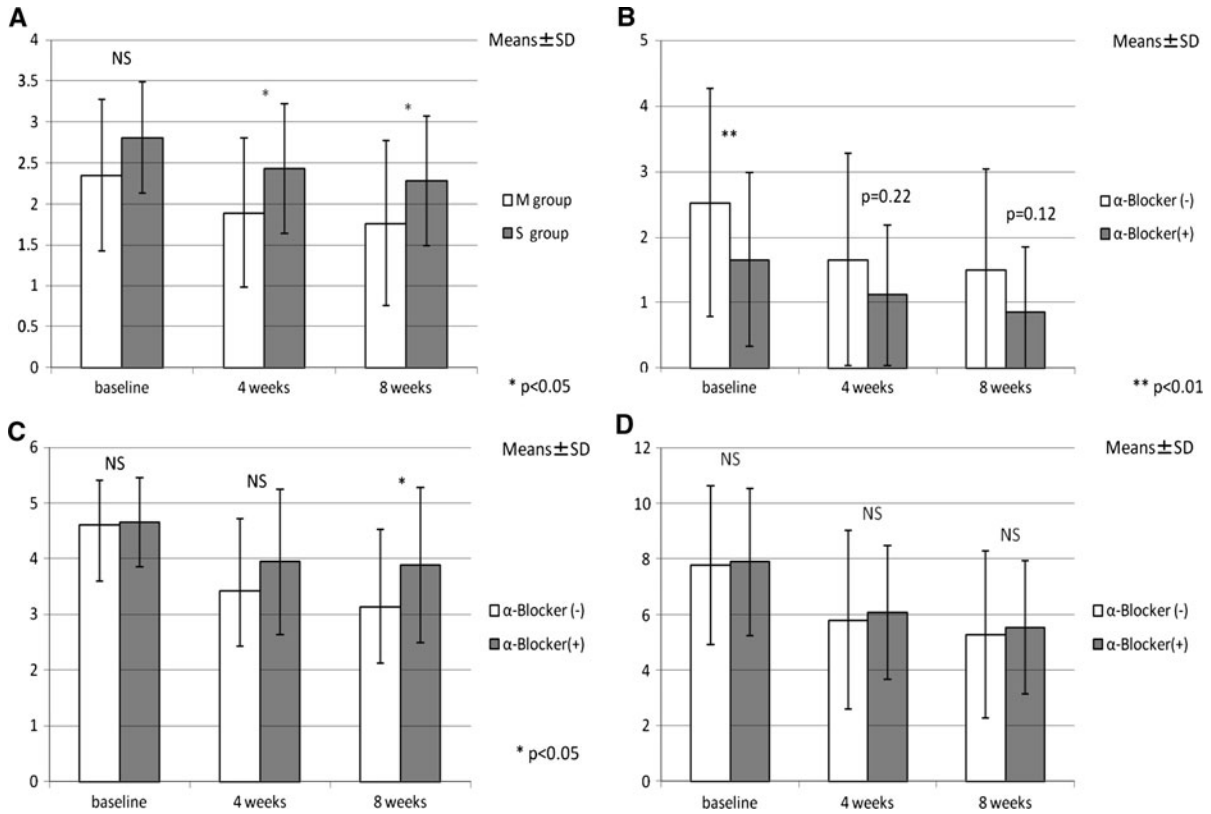

Fig. 3 Key graphs of changes of OABSS and IPSS in men. OABSS nighttime frequency score between M and S group (**a**). The score in S group was significantly higher than that of M group in the evaluations at 4 and 8 weeks. Change of urgency incontinence score with or without BPH treatment by α1-blocker (**b**). The score was higher in patients not receiving α1-blocker than men treated for BPH with α1-blocker. Change of IPSS-QOL index with or without BPH treatment by α1-blocker (**c**). QOL index was lower in patients not treated with α1-blocker at 8 weeks. Sum of IPSS voiding symptom scores with or without BPH treatment by α1-blocker (**d**). Voiding symptom scores are the sum of the scores for intermittency, weak stream, and straining, and decreased significantly with mirabegron treatment. No significant difference was seen with and without BPH treatment with α1-blocker in voiding symptoms

therapeutic satisfaction in patients treated for BPH. It is of great interest that therapeutic effects differed not with respect to the simple size of the prostate, but in BPH requiring treatment.

Mirabegron meliorated voiding symptoms in men and did not increase PVR. It seems to have almost no negative effects on detrusor contraction and micturition. Antimuscarinic therapy for men with OAB related to BPH is perceived as a potential risk for urinary retention. However, mirabegron is not only safe for male OAB with BPH, but is also effective for ameliorating voiding symptoms.

Side effects occurred in 12 patients (8.4 %): 2 cases of dry mouth and 1 case of palpitation, vertigo, insomnia, headache, dysuria, PVR increase, cystitis, constipation, paresis of the left leg, and ED, but none was serious. According to drug information on mirabegron from Astellas Inc. [14], the incidence of dry mouth or constipation is between 1 and 5 %, and the incidence of palpitation, vertigo, headache, or cystitis is less than 1 %. One case with PVR increase showed 470 ml of post-void residual urine and mirabegron was aborted. He had a history of surgery for rectal cancer and might have had latent bladder insufficiency. We should be careful with patients who have a history of pelvic surgery or functional impairment of the bladder. At least one PVR check after medication is mandatory. However, insomnia, leg paresis, and ED are not listed. It is unclear whether these symptoms are specific to mirabegron. However, we found no serious complications in this series, suggesting that mirabegron has higher tolerability and safety than antimuscarinic drugs.

In our study, OAB symptom score decreased sequentially, and this might imply that a longer period of medication leads to a greater improvement of urinary symptoms. We performed additional evaluations at 12 weeks on more than half of the participants, and some improvements were observed in OAB symptoms (data not shown). The long-term efficacy of mirabegron requires further study.

Patient selection in this study needs further clarification. The current study was neither placebo-controlled nor a randomized study. If necessary, we explained the mechanism, adverse events, and prescription interval of the drug to patients, and allowed some participants to select OAB medication, thus subjects were assigned to either the M group or control group. We did not specify one specific antimuscarinic agent for the control group because we wanted to compare the efficacy of mirabegron with general antimuscarinics; therefore, the choice of medication for the control group was left to each physician. We recognize potential selection bias in this study; however, our study was based on the results of 170 OAB patients, and we think it is sufficiently reliable.

A limitation of the current study was the small number of participants. Because mirabegron is a new medicine, medication more than once every 14 days was not permitted until the end of September 2012 in Japan. Ambulatory care every 2 weeks was necessary to continue mirabegron during our study and was a burden on patients. Some patients rejected mirabegron due to frequent ambulatory care, and others preferred to end mirabegron at week 8. If it were not for this restriction, more patients would have participated in the study.

In conclusion, β3-adrenoceptor agonist mirabegron significantly improved urinary frequency, urinary urgency, and urgency incontinence and had similar efficacy to antimuscarinic agents in our study. Mirabegron was also effective for 61.6 % of patients with OAB resistant to antimuscarinic therapy, and this provides wider range of choice for OAB treatment. Furthermore, the present study revealed the efficacy for OAB that is related to BPH in men, which resulted not only in the amelioration of male wet OAB under combination therapy with α1-blocker, but also in improvement of voiding symptoms. The incidence of adverse drug events was low (8.4 %), and the extent was slight; therefore, tolerance and safety are better than with antimuscarinics. Mirabegron is a very important option for OAB pharmacotherapy.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Abrams P, Kelleher CJ, Kerr LA, Rogers RG (2000) Overactive bladder significantly affects quality of life. Am J Manag Care 6:S580–S590
2. D'Souza AO, Smith MJ, Miller LA, Doyle J, Ariely R (2008) Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. J Manag Care Pharm 14:291–301
3. Benner JS, Nichol MB, Rovner ES et al (2010) Patient-reported reasons for discontinuing overactive bladder medication. BJU Int 105:1276–1282
4. Wein AJ, Andersson KE (2007) Pharmacologic management of storage and emptying failure. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA (eds) Campbell-Walsh Urology, 9th edn. Saunders Elsevier, Philadelphia, pp 2093–2094
5. Igawa Y, Yamazaki Y, Takeda H et al (1999) Functional and molecular biological evidence. Br J Pharmacol 126:819–825
6. Takeda M, Obara K (1999) Evidence for beta3-adrenoreceptor subtypes. J Pharmacol Exp Ther 288:1367–1373
7. Yamaguchi O (2002) Beta3-adrenreceptor in human. Urology 59(5 Suppl 1):25–29
8. Fujimura T, Tamura K (1999) Expression and possible functional role of beta3- adrenoceptor in human and rat detrusor muscle. J Urol 161:680–685
9. Woods M, Carson N (2001) Efficacy of the beta3-adrenergic receptor agonist CL-316243 on experimental bladder hyperreflexia and detrusor instability in the rat. J Urol 166:1142–1147
10. Takasu T, Ukai M, Sato S et al (2007) Effect of (R)-2-(2-aminothiazol-4-yl)-4′-{2-[(2-hydroxy-2-phenylethyl)amino] ethyl} acetanilide (YM178), a novel selective beta3-adrenoceptor agonist, on bladder function. J Pharmacol Exp Ther 321:642–647
11. Gillespie JI, Palea S, Guilloteau V, Guerard M, Lluel P, Korstanje C (2012) Modulation of non-voiding activity by the muscarinergic antagonist tolterodine and the β(3)-adrenoceptor agonist mirabegron in conscious rats with partial outflow obstruction. BJU Int 110(2 Pt 2):E132–E142. doi:10.1111/j.1464-410X.2012.11240.x
12. Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, Yamanishi T, Yamaguchi O, Takeda M, Nishizawa O (2006) Symptom assessment tool for overactive bladder syndrome–overactive bladder symptom score. Urology 68:318–323
13. Lee JY, Kim HW, Lee SJ, Koh JS, Suh HJ, Chancellor MB (2004) Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int 94:817–820
14. Astellas, Betanis (mirabegron) package insert version 3, March 2012. PMDA. http://www.info.pmda.go.jp/downfiles/ph/PDF/80126_2590014F1021_1_02.pdf. Accessed 10 Aug 2012