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Efficacy and persistence of low-dose mirabegron (25 mg) in patients with overactive bladder: analysis in a real-world urological practice

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Abstract

Purpose Mirabegron is a relatively new drug to treat overactive bladder (OAB). The therapeutic doses are between 25 and 100 mg in clinical trials. We aimed to evaluate the efficacy and persistence of low-dose mirabegron (25 mg) in patients with OAB in daily urological practice.

Methods The study was a retrospective consecutive cohort of 177 OAB patients (101 male and 76 female) treated with 25 mg of mirabegron mg since January 2016 to November 2016. The therapeutic outcomes were assessed at baseline, 4, 12, and 24 weeks.

Results Mirabegron usage was associated with a statistically significant decrease in Overactive Bladder Symptom Score, Urgency Severity Score, urge urinary incontinence, International Prostate Symptom Score (both storage and voiding symptom) at 4-week follow-up, and the therapeutic effects were further improved at 12- and 24-week follow-up. Among them, 118 patients (66.7%) and 84 patients (47.5%) were maintained on mirabegron therapy for more than 3 and 6 months, respectively. However, 29 patients (16%) had poor response with drug discontinuation within 3 months and 8 patients (4.5%) stopped medication due to adverse effects. The overall side effect was 10.2%, and the most common side effect was elevated blood pressure (2.8%) and increased post-void residual (2.8%). Between male and female patients, there was no statistical difference of symptom improvement and drug persistence rate.

Conclusions Low-dose mirabegron (25 mg) improves clinical outcomes in two-thirds of OAB patients with good safety profile and high persistence in daily urological practice. The therapeutic effect is similar between the genders.

Keywords Efficacy · Mirabegron · Overactive bladder · Persistence

Introduction

Overactive bladder syndrome (OAB), characterized by urgency, frequency with or without urinary urge incontinence (UUI), is a common medical condition with significant impact on quality of life across the world [1]. Worldwide prevalence ranges from 2.1 to 44% by different studies [2–5]. A recent internet-based study shows that 20.8% (women: 22.1%; men: 19.5%) of the population aged ≥ 40 years in China, Taiwan and South Korea fulfilled the overactive bladder symptom score criteria for OAB [6].

Treatment goals of OAB include reducing the bothers of symptoms and providing meaningful benefits to patients [7]. Currently, antimuscarinic agents are the mainstay pharmacotherapy for the treatment of OAB; they block muscarinic (M2/M3) receptors located on the urothelium, interstitial, and detrusor muscles and afferent nerves [8]. However, antimuscarinics lead to common and bothersome adverse effects such as dry mouth, constipation, headache, and blurred vision [9]. A previous antimuscarinic persistence and adherence study revealed only 28–58% patients maintained the therapy at 3 months and 20–40% at 6 months. There were 65–86% of OAB patients discontinuing antimuscarinics over a 12-month period and the most common factors reported were inadequate symptom control and/or intolerable adverse effects [10].

β3-Adrenoceptor has been identified in the human bladder and promotes detrusor relaxation and urine storage [11, 12]. Mirabegron is a potent and selective

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β3-adrenoceptor agonist for the treatment of OAB being well-tolerated [13–16]. The therapeutic doses have been reported between 25 and 100 mg in clinical trials [17, 18]. Most phase II and phase III studies of mirabegron enrolled more female OAB patients (67–91%) [15, 17, 18] and the results had mixed outcome from both genders. In Taiwan, the recommended starting treatment dose is 25 or 50 mg. In this study, we aimed to evaluate the efficacy and persistence of low-dose mirabegron (25 mg) in patients with OAB and the therapeutic outcome for each gender in daily urological practice in a tertiary referral center.

Materials and method

Patient enrollment

The retrospective consecutive cohort enrolled 177 OAB patients (101 males and 76 females) ≧ 18 years in a tertiary referral center. The study included patients who had visited our hospital with OAB symptoms as chief complaint between January 2016 and November 2016. The patients were either treatment naïve (without previous pharmaceutical therapy) or had received previous antimuscarinic agent but with poor medical response or intolerable side effect. Concomitant alpha blocker was allowed before enrollment but we did not change the prescription during the study period. Patients with active urinary tract infection, urinary tract stone, recent genitourinary tract operation within 3 months, stress urinary incontinence, and neurogenic detrusor overactivity were excluded. The study was approved by Chang Gung Memorial Hospital IRB (No. 20170005180).

Patient follow-up and efficacy/safety assessment

The evaluation tools included questionnaires with International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), Urgency Severity Score (USS), Patient Perception of Bladder Condition (PPBC), and Quality of Life (QOL). The questionnaires were evaluated at baseline, 4, 12, and 24 weeks. The uroflow study and post-void residual urine as detected by sonography were also performed at baseline and reassessed at every visit. Since the mirabegron was a new drug for OAB, we extended the study with questionnaire and uroflowmetry exam for 6-month long as possible, which was longer than the daily practice of OAB follow-up. Adverse effects such as elevated blood pressure, headache, dizziness, acute urinary retention or GI symptom including constipation, and diarrhea were recorded.

Statistical analyses

The data were analyzed using software with SPSS 22.0. The changing of symptom score and parameter in uroflow study and post-void residual urine at baseline and every visit after treatment was compared with generalized estimated equation. The treatment responses in each gender and subgroup were also analyzed with generalized estimated equation. The level of significance was considered as $p < 0.05$.

Result

From January 2016 to November 2016, there were 101 male (57.1%) and 76 female (42.9%) patients enrolled in this study. The baseline patients' characteristics are listed in Table 1. The female patients were younger and the baseline IPSS voiding subscale was lower compared with male patients. Fifty-six patients (31.6%) were refractory to antimuscarinics and 26 patients (14.7%) had previous adverse effect to antimuscarinics. The symptom scores showed improvement at 4 weeks after therapy (IPSS storage symptom: 8.2 ± 0.3–6.2 ± 0.3, IPSS voiding symptom: 7.1 ± 0.6–5.2 ± 0.5, OABSS: 8.0 ± 0.3–6.4 ± 0.3, UUI sub-score in OABSS: 1.6 ± 0.2–1.2 ± 0.2, USS: 2.1 ± 0.1–1.6 ± 0.1, PPBC: 3.0 ± 0.1–2.6 ± 0.1, QoL: 4.4 ± 0.1–4.0 ± 1.2, all $p < 0.05$. Fig. 1a–g) and nocturia also improved after treatment (2.8 ± 0.1–2.1 ± 0.2 at 4 weeks, $p < 0.05$. Fig. 1h).The therapeutic effects were further improved at 12- and 24-week follow-up. Except for the voiding symptom being better in the female group, the improvement in OABSS (including UUI subscale), IPSS storage symptom, UUS, nocturia, PPBC, and QoL were not statistically different between both genders. There were 25.7% of male and 26.3% of female patients response to mirabegron therapy with daytime frequency < 8 times while final visit.

Table 2 showed the baseline and post-treatment voiding volume, maximal flow rate, and post-void residual. The baseline maximal flow rate was lower in male patients. After mirabegron treatment, there was no significant change of voiding volume, maximal flow rate, or post-void residual urine at 4–24 weeks of follow-up no matter what gender.

The overall adverse event of treatment was 10.2% (18/177; Table 3). The most common side effect was elevated blood pressure (5 patients, 2.8%) and increased residual urine (5 patients, including 3 males and 2 females; 1 male and 2 female had baseline PVR larger than 150 ml). Eight patients (4.5%) stopped medication due to side

Table 1 Baseline characteristics of OAB patients

	Total ($N=177$)	Male ($N=101$)	Female ($N=76$)	p
Age, mean (SD), year	63.1 ± 14.2	65.3 ± 13.3	59.3 ± 16.3	0.015
Refractory to previous AM	56 (31.6%)	39 (38.6%)	17 (22.4%)	0.04
Adverse effect to pervious AM	26 (14.7%)	15 (14.9%)	11 (14.5%)	0.737
Comorbidity				
DM	32 (18.1%)	16 (15.8%)	16 (21.1%)	0.473
HTN	54 (30.5%)	30 (29.7%)	24 (31.6%)	0.668
Diagnosis				
OAB dry	110 (62.1%)	57 (56.4%)	53 (69.7%)	0.208
OAB wet (with incontinence)	67 (37.9%)	44 (43.6%)	23 (30.3%)	
Concomitant alpha blocker use, *N*	53 (29.9%)	41 (40.6%)	12 (15.8%)	0.041
Baseline IPSS total	14.6 ± 0.6	15.5 ± 7.5	13.0 ± 6.1	0.054
Baseline IPSS voiding	6.6 ± 0.5	7.5 ± 5.8	5.0 ± 4.7	0.012
Baseline IPSS storage	8.2 ± 0.3	8.3 ± 3.5	8.0 ± 2.9	0.598
OABSS	8.0 ± 0.3	8.3 ± 0.4	7.6 ± 0.4	0.209
UUS	2.1 ± 0.1	2.0 ± 0.1	2.1 ± 0.2	0.530
UUI (OABSS subscale)	1.6 ± 0.2	1.5 ± 0.2	1.6 ± 0.3	0.692
Nocturia (times)	2.8 ± 0.1	2.9 ± 0.2	2.6 ± 0.2	0.272
PPBC	2.6 ± 0.1	2.9 ± 0.1	3.3 ± 0.2	0.053
QoL	4.4 ± 0.4	4.4 ± 0.1	4.4 ± 0.2	0.859
Post-void residual urine, ml (range)	38.4 ± 4.9 (0–271)	33.9 ± 39 (0–271)	37.0 ± 50.0 (0–243)	0.608

AM antimuscarinics

effects present within days to weeks with symptoms of increased residual urine (5 patients), lower leg edema (2 patients), and elevated blood pressure with dizziness (1 patient). However, there was no acute urinary retention reported during the study period. Among patients with elevated blood pressure, one stopped medication due to intolerance of dizziness and the other four persisted in therapy due to good therapeutic effects and tolerability to transient elevated blood pressure.

There were 118 patients (66.7%) and 84 patients (47.5%) maintaining mirabegron therapy for more than 12 and 24 weeks, respectively. Thirty-four patients (19.2%) asked to discontinue the medication between 12 and 24 weeks due to good response with symptom improvement (Fig. 2). However, 29 patients (16%) had poor response and stopped mirabegron within 1–3 months and then shifted to other therapies. Regarding the drug persistence rate, there was no difference between male and female patients, and there was no other predictive factor (data not shown).

Discussion

The current study revealed that low-dose mirabegron (25 mg) improves clinical outcomes in two-thirds of OAB patients without acute urinary retention; however, 8 patients (4.5%) stopped medication due to side effects and 34 patients (19.2%) asked to discontinue the medication between 12 and 24 weeks even with good response without side effects in daily urological practice. The therapeutic effect was similar for both genders. To our knowledge, publication of 25 mg mirabegron usage longer than 3 months during daily practice is rare.

In phase III clinical trials, mirabegron at daily doses of 50 and 100 mg demonstrated significant improvement versus placebo in treating the symptoms of OAB [14, 16]. The secondary end-point of response rate (defined as 50% decrease from baseline in the mean number of incontinence episodes per 24 h) was 72.0 and 67.6% for 50 and 100 mg, respectively [14]. There was another 12-week phase II study that designed low-dose (25 mg) usage compared with higher dosage (50–200 mg) and found clear dose-dependent efficacy above 50 mg [17]. The secondary end-point of response rate (defined as < 8 time micturitions per day) was 28.7, 27.5, 32.7, and 30.1% for 25, 50, 100, and 200 mg, respectively. However, a meta-analysis study revealed that mirabegron 100 mg had a slight trend toward an increased risk of hypertension (odds ratio 1.41; $p=0.08$) and cardiac arrhythmia (odds ratio 2.18; $p=0.06$) [19]. Another phase III, multicenter study concluded mirabegron 25 and 50 mg were associated with significant improvements at 12 weeks with efficacy of reducing incontinence episodes and micturition frequency compared with placebo. However, 50 mg dosage demonstrated a greater treatment effect than 25 mg [18].

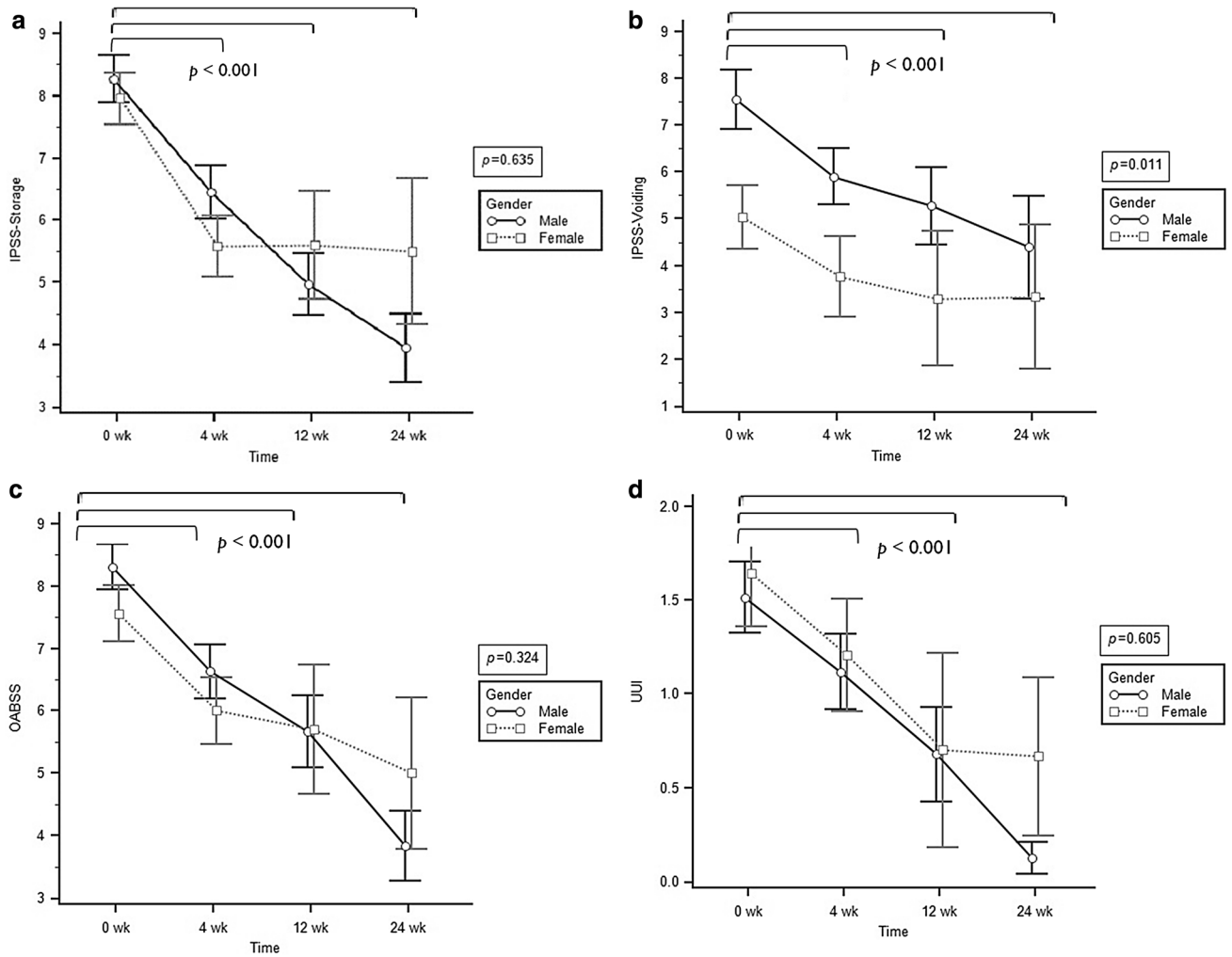

Fig. 1 **a**–**h**. Symptom score change after mirabegron 25 mg treatment **a** IPSS storage, **b** IPSS voiding, **c** OABSS, **d** UUI–OABSS subscale, **e** UUS, **f** PPBC, **g** QoL, **h** nocturia

Based on these studies, the product labeling differs between countries. In US and Canada, the recommended starting dose is 25 mg once daily (QD) with an option to increase to 50 mg. In Japan and Europe, the recommended dose is 50 mg QD with the 25 mg dose reserved for special populations (e.g., those with severe renal impairment or moderated hepatic impairment).The response rate (defined as daytime frequency < 8 times) of current 25 mg mirabegron study is similar with other publications.

Activation of β3-adrenoceptor in the human bladder induces detrusor relaxation and facilitates urine storage [11, 12]. In the current mirabegron low-dose (25 mg) study, we found no matter whether naïve or patients refractory to previous antimuscarinics obtained improvement in both IPSS storage symptoms, OABSS and USS score and IPSS voiding symptoms at 4-week follow-up and the therapeutic effect could get further improvement at 12- and 24-week follow-up. The voiding symptom also showed improvement after treatment. Chapple et al. and Kuo et al. reported a mean reduction of nocturia episodes about 0.5–0.6 times per night with 25 and 50 mg mirabegron, respectively [15, 17]. In our cohort, the female patients had good therapeutic effects on nocturia at week 4; however, the effects decreased at week 12 and 24, which was paralleled the responsive figures of PPBC. It might indicate a good correlation of nocturia with PPBC and QoL. The causes of nocturia include bladder factor, systemic factors, or nocturnal polyuria. The current cohort of female patients has more comorbidity of DM or hypertension, which might reduce the drug effect on nocturia. Compared with other studies that recruited more female OAB patients and showed symptom improvement from mixed female and male gender [15, 17, 18], this current study enrolled more male patients (57.1%) with underlying prostate enlargement and still found a statistically significant improvement in all these parameters of OAB symptoms and also voiding symptoms.

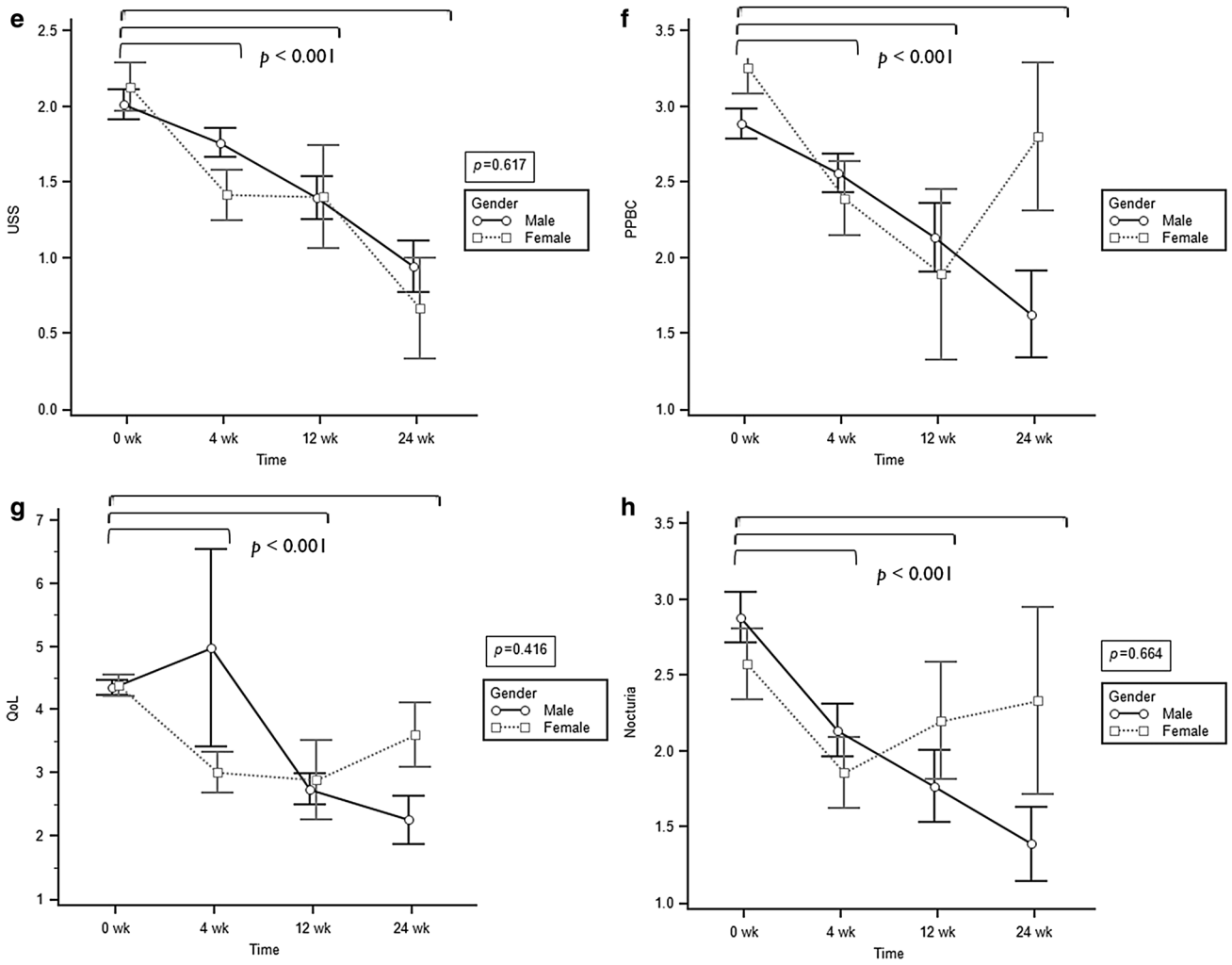

Fig. 1 (continued)

Table 2 Uroflow study and post-void residual urine

	Total	Male	Female	p^a
Voiding volume—0 week	207.3 ± 114.6	192.3 ± 111.9	224.0 ± 118.0	0.714
Voiding volume—4 week	228.3 ± 124.2	228.9 ± 126.6	216.0 ± 127.5	
Voiding volume—12 week	193.8 ± 113.4	169.8 ± 80.3	232.2 ± 163.8	
Voiding volume—24 week	259.2 ± 159.8	257.8 ± 151.3	264.0 ± 204.4	
Q_{max}—0 week	16.6 ± 10.0	14.0 ± 8.3	19.6 ± 11.2	0.138
Q_{max}—4 week	17.2 ± 10.6	16.2 ± 10.4	18.8 ± 11.5	
Q_{max}—12 week	18.1 ± 11.4	14.4 ± 7.8	24.5 ± 15.0	
Q_{max}—24 week	20.1 ± 11.4	16.9 ± 8.3	30.3 ± 14.9	
Post-void residual—0 week	37.6 ± 44.5	36.0 ± 39.4	39.6 ± 50.8	0.158
Post-void residual—4 week	31.7 ± 45.9	26.7 ± 26.5	43.0 ± 75.3	
Post-void residual—12 week	32.6 ± 40.9	32.3 ± 39.2	33.1 ± 45.6	
Post-void residual—24 week	32.0 ± 28.9	30.8 ± 30.3	36.0 ± 26.7	

Voiding volume measured from uroflowmetry

[a]Comparison between change of every visit using generalized estimated equation

Table 3 Adverse effects of treatment

	N
Total	18 (10.1%)
Elevated blood pressure	5 (2.8%)
Headache	1 (0.6%)
Constipation	2 (1.1%)
Diarrhea	2 (1.1%)
Dry mouth	1 (0.6%)
Nausea	1 (0.6%)
Lower leg edema	2 (1.1%)
Acute urinary retention	0 (0%)
Increased residual urine > 50 c.c 4–0 week	5 (2.8%)

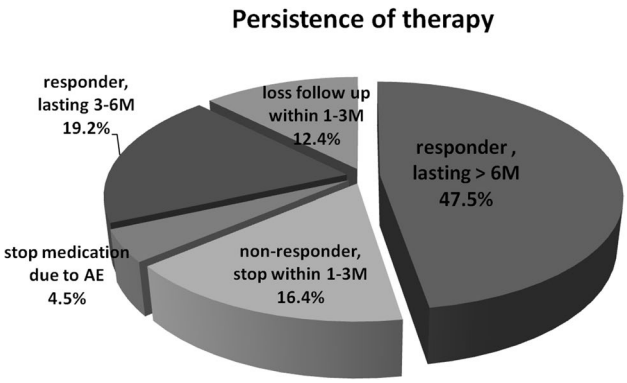

Fig. 2 Treatment response and persistence of therapy

Concern about compromising bladder contraction activity exists in pharmacological therapy for OAB. Two studies reported urodynamic evaluation of mirabegron in women. Both found detrusor overactivity could be suppressed after treatment and the maximal cystometric capacity significantly increased [20, 21]. There was no compromise of peak uroflow rate (Q_{max}) and Pdet.Qmax, so they concluded that this drug usage would not influence voiding function in woman. In this daily urological practice study with a male-predominant cohort, we further showed no reduction of Qmax and no increase of post-void residual urine. However, 5 patients (3 males, 2 females) still experienced increased residual urine and stopped medication even at the low dose of mirabegron.

A previous report showed that the antimuscarinics persistence rate was 28–58% at 3 months, 20–40% at 6 months, and 14–35% at 1 year with different medications due to inadequate symptom control or intolerable adverse effects [10]. The best performance with solifenacin succinate also showed 65% cessation of medication at 1 year. However, real-world experience with mirabegron (25–50 mg) showed 69% persistence at 3 months and 48% at 6 months [22]. Our low-dose cohort also showed a similar result that more than half (66.7%) persisted in beta-3 agonist therapy at 3 months and 84 patients (47.5%) kept up therapy at 6 months. Compared with antimuscarinics, mirabegron actually presented better persistence, adherence, and longer use [23, 24]. Besides different pharmacological action, treatment discontinuation was significantly more likely in women, in patients with more comorbidities, age < 65 year, being treatment-naive, and patients receiving two or more other medications by other multivariant analysis [23]. However, in our cohort, gender or other underlying characteristics could not predict long-term drug persistence. Interestingly, some patients did not like to keep mirabegron even with good therapeutic outcome, and without significant side effects. As OAB is not a life-threatening disease, we suggested that the treatment of OAB could be interrupted at a stable condition in daily urological practice, and patients might ask for discontinuation or restart of treatment.

The expression of β3-adrenoceptor in human smooth muscle is found not only in the bladder but also the heart, gastrointestinal tract, and gallbladder [25]; however, the most common adverse effects relating to mirabegron therapy is hypertension (0.5–11.3%) [15, 26, 27]. Most patients could tolerate this using life style modification or antihypertensive drug titration. Rather than hypertension, dry mouth, and constipation presenting after antimuscarinics use may more affect patient satisfaction and will toward maintaining long-term use. In this series, we tried to find predictive factors of successful treatment but could not find any baseline characteristics (including underling disease, pre-treatment symptom severity, or urodynamic parameters) to predict the therapeutic outcomes. Chapple et al. reviewed the phase II and III studies and found the significant benefit for mirabegron versus placebo was evident at 4 weeks after initiation [28]. Another database analysis advocated that the 30-day gap analysis could correlate with persistence outcome [24]; therefore, the treatment response in the beginning might be the only currently known factor for drug persistence.

There are some limitations in the current study. First, this was a retrospective study and some patients (12%) missed follow-up in the studied period. Second, there were more female patients with OAB dry (69.7%) and relative larger voiding volume (224 ml) representative of less severe disease. This patient bias might influence the overall outcomes. Furthermore, the real outcome of drug discontinuation is unknown as per the patients' will at stable condition of OAB. Further study with longer follow-up is needed to present the real role of low-dose mirabegron for the treatment of OAB.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Because this study is a retrospective chart review study, so informed consent was not obtained from all individual participants.

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