

# Investigation of the reasons for withdrawal from long-term treatment with mirabegron of treatment-naïve Japanese female patients with overactive bladder in the real-world clinical setting

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## Abstract

**Purpose:** The persistence of treatment with mirabegron and the reasons for withdrawal from the treatment among treatment-naïve Japanese female patients with overactive bladder (OAB) were prospectively investigated for 3 years in the real-world clinical setting.

**Materials and Methods:** A total of 62 treatment-naïve Japanese female patients clinically diagnosed with OAB were treated with mirabegron and prospectively followed for 3 years. The persistence rate was estimated using the Kaplan-Meier method. If mirabegron had to be terminated or a patient did not come to the hospital to receive a prescription, the reasons for withdrawal from treatment were determined.

**Results:** The 6-month, 1-year, 2-year, and 3-year persistence rates were 51.6%, 38.7%, 32.3%, and 25.8%, respectively. The most frequent reasons for withdrawal from treatment with mirabegron were symptom resolution (38.7%), deterioration of comorbidity unrelated to OAB (12.9%), lack of efficacy (8.1%), and adverse events (4.8%).

**Conclusions:** The persistence rate of treatment with mirabegron among treatment-naïve Japanese female patients with OAB is low for 3 years in the real-world clinical setting. Many patients discontinue the treatment for various reasons, the most frequent of which is symptom resolution. These findings provide important considerations for clinicians whose patients are continuing medication for OAB.

**Keywords:** Mirabegron, overactive bladder, reasons for withdrawal

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## INTRODUCTION

Overactive bladder (OAB) has been defined by the International Urogynecology Association and the International Continence Society as a syndrome having the symptoms of urgency, with or without urge incontinence,

usually accompanied by frequency and nocturia, in the absence of urinary tract infection (UTI) or another obvious pathology.<sup>[1]</sup> The symptoms of OAB have a negative impact on quality of life.<sup>[2,3]</sup> Antimuscarinic agents are widely and frequently prescribed for the symptoms of OAB.<sup>[4]</sup> However,

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the adherence to and persistence of use of antimuscarinics are poor.<sup>[5]</sup> Mirabegron, an orally active  $\beta_3$ -adrenoreceptor agonist that causes detrusor relaxation only in the storage phase, has been developed for the symptoms of OAB.<sup>[6]</sup> Three large, randomized, Phase III trials of mirabegron have demonstrated its significant efficacy compared with a placebo, efficacy equal to that of tolterodine and an acceptable level of side effects.<sup>[7-10]</sup> Furthermore, Phase III trials have also demonstrated the safety and tolerability of 12-month treatment with mirabegron.<sup>[11,12]</sup> Some reports have demonstrated the persistence rate of treatment with mirabegron compared to antimuscarinics.<sup>[13-16]</sup> Although the results for the persistence rate of treatment with mirabegron were up to 12 months in their reports, a further long-term investigation is required. In addition, the reasons for withdrawal from treatment with mirabegron have not been completely elucidated.

In the present study, we prospectively investigated the long-term persistence rate of treatment with mirabegron among treatment-naïve Japanese female patients with OAB in the real-world clinical setting. We also investigated the reasons for withdrawal from the treatment, including that by patients who did not come back to the hospital.

## MATERIALS AND METHODS

This prospective, single-centre, observational study in the real-world clinical setting was conducted by one particular physician at our hospital, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This hospital is the only one in the area with Urology Departments and there is no private urology clinic. It was approved by the institutional review board of our hospital (No. 2011-1). All participants provided voluntary informed consent before enrollment. The primary objective was to investigate the reasons for withdrawal from the treatment with mirabegron. The secondary objective included investigating the persistence rate of treatment with mirabegron. Due to fact that there is a warning to avoid administering mirabegron to patients of reproductive age to the degree possible in Japan, all postmenopausal treatment-naïve Japanese female patients who visited the hospital for the symptoms of OAB, including urinary frequency, nocturia, urgency, or urge incontinence, were clinically diagnosed with OAB, and who agreed to participate between October 2011 and July 2014 were eligible for this study. At baseline, patients underwent taking of a medical history, physical examination including vital signs, and urinalysis. Patients with neurogenic OAB were included in this study.

The OAB symptom score (OABSS) was determined using a self-administered questionnaire.<sup>[17]</sup> A frequency volume chart (FVC) was recorded over 2 days. The postvoid residual volume (PVR) was measured by transabdominal ultrasound (BVI 6100, Verathon Inc., Bothell, USA). Patients with premenopausal, UTI, large PVR volume (more than 150 mL), a previous treatment history for OAB, and contraindications to the use of mirabegron were excluded from this study. Patients were prescribed 50 mg of mirabegron once daily as this is the routine prescription in Japan. They were prospectively followed at 1-or 2-month intervals for 3 years. During follow-up, the OABSS, vital signs and adverse events were recorded at each visit. The FVC and PVR were recorded at 2 months, and 1, 2 and 3 years. The follow-up of the last patient ended in July 2017.

There was no similar report on mirabegron at the time the research plan was prepared. A study on another medicine for OAB reported that the rate of withdrawal for 52 weeks was 31.3%.<sup>[18]</sup> From that value, we calculated that the necessary sample size need to estimate the rate of withdrawal of the population with an accuracy of  $\pm 10\%$  error, was about 70 patients.

Persistence of treatment with mirabegron was measured by the number of months between the first dispense date and the expected end date of the last refill. The persistence rate was estimated by the Kaplan-Meier method with the use of computer software (JMP<sup>®</sup>, SAS Institute Inc., Cary, USA). If patients decided to terminate treatment during follow-up at the hospital due to adverse effects, lack of efficacy, symptom resolution, etc., the reason was determined from clinical records. Symptom resolution was defined as improvement to the extent to discontinue the medicine. If a patient did not come to the hospital to receive a prescription, the reason for not coming was inquired about by telephone. Discontinuation was the sum of patients who decided to terminate treatment at the hospital and those who did not come to the hospital. It was recorded if a patient who terminated mirabegron for symptom resolution revisited the hospital for the deterioration of the symptoms of OAB and received retreatment with mirabegron during follow-up (for 3 years after administration).

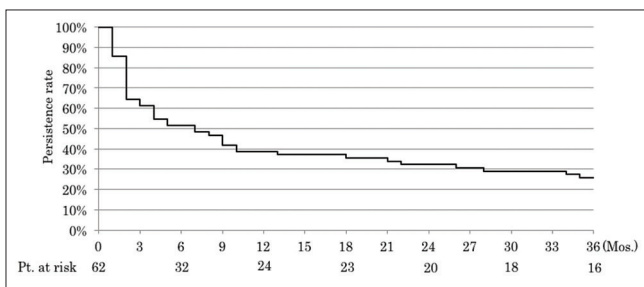
The differences of the mean values of clinical parameters between pre-and post-treatment were analyzed using the paired Student's *t*-test with Bonferroni correction.  $P < 0.05$  were regarded as statistically significant. Statistics were calculated using computer software (JMP<sup>®</sup>, SAS Institute Inc., Cary, USA).

**RESULTS**

A total of 62 Japanese female patients were enrolled. The mean age was 75.8 years, ranging from 54 to 89. Although we did not reach the desired number, the enrollment was closed due to an insufficient number of female outpatients with the symptoms of OAB. While the etiology of OAB of six patients was diagnosed as neurogenic from a history of cerebral infarction, that of the others was diagnosed as nonneurogenic. Patient characteristics at baseline are summarized in the table. All values in the Table 1 are expressed as the mean and standard deviation. The mean OABSS was 7.9, ranging from 3 to 15. On the FVC, the mean daytime frequency, nocturia, urgency and urge incontinence were 7.7, 3.2, 2.0, and 0.8, respectively. The mean voided volume was as small as 157 ml. The mean PVR volume was 14 ml.

After treatment with mirabegron, the total score of the OABSS was significantly improved and maintained for 3 years [Table 1]. The nocturia score, urgency score, and urge incontinence score were significantly improved except at 3 years. On the FVC, the average-voided volume, nocturia, and urgency were improved. However, only the average voided volume at 1 year, nocturia at 2 months and urgency at 2 months reached statistical significance. There was no change of PVR after treatment with mirabegron. There was no change of vital signs after the treatment (data not shown).

Figure 1 shows Kaplan–Meier curve for the persistence rate of treatment with mirabegron over the 3 years. The 6-month, 1-year, 2-year, and 3-year persistence rates were 51.6%, 38.7%, 32.3%, and 25.8%, respectively. In the first 6 months, the persistence rate fell sharply, after which the slope of the graph became more gradual. Sixteen patients (25.8%) continued the same medication for 3 years. Finally, 46 patients (74.2%) discontinued treatment with mirabegron because of for-cause termination in 30 patients (48.4%) and loss to follow-up in 16 patients (25.8%) [Figure 2].

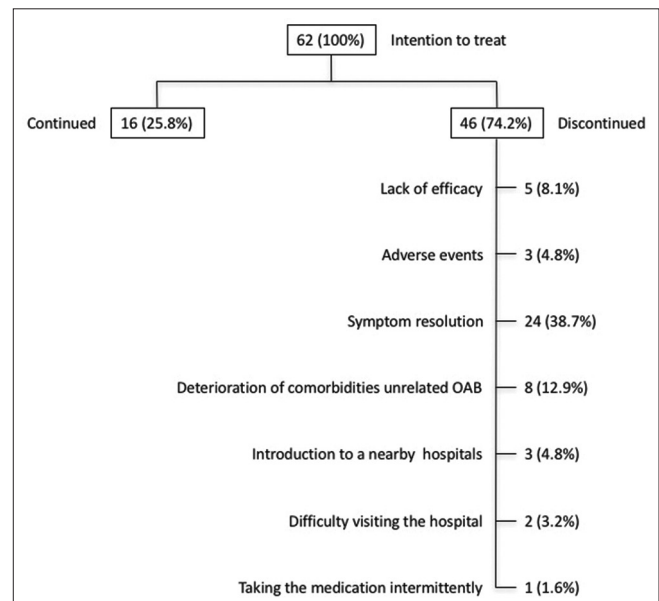


**Figure 1:** Kaplan–Meier curve for the persistence rate of treatment with mirabegron for 3 years. The 6-month, 1-year, 2-year, and 3-year persistence rates were 51.6%, 38.7%, 32.3%, and 25.8%, respectively

Of the 30 patients who decided to terminate the treatment, two terminated the medication because of adverse events (constipation). After the termination of treatment, the constipation was improved. Sixteen patients hoped to terminate the medication because of symptom resolution, five because of lack of efficacy, three because of introduction to a nearby hospital, two because of deterioration of comorbidities unrelated to OAB (liver cirrhosis and polymyalgia rheumatica), and two because of difficulty visiting the hospital.

Of the 16 patients who did not come to the hospital, eight terminated the medication themselves and stopped coming to the hospital because of symptom resolution, six because of deterioration of comorbidities unrelated to OAB (heart failure, colon cancer, liver cirrhosis, dementia, diabetes, and cholecystitis), one because of taking it intermittently and one because of adverse events (rising blood pressure and numbness of hands). After the termination of treatment, the symptoms of the adverse events were improved.

In summary, a total of 24 patients (38.7%) terminated medication because of symptom resolution, 8 (12.9%) because of deterioration of comorbidities unrelated to OAB, 5 (8.1%) because of lack of efficacy, and 3 (4.8%) because of adverse events. The 24 patients who terminated the medication because of symptom resolution had significant improvement of the OABSS at the last visit ( $P < 0.001$ ,  $7.0 \pm 3.3$  at baseline vs.  $3.2 \pm 2.4$  at the last visit).



**Figure 2:** Outcomes of the 62 female patients at 3 years after administration of mirabegron. The most frequent reasons for withdrawal from treatment with mirabegron were symptom resolution (38.7%), deterioration of comorbidity unrelated to overactive bladder (12.9%), lack of efficacy (8.1%) and adverse events (4.8%)

Four patients revisited the hospital and received retreatment with mirabegron for the deterioration of the symptoms of OAB during follow-up (at an average 5 months after termination), while 20 patients never visited our hospital for the deterioration of the symptoms of OAB.

## DISCUSSION

To our knowledge, this is the first prospective study completely revealing all the reasons for withdrawal from treatment with mirabegron among treatment-naïve Japanese female patients with OAB, including the patients who did not come back to the hospital. As OAB is a chronic disease, medical treatment of it usually has to be continued to maintain control of the symptoms.<sup>[19]</sup> The efficacy of the treatment for OAB depends on the adherence to and persistence of use of the prescribed medicines. In Phase III trials of mirabegron, the 12-month persistence rates, which were from 77.2% to 77.5% at 50 mg daily and 78.3% to 78.7% at 100 mg daily, were favorable.<sup>[11,12]</sup> However, these clinical trials had strict inclusion and exclusion criteria and were performed in selected patient populations. Chapple *et al.* reported that the 12-month persistence rate for mirabegron was 38% in a retrospective study of clinical practice.<sup>[15]</sup> Kinjo *et al.* also reported that the 12-month persistence rate for mirabegron was 20.1% in their clinical trial.<sup>[16]</sup> In the present study in the real-world clinical setting, the 6-month, 1-year, 2-year, and 3-year persistence rates were 51.6%, 38.7%, 32.3% and 25.8%, respectively. Thus, they were much lower than in the Phase III trials. Furthermore, the Kaplan–Meier curve for the persistence rate of mirabegron was characteristic. In the present study, the persistence rate fell sharply in the first 6-months, after which the slope of the graph became more gradual. This characteristic was also found in the report of Chapple *et al.* in the real-world clinical setting.<sup>[15]</sup> Many discontinuations of mirabegron took place in the early period. In addition, in a previous study, we prospectively

investigated the persistence rate of solifenacin for similar treatment-naïve female patients with OAB in the real-world clinical setting.<sup>[20]</sup> We found that the 6-month, 1-year, 2-year and 3-year persistence rates were 50.7%, 41.1%, 32.9% and 23.3%, respectively. Although they cannot be directly compared, the persistence rates for mirabegron were almost the same as for solifenacin. Kinjo *et al.* randomized treatment-naïve female patients with OAB to a mirabegron group and a solifenacin group and prospectively compared the persistence rates of the two groups.<sup>[16]</sup> There were no significant differences between them. Consequently, the long-term persistence rates for treatment with mirabegron in the real-world clinical setting were low.

To clarify why the persistence rate for treatment with mirabegron is low, investigation of the reasons for withdrawal from mirabegron is required. In Phase III trials of mirabegron, frequently given reasons for withdrawal were “withdrawal of consent” (7.8%–9.1%) and “adverse events” (5.9%–6.4%).<sup>[11,12]</sup> However, these were results for selected patient populations in strict clinical trials. In the real-world clinical setting, Kinjo *et al.* reported that the reasons for withdrawal in the mirabegron group were “lack of efficacy” (36.8%), “improvement without medication” (23.7%), “lost to follow-up” (15.8%), and “side effects” (7.9%).<sup>[16]</sup> However, it was not clear why 15.8% of their patients did not come back to the hospital. In the present study, the reason given by more than half of the patients who did not come back to the hospital was “symptom resolution.” Overall, the frequency of withdrawal from mirabegron for “symptom resolution” was 38.7%. In contrast, the frequency of withdrawal due to “adverse events” was as low as 4.8%. In our previous study, the most frequent reasons for withdrawal from solifenacin were “symptom resolution” (27.4%) and “adverse events” (20.6%).<sup>[20]</sup> Although they cannot be directly compared, the frequency of withdrawal for “adverse events” was lower in patients treated with

**Table 1: Changes of clinical parameters of the 62 female patients**

Parameters	Baseline (62)	2 months (53)	1 year (24)	2 years (20)	3 years (16)
<b>OABSS</b>					
Daytime frequency score	0.8±0.6	0.7±0.6	0.7±0.6	0.7±0.6	0.9±0.8
Nocturia score	2.6±0.7	2.1±0.9***	1.9±1.0*	2.4±0.8*	2.1±1.0
Urgency score	2.9±1.8	1.5±1.8***	1.1±1.5***	1.2±1.7**	1.9±1.7
Urge incontinence score	1.9±1.8	0.9±1.6***	1.1±1.6***	1.3±1.5*	1.4±1.4
Total score	7.9±3.4	5.2±3.5***	4.8±3.4***	5.5±3.5**	6.0±3.8*
<b>Frequency volume chart</b>					
Average voided volume	157±64	226±243	210±81**	193±84	182±74
Daytime frequency	7.7±2.7	7.0±2.7	6.8±2.4	7.1±3.7	7.7±3.5
Nocturia	3.2±1.6	2.6±1.7***	2.2±1.2	2.6±1.2	2.6±1.9
Urgency episodes	2.0±3.1	1.1±1.7**	0.9±1.7	1.4±2.4	1.2±2.0
Urge incontinence episodes	0.8±1.9	0.6±1.4	0.2±0.7	0.3±0.7	0.6±1.1
Postvoid residual volume	14±34	33±53	35±70	18±63	9±38

\* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , versus baseline, student paired  $t$ -test with Bonferroni correction. OABSS: Overactive bladder symptom score

mirabegron than with solifenacin. Kinjo *et al.* also reported that the frequency of withdrawal due to “side effects” in the mirabegron group was significantly lower than in the solifenacin group.<sup>[16]</sup> In phase III trials, while the overall rate of treatment-emergent adverse events for mirabegron was similar to those for antimuscarinics,<sup>[11,12]</sup> the incidences of dry mouth and constipation were significantly lower in patients treated with mirabegron than with antimuscarinics.<sup>[21]</sup> The anticholinergic side effects might result in discontinuation of treatment for OAB. Consequently, many patients terminated mirabegron for various reasons, the most frequent of which was “symptom resolution.”

The degree of “symptom resolution” varied. Some patients became completely asymptomatic. Most patients were still symptomatic, but no longer bothered enough to continue taking the medication. Therefore “symptom resolution” was defined as an improvement to the extent to discontinue the medicine anymore. Although the mechanism of “symptom resolution” is not known, in addition to the spontaneous improvements of the symptoms with OAB, lifestyle interventions such as modification of fluid or alcohol intake might improve the symptoms of OAB. Of the 24 patients who discontinued mirabegron treatment because of “symptom resolution,” 16 (66.7%) discontinued it in the first 6 months. Furthermore, our hospital is the only hospital in the area with urology departments, and there is no private urology clinic. It is thus not reasonable for a patient to go to a primary care provider without an introduction from us. Therefore, if the symptoms of patients who terminated mirabegron for “symptom resolution” deteriorated, they would revisit our hospital. During follow-up, only four patients revisited the hospital and received retreatment with mirabegron for deterioration of the symptoms of OAB, while the remaining 20 (83.3%) never visited our hospital for deterioration of the symptoms. In our previous study, 75% of patients who discontinued treatment with solifenacin due to “symptom resolution” never visited our hospital because of the deterioration of the symptoms of OAB.<sup>[20]</sup> The majority of the patients who discontinued medication due to “symptom resolution” had durable improvements of OAB symptoms even after termination of the medication.

The present study had several limitations. The mean age of the patients (75.8 years) was much higher than those (59.0–60.1 years) of phase III trials.<sup>[7,9]</sup> In Japan, we are advised to avoid administering mirabegron to patients of reproductive age to the degree possible, and we included only postmenopausal patients in the present study. Furthermore, Japan is rapidly aging. Approximately 40%

of the population is over 65 years old in our rural area. Therefore, the mean age of the participants was high. In a previous Japanese report on mirabegron, the mean age of the postmenopausal Japanese female patients with OAB was 70.5 years old.<sup>[22]</sup> Therefore, there might be a regional bias of the patient population. Second, placebo effects might be included in the results for uncontrolled trials. Spontaneous improvements of the symptoms of OAB might be due to such effects. Third, the number of patients was relatively small. Only 16 patients continued to take mirabegron for 3 years. This number was too small to evaluate the efficacy of the drug. The improvements of the scores of the OABSS did not reach statistical significance. Fourth, this was a single-center study conducted by one particular physician. To some extent, there might thus be a personal bias with regard to the treatment. Therefore, further large-scale, multicenter studies are required.

## CONCLUSIONS

The persistence rate of treatment with mirabegron among treatment-naïve Japanese female patients with OAB in the real-world clinical setting is low for 3 years. Many patients discontinue the treatment for various reasons, the most frequent of which is symptom resolution. These findings provide important considerations for clinicians whose patients are continuing medication for OAB.

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Nil.

## Conflicts of interest

Naoya Masumori is a consultant for Astellas and Takeda and has received payments for lectures from Astellas, Nipponshinyaku, Asahi-Kasei, AstraZeneca and Kissei.

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