

ORIGINAL ARTICLE

Efficacy of mirabegron for overactive bladder with human T cell lymphotropic virus-1 associated myelopathy

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Objective: Mirabegron is widely considered as an effective and safe drug for patients with overactive bladder (OAB). However, there is no evidence regarding the efficacy of mirabegron in human T cell lymphotropic virus-1 (HTLV-1)-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients with OAB symptoms. The aim of the present study was to clarify the efficacy of mirabegron in HAM/TSP patients with OAB symptoms.

Methods: The present study evaluated the efficacy of mirabegron treatment (50 mg, once daily) in nineteen HAM/TSP patients with OAB symptoms by assessing subjective symptoms using the overactive bladder symptom score (OABSS) and International Prostate Symptom Score (IPSS) before and 12 weeks after administration. Voided volume (VV), maximum flow rate (Q_{max}), and post-void residual (PVR) urine volume were evaluated as objective symptoms.

Results: Mirabegron treatment improved OABSS in terms of night-time frequency, urgency, and total score ($P < .001$). In addition, on the IPSS, mirabegron therapy improved urgency, nocturia, storage symptoms (Questions 2, 4 and 7 on the IPSS), as well as the total score ($P < .001$). The quality of life (QoL) on the IPSS also improved after treatment ($P < .001$). However, there were no significant changes in objective symptoms, as measured by VV, Q_{max} , and PVR, after treatment. One patient (5.3%) complained of dry mouth; because this adverse effect was very mild, the patient did not discontinue mirabegron.

Conclusions: Mirabegron administration improved subjective symptoms in HAM/TSP patients with neurogenic OAB.

KEYWORDS

human T cell lymphotropic virus-1 (HTLV-1)-associated myelopathy, mirabegron, overactive bladder

1 | INTRODUCTION

Human T cell lymphotropic virus-1 (HTLV-1) infects approximately 10–20 million people worldwide. High endemic areas include southern Japan, the Caribbean, Central and South America, the Middle East, Melanesia, and equatorial regions of Africa.^{1,2} HTLV-1, the first human retrovirus to be discovered, causes adult T cell leukemia and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP).^{3,4} In general, HAM/TSP is characterized by slow progression of lower limb

sensory disturbances and movement disorder accompanied by neurogenic bladder dysfunction caused by chronic inflammation in the central nervous system (CNS), especially the lower thoracic spinal cord.⁵ Both storage and voiding symptoms are very common and are seen even in the very early phase of HAM/TSP. In addition, these symptoms sometimes precede the development of paraparesis by many years.⁵ Moreover, lower urinary tract symptoms (LUTS) affect the quality of life (QoL) not only in HAM/TSP patients, but also in HTLV-1-infected individuals.⁶ Urinary symptoms occur in up to 100% of patients with

HAM/TSP, and overactive bladder (OAB) is the main manifestation of HAM/TSP.⁷

OAB associated with HAM/TSP is multifarious and affects patients' QoL. However, there are only a few reports on the efficacy of medications for OAB associated with HAM/TSP. Moreover, HAM/TSP patients with LUTS are not fully satisfied with the efficacy of some medications.⁷⁻¹⁰ In some of these patients, the anticholinergic agents prescribed for OAB symptoms caused severe adverse effects, such as constipation and dry mouth, which are autonomic symptoms. In contrast, although methylprednisolone has often been used in HAM/TSP patients with neurogenic bladder, it has limitations in improving LUTS.¹⁰ In addition to these treatments, some advanced medical treatments, such as botulinum toxin type A, have been tried.⁷⁻⁹ However, these studies did not conclusively prove the efficacy and safety of these treatments because of the small number of patients involved. Therefore, the lack of established curative treatments for LUTS in HAM/TSP patients with OAB symptoms is a critical problem.

Mirabegron is a β_3 -adrenoreceptor agonist and is approved for the treatment of OAB worldwide. One of the important characteristics of mirabegron is that it causes fewer adverse events, such as constipation or dry mouth, than anticholinergic agents.¹¹⁻¹³ Therefore, mirabegron appears to be advantageous in maintaining QoL in HAM/TSP patients undergoing treatment for OAB. However, there are few data regarding the adverse events associated with mirabegron treatment in these patients. In addition, the efficacy of mirabegron for OAB symptoms associated with HAM/TSP based on subjective parameters and urodynamic assessment has not been fully investigated. Hence, the aim of the present study was to clarify the efficacy and safety of mirabegron in HAM/TSP patients with OAB.

2 | METHODS

The study protocol was approved by the Clinical Studies Review Board of Nagasaki University Hospital and the study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients enrolled in the study.

2.1 | Patients and study design

HAM/TSP patients with OAB symptoms were recruited at the Nagasaki University Hospital. The present study was a prospective single-center open-label study. To be eligible for inclusion in the present study, subjects had to have had HAM/TSP with OAB symptoms (OAB symptom score [OABSS]: urgency ≥ 2 , total score ≥ 3) for at least 3 months and either not taking any medications for OAB or not responding to anticholinergic agents for at least 3 months (OABSS: urgency ≥ 2 , total score ≥ 3). All patients had normal micturition desire, and could urinate even if there were some differences in the degree of voided volume. Clean intermittent self-catheterization (CISC) was performed 4 times during the daytime by patients with a large amount of residual urine. The number of CISCs remained unchanged during the study period. Patients received oral mirabegron (Betanis; Astellas Pharma, Tokyo, Japan) 50 mg once daily after breakfast.

Changes in the OABSS and International Prostate Symptom Score (IPSS)¹⁴ were used to assess subjective symptoms, whereas uroflowmetry (UFM) and post-void residual (PVR) urine volume were used as objective measures. "Improvement" was defined when OABSS, IPSS, and IPSS-QoL decreased by 1 point or more for subjective symptoms. Furthermore, patients were divided into 2 groups: an improved group, in which the score for Question 3 on the OABSS (urgency) decreased by ≥ 1 point, and a failure group. The significance of differences between these 2 groups was evaluated. Motor function was evaluated using Osame's motor disability score (OMDS).¹⁵

Concomitant therapies, such as immunomodulators, were continued on the condition that the dose was kept constant during the study period. However, patients who had already been prescribed anticholinergic agents for their OAB symptoms stopped taking these drugs for an at least 1-week washout period before initiation of mirabegron treatment. Patients with a history of urological malignancy, pelvic radiotherapy, neurologic disease (except for HAM/TSP), active urinary tract infections, severe hypertension (systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg) not well controlled by medication, renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m²), liver impairment, intending to have a child, or those considered unsuitable for the trial by the treating physicians were excluded from the study. In addition, male patients were excluded, considering the effect of benign prostatic hyperplasia.

2.2 | UFM assessment

The maximum flow rate (Q_{max}) was measured using the Duet Logic G2 system (Mediwatch UK, Rugby, UK) on free UFM and PVR using transabdominal ultrasound (HI VISION Avius; Hitachi-Aloka Medical, Tokyo, Japan).

2.3 | Statistical analyses

All data are presented as mean \pm SD. Wilcoxon's signed-rank test was used to evaluate changes in subjective symptoms based on the OABSS and IPSS, and in objective symptoms assessed using UFM and PVR. All tests were 2-sided and $P < .05$ was considered significant. All statistical analyses were performed using JMP 13 (SAS Institute, Cary, NC, USA).

3 | RESULTS

Nineteen women were enrolled in the present study. As indicated in Table 1, the mean (\pm SD) age of patients was 68.6 ± 8.4 years (range 54-82 years), and the mean duration of illness was 16.1 ± 8.9 years (range 1-38 years). Fifteen patients (78.9%) had taken anticholinergic agents for OAB treatment and 14 (73.7%) had already performed CISC. The OMDS was 5.7 ± 2.9 (range 2-11). All patients were able to complete this clinical trial. No severe adverse events were observed during mirabegron administration.

Table 2 shows changes in the OABSS and IPSS from before to after mirabegron administration. Mirabegron treatment improved the

TABLE 1 Patient characteristics

No. patients	19
Age (y)	68.6 ± 8.4 (54–82)
Duration of illness (y)	16.1 ± 8.9 (1–38)
OMDS	5.7 ± 2.9 (2–11)
CISC	14 (73.7)
Immunomodulator therapy	
Prednisolone (10 mg)	4 (21.1)
Anticholinergic agents	15 (78.9)
Propiverine hydrochloride	3 (15.8)
Imidafenacin	2 (10.5)
Fesoterodine fumarate	3 (15.8)
Solifenacin succinate	7 (36.8)

Unless indicated otherwise, data are given as the mean ± SD (range) or as n (%). CISC, clean intermittent self-catheterization; OMDS, Osame's motor disability score.

total OABSS (from 7.9 ± 2.2 to 4.3 ± 2.8; $P < .001$), night-time frequency (Question (Q) 2 on the OABSS; $P < .001$), urgency (OABSS Q3; $P < 0.001$), and urgency incontinence (OABSS Q4; $P = .004$). In addition, mirabegron therapy improved the total IPSS (from 12.2 ± 3.9 to 9.2 ± 2.6, $P < .001$), as well as the urgency (IPSS Q4; $P < .001$), nocturia (IPSS Q7; $P < .001$), storage symptoms (IPSS Q2 + Q4 + Q7; $P < .001$) subscale scores and the IPSS-QoL (from 4.3 ± 1.1 to 3.6 ± 1.0; $P < .001$). However, there were no significant changes in the scores for incomplete emptying (IPSS Q1; $P = .520$), intermittency (IPSS Q3; $P < 1.000$), weak stream (IPSS Q5; $P < .555$), straining (IPSS Q6; $P < 1.000$), or voiding symptoms (IPSS Q1 + Q3 + Q5 + Q6; $P < .889$) following mirabegron therapy.

TABLE 2 Changes in the overactive bladder symptom score (OABSS) and International Prostate Symptom Score (IPSS) from baseline to 12 weeks after oral administration of mirabegron

	Baseline	Week 12	P-value
OABSS			
Q1 (daytime frequency)	1.0 ± 0.7	0.7 ± 0.7	.063
Q2 (night-time frequency)	2.5 ± 0.7	1.6 ± 1.0	<.001
Q3 (urgency)	2.9 ± 0.8	1.4 ± 1.1	<.001
Q4 (urgency incontinence)	1.5 ± 1.3	0.6 ± 0.8	.004
Total score	7.9 ± 2.2	4.3 ± 2.8	<.001
IPSS			
Q1 (incomplete emptying)	1.7 ± 1.4	1.9 ± 0.8	.502
Q2 (frequency)	0.9 ± 0.8	0.6 ± 0.6	.070
Q3 (intermittency)	1.1 ± 1.0	1.0 ± 0.7	1.000
Q4 (urgency)	2.9 ± 0.8	1.4 ± 1.1	<.001
Q5 (weak stream)	1.7 ± 0.9	1.6 ± 0.7	.555
Q6 (straining)	1.1 ± 0.9	1.1 ± 0.7	1.000
Q7 (nocturia)	2.8 ± 1.1	1.6 ± 1.0	<.001
Storage symptoms (Q2 + Q4 + Q7)	6.6 ± 1.6	3.6 ± 1.7	<.001
Voiding symptoms (Q1 + Q3 + Q5 + Q6)	5.6 ± 3.1	5.6 ± 1.3	.889
Total score	12.2 ± 3.9	9.2 ± 2.6	<.001
QoL score	4.3 ± 1.1	3.6 ± 1.0	<.001

Data are the mean ± SD. Q, question; QoL, quality of life.

TABLE 3 Changes in urological parameters from baseline to 12 weeks after oral administration of mirabegron

	Baseline	Week 12	P-value
Bladder capacity (mL)	287.9 ± 153.6	283.0 ± 120.8	.891
Voided volume (mL)	130.0 ± 111.8	90.4 ± 85.0	.120
Q _{max} (mL/s)	8.7 ± 7.7	7.8 ± 6.6	.598
PVR urine (mL)	156.7 ± 107.9	192.2 ± 134.8	.121

Data are the mean ± SD. Q_{max}, maximum flow rate; PVR, post-void residual.

Changes in objective measures (i.e. bladder capacity, VV, Q_{max}, and PVR) are given in Table 3. There were no significant changes from baseline to 12 weeks after mirabegron therapy in either bladder capacity (from 287.9 ± 153.6 mL to 283.0 ± 120.8 mL; $P = .891$), VV (from 130.0 ± 111.8 mL to 90.4 ± 85.0 mL; $P = .120$), Q_{max}, or PVR ($P = .598$ and $P = .121$, respectively).

Differences in characteristics between the failure and improved groups (based on changes in OABSS Q3) are given in Table 4. Patients in the improved group were younger than those in the failure group. In addition, OMDS in the failure group was higher than in the improved group. However, there were no other significant differences between the 2 groups. The changes in OABSS and IPSS in each group are given in Table 5. There were improvements in total OABSS and IPSS Q7 (nocturia) in both the improved and failure groups. In the case of objective symptoms, UFM assessment showed that PVR in the failure group increased significantly after mirabegron administration (Table 6).

A safety analysis was performed on all patients during the study. One patient (5.3%) complained of dry mouth. However, because this adverse effect was very mild, the patient did not discontinue mirabegron. None of the patients complained of constipation, dry eye, or a decline in cognitive function. In addition, none of the patients with hypertension experienced worsening of their blood pressure levels and pulse rate. Hence, all patients completed this clinical study, including all the scheduled examinations during the study period.

4 | DISCUSSION

The results of the present study indicate that the oral administration of mirabegron improves subjective symptoms, as assessed by OABSS, total IPSS, and IPSS QoL, in HAM/TSP patients with neurogenic OAB. The present study is the first to report on changes in subjective symptoms following mirabegron treatment in HAM/TSP patients with neurogenic OAB. In addition, oral mirabegron therapy was found to be safe for HAM/TSP patients, and the mirabegron therapy did not exacerbate the objective parameters Q_{max} and PVR.

In patients with HAM/TSP, OAB symptoms such as nocturia and urgency are more frequent than voiding symptoms.¹⁶ In addition, it is considered that OAB symptoms are LUTS, and even patients who are HTLV-1 carriers tend to develop OAB symptoms. OAB symptoms are precursors of HAM/TSP because they often precede the clinical manifestation of paraparesis by years.^{17,18} Furthermore, LUTS have a considerable effect on the QoL of HAM/TSP patients.^{6,7} Thus, improvement of urinary conditions is important to maintain the QoL

TABLE 4 Differences in patient characteristics between the failure and improved groups^a

	Failure group	Improved group	P-value
No. patients (%)	5 (26.3)	14 (73.7)	N/A
Age (y)	74.0 ± 5.8 (67–80)	66.6 ± 8.5 (54–82)	.094
Duration of illness (y)	18.4 ± 11.5 (9–36)	12.1 ± 8.6 (1–38)	.217
OMDS	6.4 ± 2.9 (3–10)	5.5 ± 3.0 (2–11)	.567
CISC (%)	5 (100)	9 (64.3)	.120

Unless indicated otherwise, data are given as the mean ± SD (range) or as n (%).

^aPatients were divided into 2 groups, an improved group (in which the score for Question 3 on the overactive bladder symptom score (urgency) decreased by ≥1 point) and a failure group.

CISC, clean intermittent self-catheterization; N/A, not applicable; OMDS, Osame's motor disability score.

in these patients. However, a useful and safe treatment for OAB symptoms has not yet been established. For example, anticholinergic drugs, which have been widely recognized as the standard treatment for OAB symptoms, are rather difficult to use in HAM/TSP patients because of adverse events including dry mouth, voiding difficulty, dry eye, constipation, and cognitive dysfunction, which are autonomic symptoms that lead to tissue destruction.¹⁹ Hence, the toxic effects of anticholinergic drugs may sometimes outweigh their treatment efficacy. Carneiro et al.⁸ reported the efficacy of botulinum toxin type A for HAM/TSP-associated OAB refractory to conventional drug in 3 patients. Botulinum toxin type A, a neuromuscular blocking agent, has been used to treat neurogenic OAB following detrusor overactivity in patients with multiple sclerosis and spinal cord injury.²⁰

Botulinum toxin type A is usually injected intravesically and is an invasive therapy. In addition, it has been reported that HAM/TSP patients with neurogenic bladder may also have urinary tract infection and voiding dysfunction.²¹ In fact, 1 of the 3 patients in report of Carneiro et al.⁸ showed an increase in PVR from 32 to 410 mL after botulinum toxin type A intravesical injection therapy.⁸ Thus, an effective treatment strategy for lower urinary tract dysfunction in HAM/TSP patients has not yet been established.

Mirabegron, which is approved for the treatment of OAB, is a specific agonist acting on β₃-adrenoceptors in the human bladder, the stimulation of which leads to active relaxation of the detrusor muscle in the storage phase, which, in turn, increases bladder capacity without exerting an effect on voiding.²² The efficacy and safety of mirabegron have been reported in several randomized trials, for example the SCORPIO and TAURUS studies.^{12,23} Both these studies showed improvement in storage symptoms, including urgency incontinence and increased voiding volume. The present study demonstrated that mirabegron improved subjective symptoms (especially nocturia, urgency, and urgency incontinence), which were assessed using the OABSS and IPSS, as well as the QoL of HAM/TSP patients with OAB. However, we did not observe any improvement in subjective symptoms, especially daytime frequency, in the present study. With regard to this point, patients with a large amount of PVR urine had performed CISC at a fixed time, 4 times during the day. The daytime urination frequency was the total number of times of spontaneous voiding and CISC. Patients did not change the number of CISCs performed during the study. The present might explain why the score for daytime frequency did not improve in the present study.

TABLE 5 Differences in overactive bladder symptom score (OABSS) and International Prostate Symptom Score (IPSS) after 12 weeks oral administration of mirabegron between the failure and improved groups^a

	Failure group			Improved group		
	Baseline	Week 12	P-value	Baseline	Week 12	P-value
OABSS						
Q1 (daytime frequency)	1.0 ± 0.7	0.9 ± 0.8	.833	1.0 ± 0.8	0.6 ± 0.6	.082
Q2 (night-time frequency)	2.6 ± 0.5	1.6 ± 0.5	.063	2.4 ± 0.8	1.6 ± 1.2	.028
Q3 (urgency)	2.2 ± 0.4	2.0 ± 0.6	.856	3.1 ± 0.8	1.1 ± 1.1	< .001
Q4 (urgency incontinence)	1.4 ± 1.1	0.6 ± 0.5	.099	1.6 ± 1.4	0.6 ± 0.9	.009
Total score	7.2 ± 2.6	5.4 ± 1.9	.009	8.1 ± 2.1	3.9 ± 2.9	< .001
IPSS						
Q1 (incomplete emptying)	2.0 ± 1.4	2.0 ± 0.7	.983	1.6 ± 1.5	1.9 ± 0.9	.336
Q2 (frequency)	0.6 ± 0.5	0.4 ± 0.5	.765	1.1 ± 0.8	0.6 ± 0.6	.008
Q3 (intermittency)	1.2 ± 0.8	1.4 ± 0.9	.374	1.0 ± 1.1	0.9 ± 0.5	.583
Q4 (urgency)	2.2 ± 0.4	2.3 ± 0.4	.673	3.1 ± 0.8	1.1 ± 1.1	< .001
Q5 (weak stream)	1.6 ± 1.1	1.2 ± 0.8	.648	1.8 ± 0.8	1.7 ± 0.6	.72
Q6 (straining)	0.4 ± 0.5	1.0 ± 0.7	.208	1.4 ± 0.9	1.1 ± 0.8	.272
Q7 (nocturia)	3.2 ± 1.3	1.6 ± 0.5	.016	2.6 ± 1.0	1.6 ± 1.2	.001
Storage symptoms (Q2 + Q4 + Q7)	6.0 ± 2.0	4.4 ± 0.9	.056	6.9 ± 1.5	3.4 ± 1.9	<.001
Voiding symptoms (Q1 + Q3 + Q5 + Q6)	5.2 ± 3.4	5.6 ± 1.1	.749	5.7 ± 3.1	5.6 ± 1.4	.83
Total score	11.2 ± 3.7	10.0 ± 1.9	.261	12.6 ± 4.1	8.9 ± 2.8	<.001
QoL score	4.6 ± 1.3	3.6 ± 1.1	.142	4.8 ± 1.1	3.6 ± 1.0	.006

Data are the mean ± SD.

^aPatients were divided into 2 groups, an improved group (in which the score for Question 3 on the overactive bladder symptom score (urgency) decreased by ≥1 point) and a failure group.

Q, question; QoL, quality of life.

TABLE 6 Differences between the failure and improved groups^a in urological parameters from baseline to 12 weeks after oral administration of mirabegron

	Failure group			Improved group		
	Baseline	Week 12	P-value	Baseline	Week 12	P-value
Bladder capacity (mL)	337.8 ± 257.3	324.6 ± 109.2	.857	270.0 ± 104.9	262.2 ± 125.0	.947
Voided volume (mL)	127.0 ± 159.4	57.0 ± 64.9	.438	131.4 ± 97.4	102.9 ± 90.0	.113
Q _{max} (mL/s)	5.0 ± 5.6	4.9 ± 5.9	.870	10.0 ± 8.1	8.9 ± 6.8	.472
PVR urine (mL)	210.8 ± 104.3	267.6 ± 133.8	.015	138.7 ± 106.2	165.2 ± 129.2	.910

Data are the mean ± SD.

^a Patients were divided into 2 groups, an improved group (in which the score for Question 3 on the overactive bladder symptom score (urgency) decreased by ≥1 point) and a failure group.

Patients were divided into 2 groups (failure and improved groups) on the basis of changes in the OABSS Q3 score. The success rate for mirabegron treatment was 73.7% (14/19). In the improved group, there were significant improvements in the scores for Q2 (nocturia), Q3 (urgency), Q4 (urgency incontinence), and the total score on the OABSS, as well as in scores for Q2 (frequency), Q4 (urgency), Q7 (nocturia), stage symptoms (Q2 + Q4 + Q7), and QoL on the IPSS. The total OABSS, as well as scores for Q7 (nocturia) and storage symptoms on the IPSS improved significantly, even in the failure group. However, we could not determine the effectiveness of mirabegron for objective symptoms, namely bladder capacity, PVR, VV, and Q_{max}. Although there were no statistically significant changes in VV and PVR in any patient, VV decreased and PVR increased after the study period. In the failure group, all patients performed CISC, and PVR increased significantly after mirabegron treatment. This could be because the present study included 14 patients who had already performed CISC and were expected to have irreversible voiding dysfunction. Moreover, we did not use a frequency volume chart to evaluate the bladder capacity of patients.

In the present study, we paid special attention to adverse events, especially dry mouth and constipation. In previous studies, the rate of adverse events associated with 50 mg mirabegron was similar to that associated with placebo, and was significantly lower than that associated with the antimuscarinic drug tolterodine (4 mg).^{12,23} In addition, several studies have reported that the incidence of adverse events, such as dry mouth and constipation, was similar between patients treated with mirabegron and those treated with placebo.^{11,12,24} However, some studies reported that many HAM/TSP patients suffered from constipation and dry mouth even before treatment.^{25–27} Thus, mirabegron may be more convenient to administer in HAM/TSP patients with OAB than anticholinergic agents. In fact, in the present study, only 1 patient developed mild dry mouth and no patient had constipation. Hence, mirabegron is considered to be a potential treatment option even for HAM/TSP patients who have comorbidities, including autonomic symptoms.

The major limitations of the present study include the relatively small number of patients included and the short observation period. The present study was an open label study and not placebo controlled. In addition, the study population did not include male patients. The patients included in the study did not undergo urodynamic tests, including pressure–flow studies. Moreover, we could not demonstrate the efficacy of mirabegron for the objective measures VV and Q_{max}. Because we did not analyze the placebo effect, we

cannot conclude that mirabegron improved subjective symptoms in HAM/TSP patients with OAB. Furthermore, the washout period in the present study is shorter than in other studies using sustained-release and extended-release formulations, such as solifenacin succinate and fesoterodine fumarate.^{28,29} However, the present study has demonstrated, for the first time, that oral mirabegron therapy improved subjective symptoms, as measured by the IPSS and OABSS, in HAM/TSP patients with OAB. The present study is the first to investigate the efficacy of medications used for the treatment of HAM/TSP patients with OAB using established methods. Hence, we believe that despite the study limitations, the results provide important information on the selection of treatment strategies for HAM/TSP patients with OAB. More comprehensive studies with a larger sample size are necessary to confirm the present results.

In conclusion, the results of the present study indicate that the oral administration of mirabegron is effective against subjective symptoms in HAM/TSP patients with OAB. In addition, mirabegron was considered a safe and tolerable therapeutic agent in these patients.

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Conflict of interest

The authors declare no conflicts of interest.

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