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Original Article

Comparative study of different combinations of mirabegron and antimuscarinics in treatment for overactive bladder syndrome in elderly patients

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Abstract

Objectives: To compare the therapeutic efficacy, adverse events (AEs), and patient preference in elderly patients with overactive bladder (OAB) receiving different combinations of mirabegron and solifenacin. **Materials and Methods:** Elderly OAB patients received mirabegron 25 mg (M25) daily for 1 month (1M) followed by randomization to receive M25 (Group 1), mirabegron 50 mg (M50, Group 2), solifenacin 5 mg (S5, group 3); or M25 plus S5 (Group 4) for further 2 months. Efficacy and AEs were evaluated. At the end of 3M, patients' preferred option for future treatment was investigated. **Results:** A total of 168 patients were enrolled, and 100 completed 3-month treatment. At 1M, all parameters improved significantly except postvoid residual (PVR), 23 (13.7%) patients had no symptom, 16 (9.5%) had no improvement, and 10 (6.0%) withdrew from the trial. Compared parameters at 3M with 1M revealed that quality of life, Patient's Perception of Bladder Condition scores, and voided volume improved significantly in group 1; the OAB Symptom Score (OABSS) increased in group 2; mean PVR and Global Response Assessment (GRA) deteriorated in group 3; and the OABSS and GRA improved in group 4. At 3M, the AEs prevalence increased significantly in group 3. Only 38.1% in group 4 preferred long-term usage of combination therapy. **Conclusion:** M25 daily is effective and safe in treating elderly OAB patients. Dose escalation to 50 mg or shifting to S5 does not increase the therapeutic efficacy. Combining M25 with S5 provides better treatment efficacy but is associated with lower patient compliance than M25 alone.

Keywords: *Antimuscarinics, Beta-3-adrenoceptor agonist, Overactive bladder syndrome, Treatment*

Introduction

Overactive bladder (OAB) is a symptom syndrome characterized by urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of a urinary tract infection (UTI) or other obvious pathology [1]. OAB symptoms can be quite bothersome and can negatively affect health-related quality of life (HR-QoL), increase anxiety and depression, and increase healthcare usage [2,3]. Although the cause of OAB is not fully understood, it is believed to be multifactorial [4]. The syndrome is often associated with overactivity of the detrusor muscle, a pattern of bladder muscle contraction observed during urodynamics, which may be neurogenic, myogenic, urotheliogenic, or idiopathic in origin [5].

Mirabegron, a beta-3-adrenoceptor agonist, and antimuscarinic drugs are currently the mainstay of pharmacological treatment for OAB syndrome. Both classes of drugs share similar efficacy, but mirabegron is less associated with anticholinergic adverse events (AEs; e.g., the incidence of dry mouth is comparable with placebo) [6]. In the current clinical practice of OAB pharmacotherapy, patients are often initiated on antimuscarinics. However, if a patient experiences inadequate symptom control and/or unacceptable adverse drug events with one antimuscarinic medication, then a dose modification or a different antimuscarinic medication or a beta-3 agonist may be tried [7]. Whether a beta-3 agonist should be administered before an antimuscarinic and vice versa remains to be answered.

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The combination of mirabegron with one antimuscarinic drug (solifenacin) has been shown to improve objective and subjective efficacy outcomes when compared with placebo or solifenacin alone [8]. A recent study also showed that add-on treatment of mirabegron to solifenacin in patients with incontinent OAB resulted in better improvement in OAB symptoms than solifenacin monotherapy [9]. The dose of mirabegron is recommended to start from 25 mg (M25), especially in the elderly patients who hay have potential AEs of hypertension or constipation although the large integrated clinical trial database confirmed the safety and efficacy of M25 and mirabegron 50 mg (M50) across all ages and sexes [10]. However, although mirabegron has been widely used for many years, little is known about the outcomes of dose escalation or of directly shifting to an antimuscarinic or add-on antimuscarinic in elderly OAB patients who are initially treated with low-dose mirabegron, in real-life practice. This study was conducted to prospectively compare the therapeutic efficacy, AEs, and patients' preference among different combinations of mirabegron and solifenacin in the elderly patients with OAB who were initiated on M25 therapy.

Materials and Methods

Study design and participants

Participants in this prospective study comprised patients ≥65 years with a ≥3-month history of OAB symptoms, including an average of ≥8 daily voiding episodes, and an average of one or more urgency or urge incontinence episodes per 24 h. Patients were excluded from the study if they had (1) neurogenic bladder caused by a cerebral vascular accident, Parkinson's disease, spinal cord injury, or multiple sclerosis; (2) stress urinary incontinence as the main symptom; (3) UTI, urolithiasis, interstitial cystitis/bladder pain syndrome; (4) postvoid residual (PVR) urine volume >100 mL; (5) obvious bladder outlet obstruction without adequate control; or (6) severe systemic disease accompanied by poor physical condition such as hypertension, diabetes mellitus, congestive heart failure, cardiac arterial disease, chronic kidney disease. Patients with one of the above-listed systemic diseases but with an acceptable physical status were recorded as having comorbidity. The study was approved by the Research Ethics Committee of the Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (TCGH IRB: 104-16-A). Informed consent form was obtained from all patients on enrolment. Clinicaltrial. gov: NCT03059134.

All patients who fulfilled the inclusion criteria received M25 daily for 1 month (1M). Patients were then randomized to receive: (1) M25 for an additional 2 months (group 1), (2) to receive mirabegron 50 mg daily (50, group 2), (3) to receive solifenacin 5 mg daily (S5, group 3), or (4) to receive combined M25 and S5 (group 4) for a further 2 months [Figure 1]. The randomization method was permuted block in an open-labeled study design. To avoid confusion of the therapeutic efficacy, no other medication for lower urinary tract dysfunction was prescribed such as aloha-blocker and 5-alpha-reductase inhibitor.

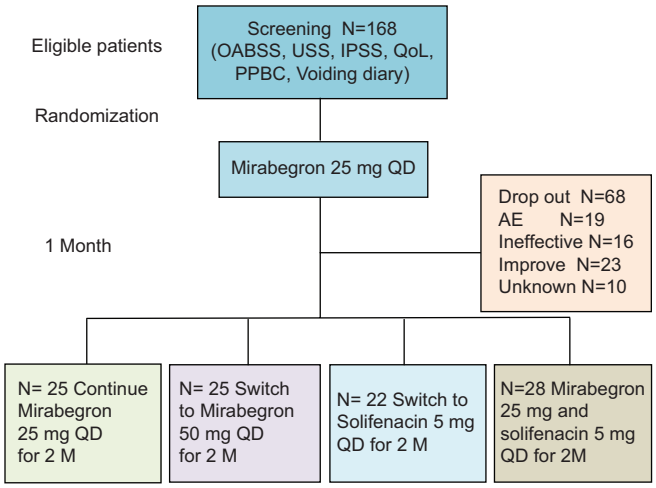

Figure 1: Flow chart of the study

Efficacy, safety, and patients' preference assessments

The International Prostate Symptom Score total (IPSS-T), voiding and storage subscores (IPSS-V and IPSS-S), quality of life, OAB Symptom Score (OABSS), Urgency Severity Scale (USS), Patient's Perception of Bladder Condition (PPBC), Global Response Assessment (GRA), and uroflowmetry parameters, for example, maximum flow rate (Qmax), voided volume (Vol), and PVR were evaluated at baseline, 1 M and 3 M after treatment. The prevalence of AEs was also recorded at 1 M and 3 M after treatment. At the end of 3 M, patients with successful treatment outcomes (defined as GRA ≥ 1) were asked which treatment regimen they preferred to continue in the proceeding treatment course.

Statistical analysis

In all patients, the mean values of parameters such as IPSS-V, IPSS-S, IPSS-T, QoL, Qmax, Vol, PVR, nocturia, OABSS, USS, PPBC, and GRA at baseline were compared with those at 1 M. In the patients who completed the study, the changes in the above parameters from 1 M to 3 M were analyzed in each group and then compared among the four groups. The prevalence of AEs at 1 M and 3 M were also compared in each group and between the four groups. Statistical comparisons between the groups were tested using the Pearson's Chi-square test or Fisher's exact test for categorical variables, and a paired *t*-test or ANOVA or a Wilcoxon rank-sum test for continuous variables. Statistical assessments were considered significant when *P* value was <0.05. All statistical analyses were performed using SPSS 18.0 statistical software (SPSS Inc., Chicago, IL).

Results

Patient demographics

A total of 168 patients (112 men and 56 women; median age, 73) were enrolled in this study. Among them, 100 patients completed the 3-month treatment protocol, which translates to a dropout rate of 40.4%. After analysis of the causes of withdrawal at 1 month, 23 (13.7%) patients had no OAB symptoms after the 1st month M25 treatment, 16 (9.5%) had no response to M25 and switched to other therapy, 19 (11.3%)

Table 1: Baseline demographics of the study patients

Group medication (Total=168)	Group 1 M25-M25 (*n*=44)	Group 2 M25-M50 (*n*=39)	Group 3 M25-S5 (*n*=44)	Group 4 M25-M25+S (*n*=41)	*P*
Age	73.6±11.4	72.3±10.4	73.9±11.9	72.3±14.0	0.253
Gender (male), *n* (%)	30 (68.2)	25 (64.1)	33 (75.0)	24 (58.5)	0.431
Comorbidities, *n* (%)	27 (61.4)	28 (71.8)	35 (79.5)	21 (51.2)	0.035*
OAB-dry, *n* (%)	29 (66.7)	12 (40.0)	24 (57.1)	19 (48.7)	0.456
OAB-wet, *n* (%)	15 (33.3)	18 (60.0)	18 (42.9)	20 (51.3)	
IPSS-V	6.09±6.06	6.76±5.93	5.79±5.93	7.68±5.94	0.481
IPSS-S	6.07±3.07	8.13±3.58	6.00±2.98	7.83±3.71	0.003*
IPSS-T	11.70±7.09	14.63±7.35	11.79±7.18	15.51±7.47	0.032*
QoL	3.36±1.41	3.69±1.26	3.34±1.26	3.95±1.24	0.109
Qmax (mL/s)	12.75±10.01	9.66±6.08	12.98±10.15	12.58±9.33	0.333
Vol (mL)	200.2±178.2	130.5±97.3	165.0±94.1	162.6±133.7	0.134
PVR (mL)	53.6±84.8	28.6±42.6	48.7±75.9	29.3±36.1	0.172
Nocturia/night	3.79±1.19	3.97±1.18	3.70±1.09	4.05±1.07	0.477
OABSS	5.47±3.27	7.38±3.94	5.77±3.37	7.12±4.10	0.041*
USS	1.67±1.86	2.82±1.70	2.07±1.89	2.34±1.88	0.041*
PPBC	3.26±1.80	3.90±1.73	3.86±1.68	4.49±1.57	0.013*

*Significant difference when compared among groups with ANOVA. M25: Mirabegron 25 mg QD, M50: Mirabegron 50 mg QD, S5: Solifenacin 5 mg QD, IPSS: International prostate symptom Score, IPSS-S: IPSS-storage domain, IPSS-T: IPSS-total score, IPSS-V: IPSS-voiding domain, OAB: Overactive bladder, OABSS: OAB symptom score, PPBC: Patient's perception of bladder condition, PVR: Postvoid residual, Qmax: Maximum flow rate, QoL: Quality of life, USS: Urgency Severity Scale, Vol: Voided volume

withdrew due to intolerable AE after 1 month, and 10 (6.0%) were lost to follow-up. The demographic data at baseline of these patients are shown in Table 1. There was no significant difference in the distribution of age, gender, OAB type, IPSS-V, QoL scores, Qmax, Vol, PVR, or episode of nocturia among the four groups. However, there were significant differences in the prevalence of comorbidities and mean IPSS-S, IPSS-T, OABSS, USS, and PPBC scores among the groups. Patients in groups 1 and 3 had less OAB wet, lower OABSS, USS, and PPBC, compared with those in group 4.

Efficacy

At 1 M after treatment with M25 daily, significant improvements, except the PVR, in mean values of IPSS-V, IPSS-S, IPSS-T, QoL, Qmax, Vol, episode of nocturia, OABSS, USS, and PPBC, could be observed in the 168 OAB patients [Table 2]. To compare the change of each measured parameter from 1 M to 3 M, we calculated the difference using the values at 1 M minus that at 3 M [Table 3]. We found that at 3 M, the mean scores of QoL and PPBC decreased and Vol increased significantly in group 1; the mean OABSS score increased significantly in group 2; the mean PVR increased and the mean GRA score decreased significantly in group 3; and the mean OABSS decreased and the mean GRA increased significantly in group 4 when compared with those at 1 M. There were also significant differences in the changes of OABSS and GRA from 1 M to 3 M between the four groups, patients in group 4 had the best improvement of GRA, whereas patients in group 3 had the worst GRA.

Tolerability

The distribution of prevalence of AEs is listed in Table 4. There was no significant change in heart rate in the four groups. Only one patient developed hypertension after one month's treatment with M25. At 1M, there was no significant difference in the prevalence of AEs among the four groups. Comparison of the overall prevalence of AEs occurred at 1M with those at 3M revealed no significant difference in the groups taking M25 or M50 (group 1 and 2). Although the groups taking S5 (group 3 and 4) tended to have a higher prevalence of antimuscarinic-associated AEs (dry mouth, constipation, and blurred vision) at 3 M than at 1 M, the difference in the overall prevalence of AEs was only significant in group 3. There was a significant difference in the prevalence of AEs among the four groups at 3 M [Table 4].

Treatment preference of the patients

At the end of 3 M, the rates of the successful treatment outcome (GRA ≥ 1) were 64% in group 1, 68% in group 2, 50% in group 3, and 75% in group 4. The preferred options for further treatment are shown in Table 5. Most patients in group 1 and group 2 favored taking M25 in the future as treatment for OAB. In group 3, less than one-half (45.5%) of the patients preferred continuing to take S5 despite having a successful outcome. Among them, 27.3% wanted to resume M25 and 18.2% were willing to try M25 plus S5. In group 4, only 38.1% of the successfully treated patients wanted to keep taking M25 plus S5, while 47.6% of them preferred going back to taking M25.

Discussion

This study revealed that M25 is feasible for the initial treatment agent and dose for elderly patients with OAB. Patients succeeded with mirabegron M25 and M50 had 64 and 68% successful rates, respectively, at 3 months and most of them would like to continue treatment with this drug. In patients switching from M25 to S5 or combined M25 plus S5, a higher success rate was observed in M25 plus S5, but only few preferred to continue S5 as their future medication for OAB.

OAB is a storage bladder disorder. Although several factors may contribute to OAB, recent researches have focused on afferent bladder function [11]. Afferent information is generated

and conveyed to the central nervous system by two signaling pathways, namely a myogenic and a urothelial pathway [12]. There are two types of contraction which have been observed in the human detrusor muscle, spontaneous involuntary contractions during bladder filling and detrusor contraction during voiding. Preclinical and clinical studies have shown that beta-3-adrenoceptor agonists have no significant negative effect on voiding contraction, thereby limiting the risk of urinary retention [13]. However, beta-3-adrenoceptor agonists have shown a pronounced effect on spontaneous contractile activity in the detrusor muscle *in vitro*, thereby reducing bladder tone and afferent input which provides the rationale for administering such agonists to treat the storage symptoms associated with OAB syndrome [11].

Table 2: Comparison of parameters between baseline and one month after treatment with mirabegron 25 mg daily in 168 overactive bladder patients

	Baseline	1 month	*P*
IPSS-V	6.40±5.82	5.08±4.94	0.002*
IPSS-S	6.88±3.41	5.30±2.56	0.000*
IPSS-T	13.1±7.15	10.4±6.26	0.000*
QoL	3.54±1.29	2.56±1.12	0.000*
Qmax (mL/s)	12.24±9.35	13.68±9.69	0.014*
Vol (mL)	167.6±135.6	203.4±153.7	0.001*
PVR (mL)	40.9±65.8	44.9±56.7	0.410
Nocturia	3.85±1.13	3.57±1.22	0.000*
OABSS	6.33±3.71	5.03±3.02	0.000*
USS	2.17±1.87	1.50±1.87	0.000*
PPBC	3.83±1.74	2.47±1.68	0.000*
GRA	0	0.67±0.47	

*Significant difference when compared between baseline and 1 month, Paired *t*-test was used. GRA: Global response assessment, IPSS: International prostate symptom score, IPSS-S: IPSS-storage domain, IPSS-T: IPSS-total score, IPSS-V: International prostate symptom score-voiding domain, OAB: Overactive bladder, OABSS: OAB symptom score, PPBC: Patient's perception of bladder condition, PVR: Postvoid residual, Qmax: Maximum flow rate, QoL: Quality of life, USS: Urgency Severity Scale, Vol: Voided volume

Mirabegron is the first beta-3-adrenoceptor agonist approved for the treatment of OAB symptoms. The recommended dose varies from country to country. In the USA, Canada, and Taiwan, patients are recommended to start on a dose of 25 mg and the dose may be increased to 50 mg if needed. In the UK and Japan, however, the starting dose is 50 mg but is lower for patients with renal or hepatic impairment [14]. The efficacy and safety of M25 for 4–8 weeks followed by escalation to M50 therapy had been confirmed in the patients aged ≥ 65yr with OAB and incontinence [15].

In this study, we investigated the safety and efficacy of OAB pharmacotherapy in elderly patients. The median age of patients was 73 years and the treatment of OAB started with M25 daily for 1 month. After the 1st month of treatment, significant improvements in scores on all the self-reported questionnaires and in all uroflowmetry parameters were noted, with the exception of PVR. In patients who continued to receive M25 for the next two months (group 1), there was the additional improvement in QoL and PPBC scores as well as Vol, a finding similar to that in the 25 mg arm of a previous phase III study [16].

Interestingly, our results also showed that increasing the dose of mirabegron to 50 mg for 2 more months (group 2) did not result in a further benefit. Although a previous study has revealed that the efficacy of mirabegron was dose dependent, the results from that study were generated from symptomatic patients in different arms receiving different doses of mirabegron from the beginning of a 12-week treatment period, which is a condition different from dose escalation to M50 in the same group of patients who had been well treated with M25 for 1 month [17]. Furthermore, in this study, more patients in group 2 were OAB wet than that in group 1 (60% vs 33.3%), the USS and OABSS were also significantly higher in group 2 than those in group 1. It is likely that patients with more severe OAB might not perceive improvement after escalation from M25 to M50, therefore, 88.2% of them preferred to continue M25 for the future OAB medication.

Table 3: Comparison of the changes of parameters from 1 month to 3 months after treatment among the four groups of overactive bladder patients

Changes of variables 1 month–3 months	Group 1 M25 (*n*=25)	Group 2 M50 (*n*=25)	Group 3 S5 (*n*=22)	Group 4 M25+S5 (*n*=28)	*P*
IPSS-V	0.80±4.88	0.20±4.33	0.52±4.07	−1.93±5.06	0.132
IPSS-S	−0.44±1.94	0.72±2.59	−0.19±1.44	1.04±2.84	0.075
IPSS-T	0.36±4.74	0.92±5.53	0.33±4.39	−0.89±6.05	0.640
QoL	0.48±0.96#	−0.08±1.29	−0.24±0.99	0.18±1.42	0.188
Qmax (mL/s)	−1.52±7.94	0.286±7.25	3.33±8.09	1.96±12.76	0.381
Vol (mL)	−51.0±112.5#	14.5±109. 7	2.11±102.1	32.3±150.1	0.119
PVR (mL)	−3.38±36.9	−3.58±76.6	−26.1±38.5#	−35.3±137.4	0.463
Nocturia	−0.24±0.93	0.08±0.86	−0.23±1.19	0.33±1.30	0.190
OABSS	−0.08±2.33	−0.76±1.62#	0.38±3.2	1.61±3.97#	0.032*
USS	0.16±1.70	−0.32±2.02	0.52±2.32	0.29±1.68	0.490
PPBC	0.72±1.40#	−0.16±2.25	−0.43±1.29	0.25±2.07	0.157
GRA	−0.08±1.71	−0.04±1.59	0.67±1.49#	−0.79±1.79#	0.031*

*Significant difference when compared between groups with ANOVA, #Significant difference when compared between 1 month and 3 months in each group. Wilcoxon signed–ranks test was used. M25: Mirabegron 25 mg QD, M50: Mirabegron 50 mg QD, S5: Solifenaicin 5 mg QD, GRA: Global response assessment, IPSS: International prostate symptom score, IPSS-S: IPSS-storage domain, IPSS-T: IPSS-total score, IPSS-V: International prostate symptom score-voiding domain, OAB: Overactive bladder, OABSS: OAB symptom score, PPBC: Patient's perception of bladder condition, PVR: Postvoid residual, Qmax: Maximum flow rate, QoL: Quality of life, USS: Urgency severity scale, Vol: Voided volume

Table 4: Adverse events at 1 month and 3 months after treatment, and causes of patient withdrawal from the study

1 month (All M25)	Group 1 (*n*=44), *n* (%)	Group 2 (*n*=39), *n* (%)	Group 3 (*n*=44), *n* (%)	Group 4 (*n*=41), *n* (%)	*P**
Any AE	4 (9.1)	4 (10.3)	4 (9.1)	7 (17.1)	0.608
Dry mouth	-	2 (5.2)	-	3 (7.3)	
Constipation	1 (2.3)	-	1 (2.3)	2 (4.9)	
Dizziness	2 (2.3)	-	2 (4.6)	1 (2.4)	
Blurred vision	1 (2.3)	-	-	-	
Hypertension	-	1 (2.6)	-	-	
Dysuria	-	1 (2.6)	-	2 (4.9)	
Slow stream	-	-	1 (2.3)		
Symptom free	8 (18.2)	5 (12.8)	7 (15.9)	3 (7.3)	
Ineffective	5 (11.4)	3 (7.7)	6 (13.6)	2 (4.9)	
Withdrawal	2 (2.3)	2 (5.2)	5 (11.4)	1 (2.4)	
3 months	**Group 1 M25 (*n*=25), *n* (%)**	**Group 2 M50 (*n*=25), *n* (%)**	**Group 3 S5 (*n*=22), *n* (%)**	**Group 4 M25+S5 (*n*=28), *n* (%)**	***P****
Any AE	0	2 (8.0)	7 (31.8)	8 (28.6)	0.005
Dry mouth	-	-	1 (4.5)	4 (14.3)	
Constipation	-	1 (4.0)	2 (9.0)	3 (10.7)	
Dizziness	-	-	1 (4.5)	-	
Blurred vision	-	-	1 (4.5)	2 (7.1)	
Dysuria	-	1 (4.0)	3 (13.6)	-	
P#	0.289	1.000	0.033	0.373	

*Compared between groups with Pearson's Chi-square test, #Compared between 1 month and 3 months in each group with Fisher's exact test. M25: Mirabegron 25 mg QD, M50: Mirabegron 50 mg QD, S5: Solifenaicin 5 mg QD, AE: Adverse events

Table 5: Patient's preference for further treatment

	Group 1 M25-M25 (*n*=25), *n* (%)	Group 2 M25-M50 (*n*=25), *n* (%)	Group 3 M25-S5 (*n*=22), *n* (%)	Group 4 M25-M25+S5 (*n*=28), *n* (%)
GRA ≥1 at 3 months	16 (64)	17 (68)	11 (50)	21 (75)
Continue M25	15 (93.8)	15 (88.2)	3 (27.3)	10 (47.6)
Shift to S5	1 (6.3)	1 (5.9)	5 (45.5)	3 (14.3)
Shift to others	-	-	1 (9.1)	-
M25+ S5	-	-	2 (18.2)	8 (38.1)
Lost to follow-up	-	1 (5.9)	-	-

M25: Mirabegron 25 mg QD, M50: Mirabegron 50 mg QD, S5: Solifenacin 5 mg QD, GRA: Global response assessment

Our results indicate that there is limited room for the use of a higher dose when OAB symptoms are significantly reduced by a lower dose of mirabegron.

In general, mirabegron has similar efficacy to antimuscarinics [7]. A systemic review and network meta-analysis of randomized controlled trials from 2000 to 2017 revealed M50 was as effective as antimuscarinic therapy with fewer common AEs. Combination treatment with S5 plus M25 or M50 was more effective than M50 alone, but with more antimuscarinic-related Aes [18]. Oral medication with antimuscarinics has been implemented to reduce OAB symptoms for a long time but can also commonly cause non-life-threatening AEs such as dry mouth, constipation, dry or itchy eyes, blurred vision, dyspepsia, UTI, impaired cognitive function, and large PVR urine volume. Meta-analysis to evaluate the safety and efficacy of M50 and S5 monotherapy for OAB during a 12-week cycle revealed the therapeutic effect of M50 is similar to that of S5, and M50 does not increase the risk of Aes [19]. Not surprisingly, we found that the mean PVR increased significantly in patients who switched to and were maintained on S5 for 2 months (group 3 and group 4). The fact that there were no differences in most of the parameters with the exception of a decreased GRA score from 1 M to 3 M in group 3 disclosed an equal or even worse therapeutic effect provided by shifting medication from M25 to S5 in this study. Patients of group 3 might perceive unwanted AEs after switching to S5 without initial therapeutic benefit from M25, therefore, the GRA at 3 months was down-graded compared with that in 1 month.

A recent study reported that mirabegron combined with solifenacin is more effective in both objective and subjective outcomes than placebo or solifenacin alone [8]. Other studies have also shown that add-on treatment of mirabegron to solifenacin in OAB patients could further improve OAB symptoms versus solifenacin monotherapy with tolerable AEs [9,20]. Antimuscarinic add-on therapy is well tolerated and effective after initial M50 treatment in OAB patients, however, 80.2% of patients experienced at least one treatment-emergent AE [21]. Taking these results together, combination therapy with a beta-3-adrenoceptor agonist and an antimuscarinic may provide better treatment efficacy than antimuscarinics alone either in parallel or add-on fashion. In contrast, our study demonstrated that after 1 month's treatment with M25, if S5 was added on to M25 for 2 more months (group 4), further significant improvements in OABSS and GRA scores could be obtained. Although PVR increased after combined M25 and

S5 therapy, the GRA still improved at 3 months. This result has demonstrated that add-on treatment of S5 to M25 in OAB patients results in better OAB symptom outcomes than M25 monotherapy.

The AE profile of the four groups in this study was consistent with the known profiles of mirabegron and solifenacin. Among the patients, 19 (11.3%) withdrew from the study due to emergent AE after the 1st month of M25 therapy. The overall prevalence of AEs increased significantly at 3M in patients who changed to S5 after 1 month's treatment with M25 (group 3). This result also reflects the fact that M25 or M50 monotherapy has lower rates of antimuscarinic-associated events than other antimuscarinic agents [7,8]. In a study of the persistence and adherence in OAB patients treated with M50 or, persistence and adherence were statistically significantly greater with M50 than with tolterodine ER or other antimuscarinics agent for OAB in the UK [22]. Our previous study also revealed that switching from solifenacin to mirabegron was effective and safe for OAB patients refractory to solifenacin treatment [23]. However, in our study, the add-on of S5 to M25 (group 4) did not result in a significant increase in overall prevalence of AEs at 3M, though dry mouth, constipation and blurred vision occurred more frequently. This finding may be due to patients in this group had better response to combined OAB medications so that they could tolerate the mild antimuscarinic-related AE such as dysuria.

Compare the therapeutic efficacy between groups 3 and 4, we noted that PVR increased in both groups, but the OABSS and GRA were only improved in group 4 but not group 3, suggesting the combination of M25 and S5 was superior to S5 alone in the treatment of OAB patients after initial M25 treatment. In a previous 12-week study, OAB patients with persistent urinary incontinence after initial S5 treatment received additional treatment with M50. Combining M50 and S5 was superior to S5 alone in improving OAB symptoms and was well tolerated [24]. In real-life practice, for OAB patients who failed the initial mirabegron treatment, adding S5 to mirabegron might be better than switching from mirabegron to S5 alone. Previous studies have shown that patients who were successfully treated with mirabegron for ≥ 3 months, nearly half requested the resumption of mirabegron after discontinuation. There is no wonder why 47.6% of patients in group 4 preferred to resume M25 after treatment with M25 + S5 in this study [25].

At the end of this study, the majority of patients in group 1 (93.8%), group 2 (88.2%), and group 4 (47.6%), and a substantial percentage (27.3%) of patients in group 3 reported that they would prefer to take M25 for future treatment, showing the advantageous position of M25 if it was used first. Interestingly, in group 3, only 45.5% of patients reported that they preferred continuing to take S5 and 18.2% reported that they would like to try M25 plus S5. Moreover, although the therapeutic effect in group 4 was significantly better than that in the other three groups, only 38.1% of successfully treated patients in that group reported that they wanted to continue taking M25 plus S5 in future. The low drug adherence rate in groups 3 and 4 may have been due to dissatisfaction with unfavorable treatment-related AEs caused by S5.

The limitations of this study include the small sample size and high dropout rate, which might have affected the true treatment effects and prevalence of AEs at 3M. However, among the drop-out patients, 33.8% (23/68) of patients had no symptoms after the 1st month of M25 treatment. If we add these patients to the final patients with GRA ≥ 1 at 3 months, the treatment success rate would increase to 53.4% (88/168). The small sample sizes in each group may have lacked the power to detect a meaningful change in some efficacy parameters and prevalence rates of AEs from 1M to 3M. Nevertheless, the efficacy and safety results in this study provide evidence for a real-life practice in treating elderly patients with OAB. The results are also comparable with those in previous OAB studies investigating combination or add-on therapy using mirabegron and solifenacin.

Conclusions

Mirabegron 25 mg daily is effective and safe as an initial medication for elderly patients with OAB. Dose escalation to 50 mg or shifting to an antimuscarinic such as solifenacin 5 mg does not further increase the therapeutic effect. Combining mirabegron 25 mg with solifenacin 5 mg may provide better treatment efficacy but results in lower patient compliance than mirabegron 25 mg or 50 mg monotherapy.

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Conflicts of interest

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