Observational Study

High satisfaction with direct switching from antimuscarinics to mirabegron in patients receiving stable antimuscarinic treatment
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Abstract
Mirabegron, which was the first β3-adrenoceptor agonist introduced for use in clinical practice, has been extensively evaluated in overactive bladder (OAB) patients in several phase II and III studies. However, most of the enrolled patients were treatment naïve or had experienced a wash-out period before the introduction of mirabegron. No study has reported the treatment results of a direct switch from antimuscarinics to mirabegron, which may more commonly occur in clinical practice. This is an observational study to assess the therapeutic efficacy and safety of directly switching from antimuscarinics to mirabegron in patients with OAB receiving stable antimuscarinic treatment. Moreover, we sought to identify the patients who benefited more from the change.

Patients aged ≥20 years with OAB receiving stable antimuscarinics for >3 months were enrolled. Antimuscarinics were discontinued in all patients and mirabegron 25 mg, once daily was initiated. Primary end-point was global response assessment (GRA) at 1 month after medication switching. Baseline parameters and parameters changed 1 month after medication switching were compared between patients with GRA ≥1 and GRA <1.

Of the 282 enrolled patients (209 men, 73 women; mean age, 74.4 years), 55.3% had better (GRA ≥1), 31.2% had similar (GRA = 0), and 10.3% had worse (GRA < 0) outcomes. The overall adverse events (AE) rate decreased from 24.1% to 12.8%. In overall patients, there was no significant improvement of OAB symptoms; but postvoid residual (PVR) urine decreased and voiding symptoms and quality of life index improved significantly. Patients with GRA ≥1 had significantly improved both storage and voiding symptoms. A total of 195 patients (69.1%) can maintain mirabegron without adding or resuming antimuscarinics for more than 3 months. Logistic regression analysis indicated that higher baseline OAB symptoms scores were predictor of satisfactory outcome. More than 50% patients exhibited better outcomes after switching from antimuscarinics to mirabegron. Significantly lower AE rates and decreased PVR were noted. Higher baseline OAB symptom scores may predict a better outcome.

Abbreviations: AE = adverse events, 5ARI = 5α-reductase inhibitor, GRA = global response assessment, IPSS = international prostate symptom score, IPSS-S = IPSS storage subscore, IPSS-V = IPSS voiding subscore, OAB = overactive bladder, OAB-SS = overactive bladder symptom score, PPBC = patient perception of bladder condition, PPIUS = patient perception on intensity of urgency scale, PVR = postvoid residual, QoL-I = quality of life index, UTI = urinary tract infection.

Keywords: adrenergic beta-3 receptor agonists, muscarinic antagonists, overactive, urinary bladder

1. Introduction
Overactive bladder (OAB) syndrome is characterized by the presence of urinary urgency, with or without urgency urinary incontinence, and is usually accompanied by frequency and nocturia.[1] Antimuscarinics are the standard 1st-line treatment for OAB syndrome.[2-3] This medication has been suggested to reduce detrusor activity and improve bladder capacity via additional mechanisms, including the direct inhibition of afferent signaling at the level of the urothelium and suburothelium.[4] However, some patients may have a suboptimal response to antimuscarinics or may experience adverse events (AEs) such as dry mouth or constipation.[5,6] Therefore, a high proportion of patients discontinue antimuscarinics, and fewer than 25% continue treatment after 1 year.[7]

Beta3-adrenergic receptors are the predominant β-receptor subtype in human’s urinary bladder[8] and are known to promote urine storage by inducing detrusor relaxation.[9,10] Mirabegron, which was the 1st β3-adrenoceptor agonist introduced for use in clinical practice, differs from antimuscarinics in its mechanism of action.[11] Mirabegron has been extensively evaluated in more than 5000 patients with OAB syndrome in phase II and III studies.[12] These studies demonstrated significant improvements in micturition frequency, urgency incontinence, and mean volume voided/micturition, and these effects were maintained throughout the treatment course. Moreover, mirabegron appeared to be well tolerated by most patients.[13]

Although several clinical trials have evaluated the efficacy and safety of mirabegron in OAB patients,[13] most of the enrolled patients were treatment naïve or had experienced a wash-out period before the introduction of mirabegron. In clinical practice, we usually switch one medication to another one directly.
However, no study has reported the treatment results of a direct switch from antimuscarinics to mirabegron. Such an investigation would yield useful information regarding the proportion of patients who would benefit from this treatment strategy in the real world setting. Hence, in the present study, we aimed to assess the therapeutic efficacy and safety of directly switching medication from antimuscarinics to mirabegron without any washout period. Moreover, we sought to identify which patients benefited more from the change.

2. Materials and methods

We enrolled 282 patients aged ≥20 years with OAB who were receiving stable antimuscarinics (solifenacin or tolterodine) for >3 months from 2014 to 2015. Antimuscarinics were discontinued in all patients, and mirabegron (25 mg once daily, which was the recommended initial dose in Taiwan) was initiated. Other concomitant medications, such as α-blockers or 5α-reductase inhibitors (5ARIs), were continuously administered at a stable dose. In the study period, discontinuation of mirabegron, resuming, or adding antimuscarinics can be chosen by physicians and patients because of AEs or poor response to mirabegron. The exclusion criteria were stress urinary incontinence as a predominant symptom at screening; urinary tract infection (UTI), urinary stone, interstitial cystitis, or a history of recurrent UTI; overt bladder outlet obstruction that was not adequately controlled; and other severe medical diseases that prevented patients from undergoing a clinical investigation. The institutional review board and ethics committee of the hospital approved this study. The study rationale was explained to each patient, and written informed consent was obtained prior to treatment.

The treatment results were assessed by using GRA, international prostate symptom score (IPSS) and subscores, overactive bladder symptom score (OAB-SS), patient perception on intensity of urgency scale (PPIUS), patient perception of bladder condition (PPBC), and quality of life index (QoL-I) at 1 and 3 months after medication switching. Patients rated their symptoms after medication switching. Patients rated their symptoms after medication switching as compared to that at baseline by using a validated GRA scale, which comprises of 7 points, from markedly worse (−3) to markedly improved (+3). The safety assessments included the reporting of AEs, clinical laboratory assessments, vital signs, physical examination, and measurement of postvoid residual (PVR) volume.

The primary endpoint was the GRA at 1 month after medication switching. Changes in parameters such as IPSS, OAB-SS, PPIUS, PPBC, and QoL-I from baseline to 1 and 3 months after medication switching were also assessed. Patients with GRA ≥ 1 at 1 month were considered to have an improved outcome. The secondary endpoints included comparisons of the baseline parameters, and parameters changed 1 month after medication switching between patients with a GRA ≥ 1 and GRA < 1 to determine predictors of improved outcome.

2.1. Statistical analysis

The sample size calculations were based on our previous studies with antimuscarinics. Results were analyzed on an intention-to-treat (ITT) basis and included all patients who had taken at least 1 dose of medication. Missing data were imputed on the principle of last observation carried forward (LOCF). Safety data were analyzed for all randomized patients. Continuous variables are expressed as mean ± standard deviation, whereas categorical data are expressed as number and percentages. Statistical comparisons between the groups were performed using Chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Logistic regression analysis was used to identify the predictors of improved outcome (GRA ≥ 1). All statistical assessments were 2-sided and considered significant at P < 0.05. Statistical analyses were performed using SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL).

3. Results

A total of 282 patients (209 men and 73 women; mean age, 74.4 years) were enrolled, including 112 patients (39.7%) classified as OAB wet and 80 patients (28.4%) with detrusor overactivity. Moreover, 192 patients (68.1%) had ≥1 comorbidities including 72 (25.5%) with diabetes, 9 (3.2%) with chronic obstructive pulmonary disease, 19 (6.7%) with coronary artery disease, 12 (4.3%) with cerebral vascular accident, 17 (6.0%) with chronic kidney disease, and 151 (72.2%) of male patients with benign prostatic enlargement. Sixty patients (28.7%) were taking α-blockers, 1 patient (0.4%) was taking 5ARI, and 18 patients (8.6%) were taking both α-blockers and 5ARI along with medication for OAB. The mean duration of the antimuscarinic therapy before the switching was 9.1 months (range, 3–48 months).

At 1 month after medication switching, 54 patients (19.1%) reported marked improvement (GRA ≥ +3), 30 patients (10.6%) reported moderate improvement (GRA = +2), 72 patients (25.5%) reported mild improvement (GRA = +1), 88 patients (31.2%) reported no significant change (GRA = 0), 15 patients (5.3%) reported mild worsening (GRA = −1), 3 patient (1.1%) reported moderate worsening (GRA = −2), and 11 patients (3.9%) reported marked worsening (GRA = −3). Nine patients (3.2%) were lost of followed at 1 month. Of all the patients, 55.3% exhibited better outcomes (GRA ≥ 1) after medication switching, 31.2% exhibited similar outcomes (GRA = 0), and only 10.3% exhibited worse outcomes (GRA < 0). Of the 273 followed patients at 1 month after medication switching, 237 patients (84.0%) kept mirabegron use without antimuscarinics. Seventeen patients (6.0%) discontinued mirabegron and resumed antimuscarinics while 16 patients (5.7%) received “add-on” antimuscarinics with mirabegron after then. Three (1.1%) patients discontinued mirabegron and received other treatment.

Of the 237 patients with mirabegron for more than 1 month, 26 (9.2%) were lost of followed, and 211 patients (74.8%) were followed at 3 months after medication switching. The total of 195 (69.1%) kept mirabegron use without adding antimuscarinics. Seventeen patients (6.0%) discontinued mirabegron and resumed antimuscarinics while 16 patients (5.7%) received “add-on” antimuscarinics with mirabegron after then. Three (1.1%) patients discontinued mirabegron and received other treatment.

When comparing the baseline parameters with those at 1 and 3 months after medication switching (Table 1), we observed that the total IPSS and IPSS voiding subscore (IPSS-V) decreased significantly after medication switching. Moreover, the QoL-I and PPBC also significantly decreased. However, there was no significant change in the measurements of storage symptoms, such as IPSS storage subscore (IPSS-S), nocturia, OAB-SS, and PPIUS in overall patients. Furthermore, no significant change was observed in voided volume and Qmax, although the average PVR decreased significantly after switching medication.

When we separated patients into those with GRA ≥ 1 and GRA < 1, patients with GRA ≥ 1 had significantly decreased total
IPSS (IPSS-T), IPSS-V, IPSS-S, nocturia, QoL-I, OAB-SS, and PPBC after medication switching. In contrast, patients with GRA < 1 had significantly increased QoL-I, OAB-SS, and PPBC. There were no significantly change of Qmax, voided volume, and PVR. The average PVR decreased significantly in both groups (Table 2).

In addition, 68 patients (24.1%) had ≥ 1 AE with antimuscarinics, including 31 (11.0%) with dry mouth, 22 (7.8%) with constipation, 20 (7.1%) with dysuria, 3 (1.1%) with slow stream, 2 (0.7%) with blurred vision, and 1 (0.4%) with dizziness (Fig. 1A). After medication switching, 35 patients (12.8%) reported AEs such as dry mouth in 7 (2.6%), constipation in 5 (1.8%), dysuria in 6 (2.2%), slow stream in 2 (0.7%), dizziness in 4 (1.5%), general weakness in 2 (0.7%), back pain in 2 (0.7%), hypertension in 2 (0.7%), UTI in 1 (0.4%), headache in 1 (0.4%), and epigastralgia in 1 (0.4%) (Fig. 1B). All the AEs were mild and tolerable. The rate of AEs decreased from 24.1% to 12.8% after medication switching. In particular, the rate of dry mouth, constipation, and dysuria decreased significantly.

When comparing the baseline parameters between patients with GRA ≥ 1 and GRA < 1 after medication switching, we observed that patients with GRA ≥ 1 had higher baseline IPSS-S, OAB-SS, and PPBC values (Table 3). The other baseline parameters were similar between these 2 groups. Logistic regression analysis also indicated that baseline IPSS-S (odds ratio [OR] = 1.114, P = 0.018) and OAB-SS (OR = 1.103, P = 0.010) could serve as predictors of satisfactory outcome (GRA ≥ 1).

4. Discussions

To our knowledge, this is the 1st study to investigate the treatment results of direct switching from antimuscarinic to mirabegron treatment in patients receiving stable antimuscarinics. Otsuki et al[16] reported mirabegron was effective in 61.6% of patients unresponsive to antimuscarinics, and a significant decrease of OAB-SS and IPSS QoL-I was observed. In another posthoc subgroup analysis,[17] mirabegron treatment was found to be beneficial for OAB patients who were antimuscarinic treatment-naive and patients who had received prior antimuscarinic treatment. In the present study, we observed that even inpatients receiving stable antimuscarinic treatment, direct

Table 1

| Parameters changed before and 1 month after medication switching. | Baseline (n=282) | 1 month after switching (n=273) | 3 month after switching (n=211) |
|---|---|---|---|
| PSS-T | 10.3 ± 5.0 | 9.0 ± 5.6 | 7.8 ± 6.1 |
| PSS-V | 5.4 ± 5.3 | 4.5 ± 4.7 | 3.5 ± 4.6 |
| PSS-S | 4.9 ± 2.9 | 4.5 ± 2.5 | 4.4 ± 2.6 |
| Nocturia | 3.3 ± 1.2 | 3.1 ± 1.2 | 3.2 ± 1.2 |
| QoL-I | 2.7 ± 1.1 | 2.3 ± 0.9 | 2.0 ± 1.0 |
| Qmax | 12.1 ± 8.5 | 12.7 ± 8.8 | 12.2 ± 8.9 |
| Voided volume | 171.3 ± 121.0 | 181.1 ± 126.3 | 175.8 ± 136.1 |
| PVR | 67.7 ± 77.1 | 50.2 ± 59.4 | 49.3 ± 62.8 |
| OAB-SS | 17.1 ± 1.9 | 15.1 ± 1.7 | 14.8 ± 1.8 |
| PPBC | 2.6 ± 1.7 | 2.1 ± 1.4 | 1.9 ± 1.4 |

Table 2

| Parameters changed before and 1 month after medication switching in patients with GRA ≥ 1 and GRA < 1. | Baseline (n=156) | 1 month after switching | Baseline (n=117) | 1 month after switching |
|---|---|---|---|---|
| IPSS-T | 11.2 ± 7.2 | 8.3 ± 5.5 | 9.1 ± 5.2 | 9.9 ± 5.5 |
| IPSS-V | 5.8 ± 5.7 | 4.1 ± 4.6 | 4.8 ± 4.6 | 5.1 ± 4.7 |
| IPSS-S | 5.3 ± 3.0 | 4.2 ± 2.1 | 4.3 ± 2.5 | 4.8 ± 2.7 |
| Nocturia | 3.4 ± 1.2 | 3.2 ± 1.2 | 3.2 ± 1.3 | 3.3 ± 1.2 |
| QoL-I | 2.7 ± 1.2 | 2.0 ± 0.7 | 2.5 ± 1.0 | 2.8 ± 1.1 |
| Qmax | 11.9 ± 8.2 | 12.8 ± 9.0 | 12.6 ± 9.1 | 12.4 ± 9.2 |
| Voided volume | 161.6 ± 117.6 | 184.2 ± 131.3 | 175.0 ± 114.1 | 172.1 ± 110.8 |
| PVR | 70.5 ± 77.1 | 54.4 ± 65.1 | 63.2 ± 80.1 | 48.6 ± 54.7 |
| OAB-SS | 5.5 ± 3.6 | 4.5 ± 2.8 | 4.2 ± 3.0 | 5.2 ± 3.4 |
| PPBC | 1.9 ± 1.9 | 1.5 ± 1.9 | 1.4 ± 1.8 | 1.6 ± 1.8 |
| PPBC | 2.7 ± 1.7 | 1.7 ± 1.1 | 2.2 ± 1.5 | 2.6 ± 1.7 |

Figure 1. (A) Adverse events (AEs) before switching medication to mirabegron. (B) AEs after switching medication to mirabegron.
switching of medication from antimuscarinics to mirabegron (25 mg, once daily) was safe and effective.

The present study showed that more than 50% patients exhibited better outcomes after medication switching. Although the QoL-I and PPBC values improved significantly, there was no significant change in OAB symptom parameters such as IPSS-S, OAB-SS, and PPIUS in overall patients. This finding suggests that a change in the medication from antimuscarinics to mirabegron (25 mg) in patients receiving stable antimuscarinics may not yield additional improvement of OAB symptoms. Our results are consistent with a previous meta-analysis reporting that mirabegron has similar efficacy to most antimuscarinics. Batista et al. also reported that both mirabegron and solifenacin improved key OAB symptoms with no statistically significant differences in OAB patients who were dissatisfied with the previous antimuscarinic treatment due to lack of efficacy. An increase in the mirabegron dose from 2.5 to 50 mg may increase the efficacy of the medication. Nevertheless, further study is needed to confirm whether 50 mg would be better than 25 mg mirabegron in such conditions as direct medication switching.

In our study, patients with GRA ≥ 1 had significantly decreased IPSS-T, IPSS-V, nocturia, QoL-I, OAB-SS, and PPBC after medication switching, while patients with GRA < 1 had significantly increased QoL-I, OAB-SS, and PPBC. Although there was no significantly change of OAB symptoms in overall population, some patients could have improved OAB symptoms. However, OAB symptoms may get worse in others. The different responses may be attributable to heterogeneous OAB subgroups and different mechanism of action of antimuscarinics and mirabegron. Patients with GRA ≥ 1 may respond to antimuscarinics better than mirabegron. Nevertheless, to improve the storage symptoms among these patients, add-on therapy with mirabegron and antimuscarinics may offer an attractive therapeutic option. In fact, Yamaguchi et al. reported that mirabegron as an “add-on” therapy to solifenacin yielded significant improvements in OAB symptoms.

Although direct switching medication from antimuscarinics to mirabegron could only result in the improvement of storage symptoms in 55.3% of the patients, the total IPSS and IPSS-V significantly improved. In addition, the PVR significantly decreased, no matter in patients with GRA ≥ 1 or GRA < 1. The improvement in voiding symptoms and decrease in PVR may explain the high rate of satisfaction. It is possible that the detrusor contractility and sustainability could be affected by antimuscarinics but not mirabegron even the average PVR < 100 mL before medication switching. Hence, patients whose voiding efficiency affected by antimuscarinics might have improved voiding condition after switching to mirabegron.

Furthermore, the rate of common AEs due to antimuscarinic treatment, including dry mouth, constipation, and dysuria, also decreased significantly. This decrease in the AE rate may also contribute to the high satisfaction rate. In addition, persistence in a specific drug depends on the fulfillment of patients’ expectations and the occurrence of AE that lead to discontinuation in daily practice. It is known that persistence in antimuscarinic use is poor. Pindoria et al. reported 69% of patients persisted with mirabegron, but the persistent rate fell to 48% by 6 months. The commonest reasons for discontinuation are unmet treatment expectations and AEs. In a retrospective claims from a Canadian Private Drug Plan database, patients using mirabegron had statistically significantly higher adherence rate than those using antimuscarinics. The persistence rate at 12 months for mirabegron was 30% to 39%. In our study, 69.1% of patients kept mirabegron use for more than 3 months. Longer follow-up is needed to report the longer-persistent rate in such condition. Although cardiovascular safety is a major concern associated with mirabegron, the cardiovascular safety of mirabegron appears to be acceptable at therapeutic doses and comparable with that of antimuscarinics in a systematic literature review. The overall AE rates decreased from 24.1% to 12.8% and only 1 patient reported hypertension in our study.

Moreover, we sought to assess which patients would benefit more from the medication switching, and found that higher baseline storage parameters, such as IPSS-S and OAB-SS, can serve as predictors of improved outcome (GRA ≥ 1). These results are consistent with previous reports, wherein storage symptom scores such as IPSS-S or OAB-SS were recommended as predictors of favorable outcomes with antimuscarinics. Chapple et al. conducted a posthoc analysis in subgroups of patients stratified according to the severity of incontinence at baseline. They observed that the treatment effect increases with an increase in the severity of incontinence. Hence, the severity of incontinence and storage symptoms should be importantly considered prior to the use of mirabegron.

One advantage of the present study is that the results can easily be applied to real world clinical practice as the study mimics the
clinical setting. Moreover, the present study found that, although the storage symptoms did not generally improve in overall patients, >50% of patients reported improved outcomes due to a decrease in AE rate and PVR and improvement in voiding symptoms. The major limitation of the present study is the lack of a placebo arm. In particular, we did not compare our results with those of patients who continued to receive antimuscarinics. Hence, it is difficult to conclude that the switching of antimuscarinics to mirabegron is more favorable than the maintenance of antimuscarinic treatment. Nevertheless, the current study describes the results of direct switching from antimuscarinics to mirabegron, and suggests the predictors of improved outcomes.

5. Conclusions

We observed that >50% patients reported better outcomes (GRA ≥1) and that a significantly lower AE rate was observed after switching from antimuscarinics to mirabegron treatment. Moreover, a significant decrease in PVR and improvement in voiding symptoms as well as in QoL-I were observed. A total of 195 patients (69.1%) can maintain mirabegron without adding or resuming antimuscarinics for more than 3 months. Higher baseline OAB symptom scores, such as OAB-SS and IPSS-S, might serve as predictors of better outcomes in OAB cases undergoing medication switching from antimuscarinics to mirabegron.

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