Original article

A pilot study of mirabegron added to solifenacin in the treatment of overactive bladder

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Abstract. Objectives: The ß$_3$ adrenergic receptor agonist mirabegron was clinically indicated as a new therapeutic drug for overactive bladder (OAB) in Japan in September 2011. However, mirabegron has yet to be investigated in detail in this context. To further characterize this agent, we administered 25 mg of mirabegron as add-on therapy to female patients with confirmed OAB who displayed persisting OAB symptoms despite receiving solifenacin and investigated clinical efficacy by comparing overactive bladder symptom scores (OABSS) and residual urine volume and determining whether adverse drug reactions were worsened at Weeks 4, 8, and 12.Methods: Participants in the study comprised 20 female patients with persisting symptoms of OAB despite solifenacin treatment and with OABSS ^{3}3 (and urgency score ^{3}2). Mean age was 73.4 years (range, 44-90 years). Results: OABSS totals were significantly improved at Week 4 and had decreased on average by 3.95±2.11 by Week 12. At Week 12, 16 (80%) of subjects achieved a reduction of ^{3}3 points in total OABSS, and no subject showed worsening of adverse drug reactions. Urge urinary incontinence resolved in 6 of the 12 affected subjects (50%). No significant differences were present in residual urine volume, no subject reported worsening of dry mouth or constipation as an adverse drug reaction, and no subject was discontinued from treatment. Conclusions: Used concomitantly with an anticholinergic drug, mirabegron produced an excellent therapeutic effect in OAB and presented no safety concerns. This combination could provide a new option for patients showing OAB refractory to anticholinergic drugs or severe OAB.

Key words: OAB; Mirabegron; Solifenacin; OABSS; UUI.

INTRODUCTION

The International Continence Society in 2002 defined overactive bladder (OAB) as a symptom syndrome characterized by urinary urgency with frequency, nocturia, and urge urinary incontinence.[1] The ß$_3$ adrenergic receptor agonist mirabegron was first clinically indicated as a new therapeutic drug for OAB in Japan, receiving this designation in September 2011, but in this context has yet to be investigated in detail. Currently phase III testing is underway in the European Union on the concomitant use of the ß$_3$ adrenergic receptor agonist mirabegron with anticholinergic drugs.[2] The concept of anticholinergic drugs as combined therapy with mirabegron has never been studied previously. To increase the understanding of mirabegron, we investigated the efficacy of add-on mirabegron administered to female OAB patients who had persisting OAB symptoms despite receiving solifenacin treatment and who were unable to take a higher dose or were forced to take a lower dose of solifenacin because of adverse drug reactions.

We tried this study as Pilot Study.

PATIENTS AND METHODS

Subjects enrolled in the study were female OAB patients in the Department of Urology, Kobayashi Hospital (an affiliate hospital of Showa University Northern Yokohama Hospital) who experienced improvement but still had persisting OAB symptoms following 3 months of treatment with the anticholinergic drug solifenacin, who still satisfied the diagnostic criteria for OAB after treatment (i.e., urgency score 2 and total of 3), and who were unable to take a higher dose or were forced to take a lower dose of solifenacin because of adverse drug reactions. Subjects were given 25 mg of mirabegron with solifenacin once daily after breakfast for 12 weeks. Subjects were evaluated in Weeks 4, 8, and 12. OABSS, number of night-time episodes, and residual urine volume were determined, and worsening of adverse drug reactions was monitored. The Wilcoxon signed-ranks test was used to evaluate OABSS, and a paired t-test was used to analyze residual urine volume data. Values of $p<0.05$ constituted a significant difference. Informed consent was obtained from all patients.

RESULTS

Backgrounds, OABSS, residual urine volume, and symptoms prior to mirabegron treatment of the 20 subjects enrolled in the study are shown in Table 1. Significant improvement was seen in the OABSS items of "daytime frequency" and "urge urinary incontinence" beginning at Week 8, "nocturia" beginning at Week 12, and "urinary urgency", as the number of night-time episodes, and OABSS total beginning at Week 4. Mean OABSS total had decreased by 3.95±2.11 by Week 12. Ten (50%) of the subjects in Week 4 and 16 (80%) in Week 12 had achieved a

TABLE 1. – Pre-treatment symptoms.

Background		
Age	73.4	(44-90)
Solifenacin		
10mg	1	(5.0%)
5mg	11	(55.0%)
2.5mg	8	(40.0%)
OABSS		
mild(0-5)	0	0
moderate(6-11)	18	(90%)
severe(12-15)	2	(10%)
OABSS Total score	8.75	±2.27
Daytime frequency	0.95	±0.69
Nocturia	2.3	±0.92
Urinary urgency	3.7	±0.92
Urge urinary incontinence	1.8	±1.82
OAB wet	12	(60.0%)
Dry mouth	11	(55.0%)
Constipation	2	(10.0%)
Post Voiding Residual (Rate)	13.4ml	±39.23

reduction of 3 in OABSS total, and no subject showed worsening of adverse drug reactions. Urge urinary incontinence resolved in 6 of the 12 subjects (50%) with urge urinary incontinence at baseline. Residual urine volume did not differ significantly (Figure 1). No subjects reported worsening of dry mouth or worsening of constipation as adverse events, and no subject was discontinued from treatment.

DISCUSSION

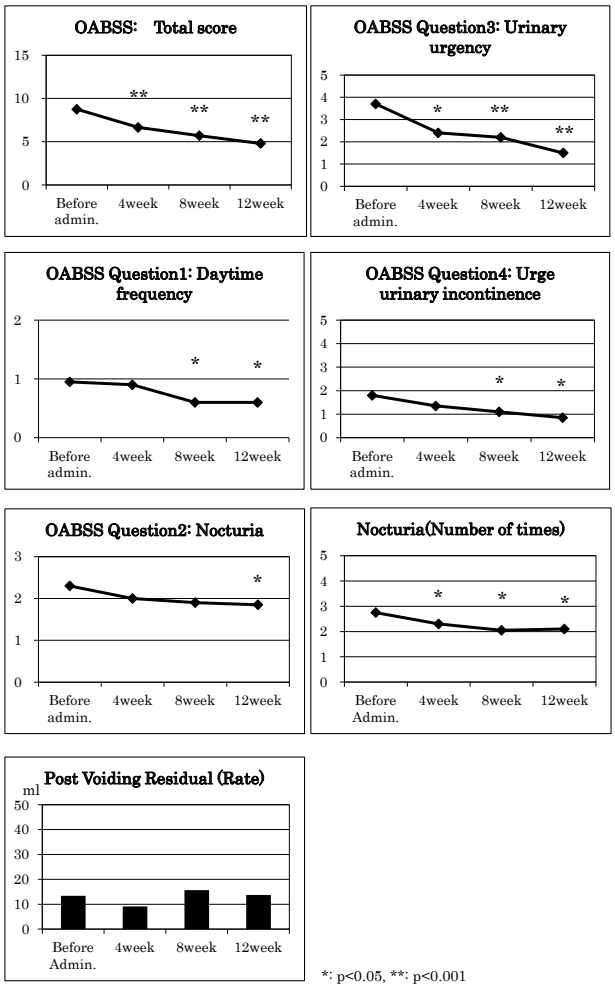
The prevalence of OAB in Japan is 12.4% among individuals 40 years old, increasing to 37% in individuals 80 years old. Twenty-three percent of affected individuals seek medical help for OAB.[3] Urodynamic investigation is not needed to diagnose OAB, which can be diagnosed on the basis of the presence of urinary urgency as a symptom. A diagnosis of OAB is made when there is at least one weekly episode of urinary urgency as assessed with the OABSS, with a total OABSS score 3.[4] Gotoh et al. reported that the minimal clinically important change in total OABSS score is -3 points.[5]

The mechanism of urinary urgency has been characterized. Expansion of the bladder causes the release of various factors from the epithelium of the urinary tract. Prostaglandins (PG), tachykinin (TK), adenosine triphosphate (ATP), and acetylcholine (Ach) stimulate sensory C-fibers, and nitric oxide (NO) and vasoactive intestinal peptide (VIP) suppress sensory nerve activation. Under pathological conditions, changes in these factors occur. Sensory nerve (primarily C-fiber) stimulation promotes the voiding reflex. This is one postulated cause of OAB.[6] Anticholinergic drugs inhibit acetylcholine, which in turn inhibits stimulation of sensory C-fibers and thereby inhibits urinary urgency. The most widely distributed adrenoceptor in the human bladder is the ß3 receptor.7 The release of NO is promoted by ß3 agonists via the ß3 adrenergic receptor, enhancing the suppression of sensory C-fiber activation. G protein concurrently released from the ß3 receptor activates adenylate cyclase, facilitating the breakdown of ATP into cyclic adenosine monophosphate. This breakdown of the ATP-stimulating sensory C-fibers suppresses urinary urgency. The therapeutic efficacy of ß3 agonists on OAB derives from these two pathways.

Options for OAB treatment include pharmacotherapy, interferential low-frequency therapy, and botulinum toxin injection. Pharmacotherapy is the most widely used option. OAB guidelines give most anticholinergic drugs a recommended grade of A.[1,4] Adverse drug reactions to anticholinergic drugs, however, include dry mouth and constipation due to muscarinic receptor inhibition and urinary disturbances, and urinary retention due to the extended suppression of bladder hyperactivity. These adverse drug reactions occur more frequently than is commonly thought and are sometimes not reported to the attending physician.[8] Doctors must weigh the likely benefits of treatment against the potential adverse reactions to these drugs when administering treatment. Ito et al. found that dry mouth and constipation are more severe in untreated OAB patients than in non-OAB patients. Anticholinergic drugs must be given with care to OAB patients, who are already at increased risk of oral dryness and constipation, because of the potential to reduce patient quality of life and cause potential poor compliance.[9] The shortcomings of anticholinergic drugs led to the development of drugs with different mechanisms of action and fewer adverse drug reactions. The ß3 agonists do not act on cholinergic receptors and therefore do not cause adverse drug reactions such as dry mouth and constipation as frequently as anticholinergic drugs. Although a direct comparison with anticholinergic drugs is not possible, the general impression is that the efficacy of ß3 agonists is somewhat inferior (Table 2).[10,11] Anticholinergic drugs have been found to be effective beginning in the early stage of treatment.[12] When an anticholinergic drug was used with mirabegron, total OABSS had improved by Week 4 and continued improving through Weeks 8 and 12.

In Japan, 5.80 million people suffer at least one urge urinary incontinence episode per week, and 3.40 million have at least one episode daily.[13] Urinary incontinence resolved in 50% of subjects receiving 5 mg or 10 mg of solifenacin in a Japanese phase III study.[11] In the STAR trial, urinary incontinence resolved in about 60% of solifenacin group patients.[14] In research conducted by Suzuki et al., urinary incontinence resolved in 28.6% of patients switched to solifenacin because

Figure 1.



*: p<0.05, **: p<0.001

TABLE 2. – An effect and side effect incidence in the Japanese phase III trial of Mirabegron and Solifenacin.

	Mirabegron 50 mg	Solifenacin 5 mg	Solifenacin 10 mg
Effect			
Urinary frequency (×/24H)	-1.67±2.212	-1.93±1.97	-2.19±2.09
Urgency (×/24H)	-1.85±2.555	-2.41±2.88	-2.78±2.82
UUI (×/24H)	-1.01±1.338	-1.45±1.89	-1.52±1.77
Nocturia	-0.44±0.933		
Residual urine	8.76ml → 9.58ml		
Voided volume	+24.3ml ±35.5ml	+35.8ml ±43.4ml	+43.6ml ±44.5ml
Side effects			
Oral aridity	1.70%	41.30%	
Constipation	2.90%	19.80%	
Blurring of eyes	0%	5.20%	
Difficult voiding	0.10%	4.00%	
Vertigo	0.20%	2.40%	

of a failure to respond adequately to imidafenacin.[15] Treatment with once-daily mirabegron achieved improvements in urge urinary incontinence in a Japanese phase III study of the drug. In the present add-on study, urge urinary incontinence resolved in 6 of the 12 affected patients (50%), indicating the beneficial effect of add-on mirabegron.

During voiding, acetylcholine normally binds to muscarinic receptors to suppress adenylate cyclase activity and thereby promote bladder smooth muscle contraction. The ß$_3$ agonists activate adenylate cyclase, but do not result in bladder smooth muscle relaxation associated with the suppression of adenylate cyclase by acetylcholine and therefore do not impact detrusor muscle contraction during voiding.[16] Patients in the present study, who were first treated with solifenacin and were in a state without adenylate cyclase suppression, may have achieved greater relaxation of bladder smooth muscle when ß$_3$ agonist treatment synergistically activated adenylate cyclase. Even so, these patients experienced no changes in residual urine volume or urinary retention. Mirabegron thus may not impact the voiding profile of patients who experience no urinary disturbance and may not cause smooth muscle relaxation in association with anticholinergic drug treatment.

In our study, mirabegron was added to prior solifenacin treatment. To improve safety, beginning treatment with mirabegron may be better, as this agent is associated with fewer adverse drug reactions, but subsequent addition of an anticholinergic drug could result in urinary disturbance. However, in terms of efficacy, beginning treatment with solifenacin as in this study and then adding mirabegron after confirming the absence of urinary disturbance may be better.

The adverse drug reactions associated with anticholinergic drugs lower patient quality of life and sometimes force treatment to be changed, reduced, or discontinued. Concomitant treatment with mirabegron and an anticholinergic drug thus may not only produce greater therapeutic effects in OAB, but, provided concomitant treatment alleviates the symptoms of OAB, may also allow the dose of anticholinergic drug to be reduced and therefore reduce adverse drug reactions, improving patient quality of life. This combination could become a new option for treating OAB refractory to anticholinergic drugs or severe OAB.

This is the first report anywhere to describe concomitant treatment with a ß$_3$ agonist and an anticholinergic drug. The next logical step is to follow patients to determine long-term treatment outcomes and whether anticholinergic drug doses can be reduced.

And a larger study is required to assess any patient benefit.

A presentation describing this study was given at the 19th Conference of the Neurogenic Bladder Society of Japan.

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