



Review Article

Individualizing medical treatment of overactive bladder

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ABSTRACT

Overactive bladder (OAB) syndrome is highly prevalent in both men and women and might have negative impact on quality of life. Clinical trials of OAB usually highly select participants that may not reflect the real-world practice of OAB patients. The spectrum of OAB includes patients with idiopathic, neuropathic, with bladder outlet obstruction, and patients in elderly and medical comorbidities. Patients might have poor response to OAB medication or have adverse events after treatment. Therefore, treatment of OAB should be individualized to obtain therapeutic efficacy and avoid unacceptable adverse events. This article reviews the recently published literature and provides a guide for physicians to choose the appropriate treatment for different OAB patients.

KEYWORDS: *Bladder, Efficacy, Side effect, Urinary incontinence*

INTRODUCTION

Overactive bladder (OAB) is a clinical diagnosis of a syndrome with core symptom of urgency, accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI) [1]. Although the initial definition of OAB is a syndrome with urgency-frequency with and without UUI but no identifiable pathology can be found, nowadays the spectrum of OAB has been extended to cover urgency bladder symptoms caused by systemic or lower urinary tract disorders. The strongest predictor of OAB-associated bother is urinary urgency [2]. OAB symptoms can be quite bothersome and can negatively affect health-related quality of life [3,4]. Patients with medical comorbidities such as congestive heart failure (CHF) and diabetes mellitus (DM) may have greater risk of OAB, especially in elderly patients [5].

SPECTRUM OF OVERACTIVE BLADDER SYNDROME

Although the initial diagnosis of OAB is a syndrome without definite etiology or underlying diseases, nowadays, OAB has been widely used in describing the urgency-frequency symptoms occurring in patients with or without identifiable diseases. Under this concept, OAB has been widely used to describe idiopathic detrusor overactivity (IDO), associated with bladder outlet obstruction (BOO) and DO, combined detrusor overactivity and inadequate detrusor contractility (DHIC), in patients with latent neuropathy such as cerebral vascular accident (CVA), Parkinson's disease, dementia, intracranial lesion, mixed intrinsic sphincter deficiency and DO, or in patients with systemic diseases such as DM, CHF, chronic kidney disease, and cardiovascular disease [6]. Patients with OAB may have urinary incontinence at the urge

sensation (OAB wet) or urgency without urinary incontinence (OAB dry).

Treatment of OAB has been well documented in the AUA and EAU guidelines [7,8]. All guidelines recommended that the first-line OAB treatment should be patient education and lifestyle modification. Pharmacological treatment with oral antimuscarinics or beta-3 adrenoceptor agonists serves as second-line therapy. If a patient experiences inadequate symptom control or having unacceptable adverse drug events with one antimuscarinic agent, then a dose modification or a different antimuscarinic agent or a beta-3 adrenoceptor agonist may be tried [7]. In 2017 EAU guidelines on urinary incontinence, mirabegron was further recommended for patients with OAB and inadequate response to conservative treatment although the efficacy was considered equal between mirabegron and antimuscarinic agent [8].

Mirabegron is a beta-3 adrenoceptor agonist which is a new class drug for the treatment of OAB [9]. In Phase 2 and Phase 3 clinical trials, mirabegron has been demonstrated significant dose-dependent improvements in key OAB symptoms [10]. In pooled efficacy and safety analysis, mirabegron at 50 and 100 mg dose was shown superior to placebo. Mirabegron significantly decreases the urgency severity and the number of urgency and UUI episodes than placebo, and the efficacy was similar between 50 and 100 mg [11]. In Asian multicenter clinical trial, mirabegron was also demonstrated effectively

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improved micturition episodes and voided volume compared with placebo and Detrusitol [12]. The results of Asian mirabegron study were similar to the studies of Japan, Europe, and the United States [13].

OVERACTIVE BLADDER TREATMENT IN PATIENTS WHO FAIL THE FIRST MEDICATION

In the real-life practice, not all OAB patients can have symptom relief after conservative treatment and antimuscarinic therapy. In patients who fail the first OAB medication therapy, we may increase the dose of antimuscarinic medication, increase treatment duration, shift to another antimuscarinic medication, shift to mirabegron, combine antimuscarinic agent and mirabegron, or consider botulinum toxin A injection [14]. However, higher dose of antimuscarinic agent or combined two or more OAB medications may also increase rates of adverse events of drugs. In addition, we should search for underlying BOO or neurogenic lower urinary tract dysfunction and treat appropriately [8].

In a clinical trial of adding a second antimuscarinic agent on the first antimuscarinic agent in treatment of refractory OAB, only 24% of patients continued the combination medication for up to 12 months. Discontinuation of the combined medication was noted in 21.7% of patients due to adverse events and 54.3% of patients due to lack of efficacy [15]. In another clinical trial, we directly switched OAB medication from stably treatment with antimuscarinic agent to mirabegron [16]. The OAB symptom improvement was noted in 57.1% of patients and the rates of adverse events decreased after switching medication. Patients who have a higher IPSS storage subscore and OAB symptom score after initial antimuscarinic medication may predict a better mirabegron treatment outcome. In a recent Phase 2 clinical trial, combination treatment with mirabegron 25 or 50 mg with different doses of solifenacin showed that combination therapy significantly increased the maximal voided volume, reduced frequency, and urgency episodes than solifenacin monotherapy [17]. It is reasonable to use combination treatment in OAB patients who fail the first medication of antimuscarinic agent or mirabegron alone.

OVERACTIVE BLADDER TREATMENT IN MALE PATIENTS

In male patients with OAB, the selecting medication usually includes drugs for BOO. Antimuscarinics are usually reserved as second-line medication in men with OAB because of fearing of the risk of precipitating urinary retention. In an analysis of the pathophysiology of 2991 male patients with lower urinary tract symptoms (LUTS) by video urodynamic study, BOO was noted in 1941 (64.9%) patients and bladder dysfunction in 919 (30.7%), including DHIC in 159 (5.3%) and DO in 508 (17.0%) patients [18]. The incidence of bladder dysfunction increases with increasing age but decreases with increasing total prostate volume [19]. A previous study revealed that antimuscarinic therapy alone or in combination with alpha-1 receptor antagonists improves OAB symptoms in men with and without BOO [20]. The current guidelines suggest that antimuscarinic monotherapy can be used for

men without BOO, while combination therapy is usually suggested for men with concomitant BOO and OAB [21,22]. In a recent study, Liao *et al.* found that first-line antimuscarinic monotherapy is safe and effective for men with enlarged prostate and predominant storage symptoms. Small total prostate volume, higher maximum flow rate, and greater IPSS storage subscore are predictors of successful first-line antimuscarinic monotherapy [23].

In male patients with BOO, OAB symptoms may persist after medical treatment for OAB. For the patients with OAB after BOO treatment, a high success rate was noted in 75% of patients after adding on antimuscarinic medication [24]. However, our recent study showed that the therapeutic effect of mirabegron 25 mg daily monotherapy on patients with OAB due to BOO was not as effective as that in OAB patients without BOO [25]. Therefore, combined antimuscarinics or mirabegron with alpha-blocker treatment is generally more effective than monotherapy or placebo. A previous urodynamic study revealed that mirabegron therapy did not affect detrusor contractility, and it is reasonable to consider mirabegron as the first-line therapy for patients with OAB due to BOO [26].

OVERACTIVE BLADDER TREATMENT IN ELDERLY PATIENTS AND PATIENTS WITH DHIC

Patients with DHIC or older age usually have low detrusor contractility, low Qmax, and large postvoid residual (PVR). Antimuscarinic treatment in patients with DHIC might increase risk of difficult urination and large PVR and subsequent urinary tract infection (UTI). Adding antimuscarinic medication on alpha-blocker has been shown safe and effective in improving LUTS in short term without increased PVR and urinary retention [27]. Our previous study also showed the safety and efficacy of antimuscarinic add-on alpha-blocker in elderly male patients with clinical benign prostatic hyperplasia (BPH) [28]. Our recent study revealed that the use of mirabegron in elderly patients is safe and effective in improvement of OAB symptoms without increase of PVR [29]. Both patients with DO and DHIC can have improvement in patient perception of bladder condition, but the efficacy was less in DHIC patients, although PVR did not increase after mirabegron treatment [30]. Another concern on long-term antimuscarinic therapy in the elderly is cognitive dysfunction. It has been noted that antimuscarinic long-term use may increase risk of cognitive dysfunction in patients with OAB due to Alzheimer's disease [31]. Therefore, mirabegron should be considered the first choice of medication for elderly patients with OAB [8].

In elderly patients with central nervous system (CNS) lesions such as CVA, Parkinson's disease, or early dementia, antimuscarinic therapy has a high success rate, but cognitive dysfunction and impaired bladder emptying during treatment with nonselective antimuscarinic medication for OAB are of growing concern [32]. Mirabegron at the dose of 25 mg QD has been demonstrated safe and effective in improving OAB symptoms without impairment of voiding efficacy in this group of patients [33]. However, mirabegron at the dose of 25 mg seems not effective in improvement of nocturia in patients with hypersensitive bladder without OAB [34].

HOW LONG SHOULD WE GIVE OVERACTIVE BLADDER MEDICATION TO PATIENTS?

OAB symptoms usually show improvement 2 weeks after medical treatment, and the effect will continue to improve up to 3 months. There is no consensus regarding the most appropriate therapeutic duration of antimuscarinic or mirabegron treatment. After discontinuing antimuscarinic therapy for 3 months, the micturition frequency and urgency episodes increase, 65% requests retreatment and 62% experienced symptom relapse [35]. In another long-term follow-up of OAB medication, adherence revealed that patients usually discontinue treatment in a mean duration of 3.3 months [36]. The reasons of discontinuation of antimuscarinics are improved OAB symptoms (46.7%), tolerable OAB symptoms (33.3%), no change of OAB symptoms (1.3%), side effects (8.0%), and no desire to take long-term medication (10.7%). Patients older than 60 years are more likely to persist with prescribed therapy over the 12-month period than those younger than 60 years [37]. Among the OAB medications, persistence at 12 months was the higher in mirabegron (39% and 30%) than that in antimuscarinic agents (14%–35% and 14%–21%) in experienced patients and treatment naïve patients, respectively [38].

In one recent clinical trial, mirabegron treatment was discontinued in OAB patients with symptom improvement after 3-month medication [39]. Among 682 patients treated with mirabegron for 3 months, 321 (47.1%) did not come back, 109 (16.0%) continue mirabegron treatment due to symptom persist, and 252 (36.9%) discontinued medication and return for follow-up visit. Among the 252 patients discontinued mirabegron, 83 (32.9%) resumed medication due to symptom relapse. Multivariate analysis revealed that an urgency severity scale of >1 after mirabegron therapy for 3 months is the predictor for resuming OAB treatment. Based on this result, if patients still have urgency with a severity score of >1 after 3-month medication, mirabegron treatment should be continued to avoid symptom relapse. If patients do not have urgency sensation after 3-month medication, the OAB treatment may be discontinued and the medication is resumed on demand.

WHAT IS THE APPROPRIATE DOSE FOR OVERACTIVE BLADDER PATIENTS?

The recommended dose of mirabegron for OAB was 50 mg QD in Europe, Japan, and most countries. However, because of the adverse event of hypertension, the starting dose of mirabegron is 25 mg which is recommended in the United States, Taiwan, Singapore, and some Asian countries. If the initial mirabegron dose fails to eradicate OAB symptoms, the dose is recommended to 50 mg for a better treatment outcome. In our recent study, we found that escalating dose of mirabegron from 25 to 50 mg can increase the rates of patients with USS improvement in patients who received initial 25 mg treatment for 1 month and followed by 50 mg for 2 months, in comparison with those received 25 mg for 3 months (34.5% vs. 15.6%, $P = 0.031$) [40]. The episodes of UUI also decreased significantly from 1 to 3 months after escalating from 25 to 50 mg of mirabegron. The rates of adverse events are equal between two groups. It

is rational to increase dose of mirabegron if the initial treatment with a lower dose fails. However, if there is only one choice for selecting mirabegron in the hospital, a 50-mg dose should be appropriate as a starting medication.

WHAT IF ALL OVERACTIVE BLADDER ORAL DRUG TREATMENTS FAIL?

In patients who failed conservative treatment and oral OAB drug treatment, intravesical botulinum toxin A injection should be given to eradicate OAB symptoms. This treatment has been listed in the OAB treatment guidelines in AUA and EAU [7,8]. A dose of 100U onabotulinumtoxinA is recommended to inject into the bladder wall at 20 points [41]. There have been well documented that onabotulinumtoxinA injection can decrease daily micturition episodes, urgency, and UUI episodes and improve quality of life, and the therapeutic efficacy of single injection lasts for >9 months and is durable in the long-term follow-up [42-44]. However, increase of PVR and decrease of voiding efficiency are unavoidable adverse events in the 1st month after onabotulinumtoxinA injection. UTI might also occur in patients who have greater PVR after onabotulinumtoxinA injection [45]. Therefore, clean intermittent catheterization should be instructed to patients who are planning to receive this treatment. Frail elderly patients are more vulnerable to experiencing complications [46]. The onabotulinumtoxinA injection treatment should be cautiously given in the frail elderly OAB patients who might have a higher rate of PVR >150 mL or acute urinary retention [47]. The cumulative success rate was also significantly lower in the frail OAB patients [48]. To avoid the adverse effects of acute urinary retention or large PVR, selecting trigonal injection of onabotulinumtoxinA might be a better choice, especially in the patients who have PVR >100 mL before injection [49].

CONCLUSION

OAB treatment with antimuscarinics or beta-3 adrenoceptor agonist (mirabegron) is feasible as the first-line medication. Initial experience of low-dose mirabegron treatment seems effective in OAB patients, patients with BOO or non-BOO, very old OAB patients, DHIC, and patients with CNS lesions. In patients who have less favorable response to antimuscarinics, immediate switching to mirabegron had better outcome. In patients who are stably treated with antimuscarinics, shifting to mirabegron may decrease adverse events and have similar or better therapeutic effect. Starting from a small dose of mirabegron (25 mg) is effective for OAB. For patients with suboptimal effect to mirabegron 25 mg, escalating to mirabegron 50 mg or combination with antimuscarinics can improve therapeutic efficacy. Intravesical botulinum toxin A injection provides therapeutic effects on OAB refractory to antimuscarinics or mirabegron treatment. Men with persistent OAB after medical treatment for LUTS suggestive of BPH and BOO should be considered and adequately treated. Although adding mirabegron is also effective in patients with BOO, mirabegron monotherapy has less favorable effect than OAB patients without BOO. Treatment duration of 3 months for OAB is adequate for most OAB patients. An urgency severity score of >1 predicts resuming mirabegron medication after discontinuing

from 3-month treatment. If OAB relapsed after discontinuation, life-long treatment might be necessary.

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Conflicts of interest

There are no conflicts of interest.

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