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REVIEW

Clinical Utility of β_3-Adrenoreceptor Agonists for the Treatment of Overactive Bladder: A Review of the Evidence and Current Recommendations

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Abstract: This nonsystematic review provides a summary of current evidence on the use of β_3-adrenoreceptor agonists (β_3-ARAs) for the treatment for lower urinary tract symptoms. Soon after their discovery in 1989, β_3-ARs were identified as a predominant adrenoreceptor subtype in the human urinary bladder. Although it is widely believed that β_3-ARAs cause detrusor relaxation, the effect on bladder afferent signaling likely plays an important role in their mechanism of action as well. In 2011 and 2012, mirabegron was approved for clinical use in overactive bladder (OAB) patients. Pooled analysis of data from prospective randomized studies on >60,000 OAB patients showed that when compared to placebo, mirabegron was superior with respect to reducing the frequency, number, and severity of urgency episodes, number of incontinence episodes and increasing dry rate, but not in reduction of nocturia episodes. The only side effect showing significantly higher incidence than placebo was nasopharyngitis. Mirabegron is approved for OAB treatment in all age-groups and in pediatric patients with neurogenic bladder. Vibegron is another β_3-ARA approved for OAB treatment in the US and Japan. Several large, multicenter, double-blind, randomized trials have documented statistically significant superiority of vibegron over placebo on all efficacy end points. Other β_3-ARAs are being developed; however, to date none has been introduced to clinical use. All β_3-ARAs provide efficacy similar to anticholinergics. They have a favorable safety profile and are well tolerated. Due to their different mechanisms of action, combination of β_3-ARAs with anticholinergic compounds allows for increased efficacy.

Keywords: urinary bladder, beta-mimetics, efficacy, safety, mirabegron, vibegron

Introduction

Overactive bladder (OAB) syndrome is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence in the absence of urinary tract infection or other obvious pathology.[1] OAB affects 12%–16% of the adult population in Europe and the US.[2] Although OAB is not associated with high mortality, it has a detrimental impact on quality of life.[3] Lifestyle interventions and behavioral therapy are considered first-line OAB treatment. If those interventions fail, pharmacological treatment using anticholinergics (AChs) or β_3-adrenoreceptor agonists (β_3-ARAs) is recommended. The general aim of this nonsystematic review is to provide an overview of current evidence on the use of β_3-ARAs for OAB treatment.

Role of β_3 Adrenoreceptors in Bladder Control under Physiological Conditions

The main role of the lower urinary tract (LUT) is accumulation of urine during the storage phase and its periodical elimination during the voiding phase of the micturition cycle. The function of the LUT is under constant control of the neural system, including peripheral nerves, the spinal cord, and supraspinal centers in the brain. Any disruption of this

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control pathway may lead to development of LUT symptoms (LUTSs).[4] At the peripheral nerve level, parasympathetic efferents are responsible for detrusor contraction during voiding, while sympathetic nerves drive detrusor relaxation during the storage phase.

Adrenoreceptors (ARs), both α and β classes, mediate the effect of the sympathetic nervous system by binding norepinephrine and epinephrine. The role of ARs in the regulation of heart function and vascular and pulmonary tonus has been known for >70 years.[5] There are three subtypes of β-ARs (β_1, β_2, and β_3), encoded by three genes. Stimulation of β_1-ARs has positive chronotropic, dromotropic, and inotropic effects on the heart, while stimulation of β_2-ARs results in smooth-muscle relaxation (bronchodilatation, uterolysis). β_3-ARs were first described in 1989,[6] and are expressed in several tissue types and organs, such as the brain, retina, myocardium, adipose tissue, and myometrium. In the urinary system, particularly the urinary bladder, β_3-ARs play a key role.[7] β_3-AR are the predominant AR subtype in the human urinary bladder. β_3-ARs account for >97% of all ARs expressed in the urinary bladder, while β_1-ARs and β_2-ARs account for only 1.5% and 1.4%, respectively.[8]

Activation of β_3-ARs leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) levels and subsequent activation of cAMP-dependent PKA. PKA phosphorylates myosin light chain kinase (MLCK), which suppresses calcium-calmodulin–dependent interaction of myosin with actin, resulting in detrusor-muscle relaxation.[9] In addition, the increase in cAMP activity results in decreased intracellular calcium-ion concentration by removal of Ca^{2+} ions from the cytoplasm. Some suggest the involvement of other cAMP-independent mechanisms, such as the large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels in the process of β_3-AR activation–induced detrusor relaxation.[10] Some authors have proposed β_3-AR activation–induced decrease in acetylcholine release from both neuronal and nonneuronal sources (eg, from the urothelium and detrusor) during physiological bladder filling, thus suppressing parasympathetic activity.[11] However, despite extensive scientific inquiry over the last 30 years, the complex role of β_3-ARs in the control of bladder relaxation during the filling phase has not been fully elucidated.

Mechanism of Action of β_3-Adrenoreceptor Agonists in OAB Treatment

Early studies using animal OAB models indicated that the effect of β_3-ARAs was mainly through a direct relaxant effect on the detrusor, due to activation of cAMP and BK_{Ca} channels.[12,13] This theory has been questioned by several studies documenting that plasma concentrations after oral administration of mirabegron do not reach the concentration necessary to achieve detrusor relaxation during in vitro experiments using both animal and human isolated bladder strips. Since abundant expression of β_3-ARs has been documented at afferent nerve endings and interstitial cells in the suburothelial layer, as well as in the urothelium, it was proposed that a reduction in bladder afferent signaling could be the most important mechanism leading to detrusor relaxation.[14] This theory was supported by an evident decrease in afferent activity of both A_δ and C fibers after mirabegron administration, which was associated with decreased spontaneous phasic activity of the urinary bladder wall in animal studies.[15]

Detrusor contraction during physiological voiding is mediated mainly by M_2 and M_3 muscarinic receptors. While M_3 receptors probably play a key role in the initiation of detrusor contraction, the overrepresented M_2 receptors are responsible for its maintenance. Nonadrenergic, noncholinergic mediators, such as ATP or bradykinin, are associated with increased nonvoiding detrusor-contraction activity under pathological conditions. β_3-ARAs inhibit detrusor contractions elicited by other stimuli more effectively than those elicited by cholinergic agonists.[16] This may explain the observation that β_3-ARAs attenuate pathologically increased phasic detrusor activity without interfering with physiological micturition contraction. In the long term, animal studies have shown that β_3-ARAs can protect bladder function and morphology during chronic ischemia. Should these data be confirmed in humans, β_3-ARAs may represent a new modality to prevent chronic ischemia-related bladder pathology.[17]

β_3-Adrenoreceptor Agonists Currently Available for OAB Treatment

Mirabegron was originally intended as a treatment for diabetes, but was later repurposed for the treatment of OAB.[18] It obtained Japanese marketing approval for the treatment of OAB in July 2011. The US Food and Drug Administration (FDA) and European Medicines Agency approved mirabegron for clinical use in the US in June 2012 and Europe in December 2012. In May 2018, the FDA approved mirabegron in combination with solifenacin for the treatment of OAB.

In March 2021, the FDA expanded the indication to treatment of neurogenic detrusor overactivity (NDO) in children aged 3 years and older. Vibegron was developed in a collaboration of Kyorin Pharmaceutical, Kissei Pharmaceutical, and Urovant Sciences. Based on results of the global phase III EMPOWUR trial, vibegron was granted approval in Japan in September 2018 and the US in December 2020.[19]

Another drug under clinical development is solabegron. It showed OAB-symptom reduction in a randomized, placebo-controlled phase II trial. Solabegron 125 mg produced a statistically significant difference in incontinence episodes and micturition frequency over 24 hours and an increase in voided volume.[20] More recently (June 2021), Velicept Therapeutics, which acquired all assets related to solabegron from GlaxoSmithKline in March 2011, announced that solabegron had met the primary end point in a phase IIb study in patients with OAB. This 12-week placebo-controlled study enrolled 435 women and demonstrated a statistically significant improvement in number of micturitions, number of urgency episodes, and urge urinary incontinence episodes over 24 hours in a solabegron-treated group compared to placebo. These results have not been published yet. In contrast, ritobegron (Kissei Pharmaceutical) failed to meet the primary end point in a phase II trial (NCT00742833) in 2008, and further clinical development ceased. Several phase I studies using other β_3-ARAs (AJ9677, 138-335, TRK380, and ZD7114) were performed during the early 2000s; however, none of these compounds advanced to the next stages of clinical development.[21]

Mirabegron

Pharmacological Properties

Mirabegron is rapidly absorbed after oral administration, reaching maximum plasma concentration in 3–5 hours whether taken with or without food. When administered as a single daily dose of 50 mg, steady-state concentrations are usually achieved within 7 days. The compound is highly lipophilic, metabolized in the liver, and eliminated in the urine (55%) and feces (34%), mainly in unchanged form. Terminal elimination half-life is about 23–25 hours. Mirabegron shows minimal interactions with other frequently prescribed drugs, such as digoxin, warfarin, metformin, and oral contraceptives. On the other hand, caution is advised when prescribing mirabegron to patients on certain antiarrhythmics (thioridazine) or tricyclic antidepressants (imipramine, desipramine).[22] Due to a lack of data, mirabegron should not be prescribed to patients with severe impairment of renal and/or liver function.[22,23]

Clinical Efficacy

A strong body of evidence from numerous prospective randomised studies on >60,000 participants (66%–75% female) proved the efficacy of mirabegron. When compared to placebo, mirabegron was superior with respect to reducing frequency, number, and severity of urgency episodes, number of incontinence episodes, and increasing dry rate. In contrast, reduction in nocturia episodes for mirabegron has been seen in few studies. After 12 weeks of treatment with mirabegron, one may expect a reduction in number of voids of 16%–25%, number of severe urgency episodes of 33%–40%, and number of incontinence episodes of 53–63%. Increase in volume per void of 13%–15% has also been documented.[24] A majority of studies have documented both reduction of symptom severity and improvement in treatment satisfaction and quality of life.[25]

The fact that a significant proportion of studies enrolled patients who had discontinued previous ACh treatment may imply that mirabegron is more effective than AChs. However, this is not the case. Based on randomized trials comparing mirabegron with AChs, mirabegron 50 mg once daily showed comparable overall efficacy; however, individual AChs were more efficacious than mirabegron with respect to certain variables (eg, solifenacin 10 mg was superior with respect to micturition frequency, fesoterodine 8 mg with respect to number of incontinence episodes, and trospium 60 mg, solifenacin 10 mg, and fesoterodine 8 mg with respect to dry rate).[26] In the FAVOR study, which included patients after withdrawal of AChs, there were no significant differences observed in mirabegron efficacy between those who discontinued AChs due to low efficacy and those who discontinued due to adverse effects.[27] Generally, the onset of effect in mirabegron recipients is usually observed within 1 month, reaching a maximum within 12–16 weeks after treatment initiation. The effect remains stable over 1 year if the drug is taken regularly.[28]

Clinical Efficacy in Specific OAB-Patient Cohorts

Mirabegron in Men

Our current knowledge on the clinical efficacy of mirabegron in men is based mainly on pooled analysis of previously conducted phase II and III trials enrolling both men and women.[29] Studies designed primarily to assess the efficacy of mirabegron in the treatment of OAB symptoms in men are rather sparse.[30] A majority of placebo-controlled studies have documented statistically significant superiority of mirabegron on some end points. However the difference in most cases was small and the clinical value of such improvement questionable. In addition, data showing that female patients have better adherence to mirabegron treatment than men may implicate lower efficacy in men than women.[31] This is consistent with previous findings demonstrating that male patients suffering from OAB symptoms generally have a lower response rate when treated using AChs than women. This probably reflects the fact that the etiology of male LUTSs is more complex, as it may include additional factors, such as bladder-outflow obstruction, resulting in urothelial dysfunction, chronic bladder ischemia, and inflammation.[32]

Mirabegron in Adults with Neurogenic Detrusor Overactivity

Evidence on the efficacy of mirabegron in treatment of NDO is inconsistent and based on several small single-center studies on patients with NDO due to various underlying pathologies. Vasudeva et al reported results in a group of 30 patients with spinal cord injury treated with a single daily dose of mirabegron 50 mg for 6 weeks. They observed significant improvement in bladder diary–derived variables, such as mean catheterization frequency, mean catheterization volume, and mean number of incontinence episodes, as well as in urodynamic parameters (mean cystometric capacity and maximum amplitude of detrusor pressure).[33]

Two studies published by Krhut et al and Welk et al piloted the use of mirabegron in patients with NDO due to multiple sclerosis.[34,35] Subsequently, another two studies demonstrated similar efficacy for mirabegron and solifenacin in multiple sclerosis patients.[36,37] In contrast to an initially prospective study by Gubbiotti et al that reported improvement in OAB symptoms in patients with Parkinson's disease, the prospective randomised PaDoMi study did not find any statistical difference between mirabegron and placebo groups in bladder diary–derived variables or quality of life after 12 weeks of treatment.[38,39] Solid evidence on mirabegron efficacy in other diseases resulting in NDO is lacking. In summary, the evidence on mirabegron in NDO patients is limited, and further well-designed prospective trials in well-specified homogeneous populations are warranted.

Mirabegron in the Elderly

Given the increasing prevalence of OAB symptoms with age, special attention should be paid to elderly OAB patients. It has been demonstrated that they suffer from more comorbidities, especially cardiovascular, neurological, and psychiatric, than age-matched individuals without OAB.[40] This is often associated with polypharmacy, with many of the most commonly prescribed drugs having a strong ACh effect that can be further increased by drug interactions.[41] Additional use of AChs for OAB may lead to a significant increase in ACh load with an increased risk of cognitive impairment and dementia.[42] Other common ACh side effects, such as dry mouth, constipation, and QT prolongation, to which older people are particularly susceptible, should also be taken into consideration. Therefore, the use of mirabegron or other β_3-ARAs may represent a valuable alternative to AChs in this vulnerable population.

The efficacy of mirabegron in patients aged >65 years was assessed in a large double-blind, randomized, placebo-controlled, multicenter study that enrolled 888 subjects with OAB wet in the US and Canada.After 12 weeks of treatment, the authors found significant superiority of mirabegron over placebo with respect to reduction in frequency, number of urgency and incontinence episodes, and mean voided volume.[43] These findings are consistent with those published previously, which reported a pooled analysis of patients aged >65 years enrolled in three phase III studies.[44] These data were also supported by work of Lozano-Ortega et al who proved that mirabegron was similarly as effective as ACh across all efficacy end points in an older population.[45]

Mirabegron in Children

OAB affects 5%–12% of 5- to 10-year-old children and 0.5% of adolescents (16–18 years of age). Around a third of individuals who had had OAB during childhood are likely to suffer from OAB in adulthood.[46] Pharmacokinetic data on

mirabegron in a pediatric population were published recently; however, clinical data are limited.[47] Blais et al performed an open-label study that enrolled 58 patients (14 girls, 44 boys) with a mean age of 10.1 years. Clinical response, defined as 50% reduction in OAB symptoms, was achieved in 89% of patients.[48] Based on data from a retrospective study on 45 children with idiopathic OAB, Kim et al suggested that mirabegron had comparable efficacy to solifenacin.[49] Recently, a beneficial effect of treatment with mirabegron on both subjective variables and urodynamic parameters was documented in a cohort of 68 children suffering from NDO.[50] Given the low prevalence of neurogenic OAB in children, the existing data were found to be sufficient to grant approval for mirabegron as treatment of NDO in children aged ≥3 years.

Clinical Efficacy of Mirabegron in Combination Treatment

Both AChs and β_3-ARAs are standard treatments for OAB. Given their different modes of action, simultaneous administration of both drug classes is a logical way to improve efficacy if monotherapy is unable to control OAB symptoms sufficiently. In addition, especially in older individuals, the combination of AChs and β_3-ARAs allows for limiting unwanted ACh load. Combinations of AChs and β_3-ARAs have been assessed in several large-scale, multicentric prospective, randomised phase II and III studies that recruited mostly women (66%–77%) suffering from OAB wet (BESIDE, SYNERGY, SYNERGY II, and SYMPHONY). These trials documented the superiority of the combination over monotherapy on a majority of end points, showing a 31%–50% higher likelihood of achieving continence using the combination than monotherapy.[51] A pooled analysis of the BESIDE study of patients aged >65 years documented that the combination of mirabegron and solifenacin was superior to solifenacin monotherapy without increasing the rate of adverse events.[52]

There is a well-known association between OAB and benign prostatic hyperplasia–induced bladder-outlet obstruction (BOO) in men. Up to 50% of men with LUTSs and urodynamically confirmed BOO have detrusor overactivity.[53] α_1 blockers (α_1Bs) are considered first-line pharmacological treatment for LUTSs in men with clinical evidence of BOO. They have proved to improve voiding symptoms and well-being in men; however, they often fail to improve OAB symptoms. Therefore, AChs are recommended to be administered simultaneously or as an add-on for those with persistent OAB symptoms. In order to avoid ACh burden, a combination of α_1Bs with mirabegron has been proposed in place of AChs. This concept has been assessed in two large, prospective, double-blind, placebo-controlled studies (PLUS, n=676; MATCH, n=568) and several smaller trials.[54,55] Despite some controversies over outcomes in individual variables, all studies generally support the benefit of combination therapy over monotherapy.[56]

Safety and Tolerability

A recently published systematic review of mirabegron safety compared to placebo analyzed 6,135 patients recruited in ten trials. Most frequently reported side effects were nasopharyngitis, dry mouth, hypertension, constipation, headache, dyspepsia, urinary tract infection, dizziness, blurred vision, nausea, cardiovascular events, influenza, prolonged QT interval, and upper respiratory tract infection. With the exception of nasopharyngitis, no significant difference was found in the incidence of side effects between mirabegron 50 mg and placebo (OR 1.54, p=0.03).[57]

Several other studies have evaluated the safety of mirabegron in specific patient subgroups. Nitti et al reported the effect of mirabegron on urodynamic parameters in aged > 45 years with LUTSs and BOO. They found that mirabegron 50 mg and 100 mg did not negatively affect voiding efficacy compared to placebo after 12 weeks of treatment (−0.4 mL/s in maximal flow rate and −1.4 cm H_2O in detrusor pressure at maximum urinary flow).[58] These findings correlate with clinical data indicating low incidence of acute urinary retention episodes and minimal increase in postvoid residual in men treated with mirabegron.[59] Very good safety profiles of mirabegron in children and neurogenic patients have been documented in several studies.[60,61] Recently, Griebling et al found no increased risk of cognitive impairment in elderly patients receiving mirabegron for 12 weeks (Pillar study).[62] Another study based on data obtained from national health registers (Denmark, Spain, Sweden, UK, US) did not reveal any increased risk of cancer among mirabegron users compared with ACh medications in men or women.[63]

Adherence and Persistence

OAB is a chronic condition that requires long-term treatment, with only a small proportion of patients able to discontinue the treatment due to symptom cessation.[64] Mirabegron seems to have a well-balanced efficacy:side effects ratio; therefore, adherence to mirabegron and treatment persistence should be significantly better than AChs. However, a recent systematic literature review of real-world data documented that 1-year persistence rates were 12%–25% and 32%–38% for antimuscarinic agents and mirabegron, respectively. Median time to discontinuation was 5–6.5 months for AChs and 5.6–7.4 months for mirabegron.[65]

Vibegron

Pharmacological Properties

Vibegron reaches peak plasma concentration 1–3 hours after oral administration, and constant blood concentration is achieved in 7 days of once-daily administration. It is excreted in feces and urine as unchanged drug. The plasma concentration of the drug increases in people >65 years of age and those with moderate–severe renal impairment. Vibegron does not induce or inhibit the activity of CYP2D6 and CYP3A4 enzymes, and thus drug–drug interactions with most frequently prescribed agents are limited. The elimination half-life is approximately 70 hours.[19]

Clinical Efficacy

A multicenter phase IIb dose-finding study randomizing 1,395 subjects showed significant superiority of vibegron 50 mg and 100 mg over placebo with respect to decreased frequency, reduced urgency-incontinence episodes, incontinence episodes, and urgency episodes per day. Data from the second part of this study documented the additive effect of the concomitant administration of vibegron plus tolterodine 4 mg once daily.[66] A large multicenter double-blind randomized phase III study (EMPOWUR, n=1,518) comparing vibegron 75 mg to placebo and tolterodine 4 mg extended release as active control documented statistically significant superiority of vibegron over placebo on all efficacy end points.[67] In the open-label extension of this study (n=505), significant superiority of vibegron 75 mg over tolterodine was observed in respect of mean change from baseline in urgency-incontinence episodes after 52 weeks of treatment. No other outcomes for efficacy end points differed.[68] Meaningful clinical data on the efficacy of virabegron in specific OAB-patients cohort are not yet available.

Safety and Tolerability

Based on the results of the available phase IIb and III trials, virabegron seems generally safe and well tolerated.[69] The incidence and severity of drug-related side effects are comparable to placebo. A recently published pooled analysis of the EMPOWUR study confirmed the very good safety profile of virabegron in patients aged ≥65 years.[70]

Recommendations on the Use of β_3-Adrenoreceptor Agonists in OAB Treatment

Orally administered AChs are considered the standard pharmacological treatment. β_3-ARAs should be offered as an alternative to AChs in both men and women. If monotherapy is not effective, combination treatment with AChs and β_3-ARAs may lead to greater benefit.[71–73]

Conclusion

β_3-ARAs represent a valuable addition to pharmacological treatment of OAB syndrome. They provide better efficacy than placebo and similar efficacy to ACh. β_3-ARAs have a favorable safety profile and are well tolerated. Due to their different mechanisms of action, combinations of β_3-ARAs with AChs, α_1Bs, or other compounds allow for higher efficacy.

Disclosure

JK is a researcher and consultant for Astellas, Coloplast, STIMVIA, and Medtronic outside the submitted work. The authors report no other conflicts of interest in this work.

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