

Mirabegron – a selective β_3 -adrenoreceptor agonist for the treatment of overactive bladder

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Abstract: Overactive bladder is a common condition that significantly impacts overall quality of life. Antimuscarinics are the current main pharmacological option for treatment; however, many patients fail to adhere to therapy due to troublesome side effects. Mirabegron is a new beta-3 adrenoreceptor agonist which causes detrusor smooth muscle relaxation and has been proposed to be effective for treating overactive bladder symptoms. Mirabegron has been shown to be superior to placebo for reducing the mean number of incontinence episodes per 24 hours and the mean number of micturitions per 24 hours. Side effects such as dry mouth were observed at similar or lower rates than those seen for placebo and antimuscarinics. Higher doses of mirabegron were associated with minor increases in pulse rate and mean blood pressure. Mirabegron offers a new alternative for treating overactive bladder in patients for which antimuscarinics are either not tolerated or not appropriate.

Keywords: beta-3 adrenoreceptor agonist, mirabegron, overactive bladder

Introduction to the management of overactive bladder

Overactive bladder (OAB) is defined by the International Continence Society (ICS) as a symptom syndrome characterized by the feeling of urgency to urinate, with or without urgency incontinence, typically accompanied by frequent daytime and nocturnal urination, in the absence of proven infection or other obvious pathology.¹ In addition to conservative measures such as bladder retraining and lifestyle modifications, antimuscarinic drugs are the primary pharmacological therapy used for treating OAB. Antimuscarinic drugs are thought to act by blocking muscarinic receptors on the detrusor muscle, decreasing the ability of the bladder to contract and potentially increasing bladder capacity. They act primarily during the storage phase of micturition. However, antimuscarinics have been suggested to act on muscarinic receptors on the urothelium and exert their effects by influencing sensory pathways involved in micturition.² National Institute of Clinical Excellence (NICE) guidelines published in 2006³ recommend that immediate release non-proprietary oxybutynin should be offered to women with OAB as a first-line drug treatment if bladder training has been ineffective. If immediate release oxybutynin is not well-tolerated, darifenacin, solifenacin, tolterodine, trospium, or an extended release or transdermal formulation of oxybutynin should be considered as alternatives. NICE guidelines do not recommend the use of flavoxate, propantheline, or imipramine.

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Side effects of antimuscarinics are related to the presence of muscarinic receptors elsewhere in the body (eg, salivary glands, gastrointestinal tract, and central nervous system). These side effects include dry mouth, gastrointestinal disturbances including constipation, flatulence and taste disturbances, blurred vision, dry eyes, drowsiness, dizziness, and fatigue. In rare cases, precipitate acute closed angle glaucoma can occur. Central nervous system effects include restlessness, disorientation, and hallucinations. Antimuscarinics are contra-indicated in patients with myasthenia gravis, significant bladder outflow obstruction (as can cause urinary retention), severe ulcerative colitis, toxic megacolon, and gastro-intestinal obstruction. They should be used cautiously in the elderly and can worsen hyperthyroidism, coronary artery disease, congestive heart failure, hypertension, arrhythmias, and tachycardia.

Recently, β -1, -2, and -3 adrenoreceptors have been identified in human urothelium and detrusor muscle.⁴ These receptors offer a potential new target for drug therapy for treating OAB. Studies have demonstrated that stimulating human β -2 and β -3 adrenoreceptors causes detrusor smooth muscle relaxation via G protein activation. Beta-3 adrenoreceptors appear to be the predominant subtype, and thus are the most likely drug targets; this information led to the identification and study of mirabegron and its effects on OAB.⁵⁻⁸

Review of pharmacology, mode of action, and pharmacokinetics of mirabegron

Mirabegron has been identified as an orally selective beta-3 adrenoreceptor agonist. Animal studies have shown that mirabegron administration decreases the frequency of bladder contractions during the filling phase.⁷ Mirabegron is metabolized in the liver. Importantly, mirabegron acts as a substrate for and is metabolized by cytochrome P450 3A4 (CYP3A4) and 2D6 (CYP2D6). CYP2D6 possesses a genetic polymorphism and shows phenotypic variability, making individuals either poor or extensive metabolizers. A phase 1 study compared single dose pharmacokinetics of mirabegron in CYP2D6 poor and extensive metabolizers (PM and EM). After fasting, subjects received a single oral dose of 160 mg of mirabegron. Plasma and urine samples showed that the percentage of the unchanged dose excreted in the urine was higher in the PM subjects ($15.4\% \pm 4.2\%$) than in the EM subjects ($11.7\% \pm 3.0\%$).⁹

Studies have also assessed the interactions of mirabegron with various drugs and in different populations.

A study involving 28 healthy patients who were genotyped as extensive CYP2D6 metabolizers examined the effect of multiple mirabegron doses on desipramine (CYP2D6 substrate). Subjects received 50 mg desipramine on days 1, 18, and 38 in addition to mirabegron 100 mg from day 5 through day 23. The half-life of desipramine was prolonged, with a 1.8 increase in C_{max} .¹⁰

Another phase I trial has evaluated the use of mirabegron together with metformin. No clinically relevant adverse interactions were observed, and the authors concluded that mirabegron use was safe for use in type 2 diabetics taking metformin.¹¹ Further studies are required to evaluate interactions between mirabegron and rifampicin, warfarin, metoprolol, ketoconazole, and the oral contraceptive pill.

Efficacy studies including comparative studies

Mirabegron has been compared with tolterodine and placebo in a phase II trial. This was a multicenter trial involving 260 patients. After a 2-week placebo period, patients were randomized into 4 groups: placebo, mirabegron 100 mg twice daily, mirabegron 150 mg twice daily, and tolterodine 4 mg once daily for a four-week period.¹² Sixty-five patients received 100 mg and 65 patients received 150 mg mirabegron twice daily, 66 received placebo and 64 patients received tolterodine 4 mg once daily. Both doses of mirabegron resulted in a statistically significant reduction of mean micturition frequency compared to placebo and tolterodine. The mean difference for both mirabegron doses versus placebo was 1.0 micturitions/24 h.

A European phase IIB trial aimed to determine the efficacy and safety of once-daily mirabegron in 919 patients with OAB.¹³ Patients were randomly assigned to receive placebo or mirabegron 25 mg, 50 mg, 100 mg, and 200 mg for a 12-week period. A statistically significant dose-dependent reduction in the mean number of micturitions per 24 hours was observed for the mirabegron 50, 100, and 200 mg groups compared to placebo (-2.1 , -2.1 , and -2.2 respectively, $P < 0.05$). Mirabegron also decreased the number of incontinence episodes (-0.5 , -1.2 , -1.1 , and -1.1 for placebo; 50, 100, and 200 mg respectively, $P < 0.05$), the number of urgency incontinence episodes (-0.4 , -1.1 , -1.2 , and -1.2 for placebo; 50, 100, and 200 mg respectively, $P < 0.05$), and the number of urgency episodes (-1.1 , -1.7 , -2.3 , and -2.5 for placebo; 50, 100, and 200 mg respectively, $P < 0.05$) compared to placebo.

A randomized, double-blind, active and placebo-controlled, multicenter dose-ranging study is currently

underway to evaluate the efficacy, safety, and tolerability of six dose combinations of solifenacin succinate and mirabegron compared to mirabegron and solifenacin succinate monotherapies for treating overactive bladder. The primary outcome measure is the change from baseline in mean volume voided per micturition (NCT01340027).

A phase III trial in Europe and Australia examined the efficacy and tolerability of mirabegron in patients with OAB.¹⁴ Patients received either placebo, mirabegron 50 mg, mirabegron 100 mg, or extended-release tolterodine 4 mg once daily for 4 weeks. A total of 1978 patients were randomized. Results showed both mirabegron groups to have a significant reduction in the number of incontinence episodes and the number of micturitions/24 h from baseline compared to placebo.

Similar findings were reported from a phase III study in North America.¹⁵ A total of 1328 patients were randomized to receive placebo, 50 mg mirabegron, or 100 mg mirabegron. Results showed both mirabegron groups to have significant improvement in the number of incontinence episodes in 24 h and in the number of micturitions in 24 h compared to placebo.

Long term data is now available from a 52-week trial in which OAB subjects received either mirabegron 50 mg, 100 mg, or tolterodine SR 4 mg once daily.¹⁶ Efficacy variables included change in symptoms from baseline at 1, 3, 6, 9, and 12 months as collected in each patient's micturition diary. A total of 2444 patients were randomized in this study to receive one of the 3 treatments (812 patients received mirabegron 50 mg, 820 patients received mirabegron 100 mg, and 812 patients received tolterodine 4 mg). In terms of efficacy, improvement in OAB symptoms was observed for both mirabegron and tolterodine beginning at month 1, which was maintained throughout the follow-up period.

Safety and tolerability, patient-focused perspectives, QOL, patient satisfaction, acceptability, and adherence

The BLOSSOM proof of concept study examined mirabegron versus placebo and tolterodine.¹² The incidence of adverse effects in the mirabegron group was 39.2% compared with 36.4% in the placebo group and 48.4% in the tolterodine group. Headache and gastrointestinal upset were most common side effects reported in the mirabegron group (6.9% and 13.8%, respectively), but these were lower than those observed in the tolterodine group (9.4% and 23.4% respectively). The discontinuation rate due to adverse events

was 4.6% and 7.7% for the mirabegron 100 and 150 mg groups, respectively compared with 1.5% in the placebo group and 3.1% in the tolterodine group.

The DRAGON study¹³ assessed safety of mirabegron at 4 different doses (25, 50, 100, and 200 mg). In the mirabegron group, the incidence of adverse events was between 43.8%–47.9% compared with 43.2% in the placebo group. There was a lower incidence of dry mouth compared to that reported with antimuscarinics.¹⁷ The most common adverse effects in the mirabegron group were infections and infestations (14.1%) as well as gastrointestinal disorders. In the placebo group, 3% of patients stopped treatment due to adverse events compared to 2.4%–5.3% in the mirabegron groups. Higher doses of mirabegron (100 mg and 200 mg) were associated with a mean increase in heart rate from baseline of 1.6 to 4.1 beats per minute. The reported increase in pulse rate is thought to be due to the higher doses of mirabegron acting on beta-1 adrenoreceptors, whereas the lower 50 mg dose is associated with an increase in pulse rate of approximately 1 beat per minute.

A less than 1.5 mmHg change in blood pressure from baseline was also observed. However, these changes were not associated with an increased incidence of adverse cardiovascular events.

The larger phase III European-Australian RCT¹⁴ reported incidence rates for adverse events to be 43.3%, 46.7%, 42.8%, and 40.1%, for the placebo, tolterodine slow-release, and mirabegron 50 and 100 mg groups, respectively. The incidence of hypertension was 7.7%, 8.1%, 5.9%, and 5.4%, dry mouth was 2.6%, 10.1%, 2.8%, and 2.8%, and headache was 2.8%, 3.6%, 3.7%, and 1.8% for the respective groups.

The North American phase III trial¹⁵ reported the overall incidence of adverse events to be 50.1%, 51.6%, and 46.9% in the placebo and mirabegron 50 and 100 mg groups, respectively. The incidence of hypertension was 6.6%, 6.1%, and 4.9%, whereas headache was 2.0%, 3.2%, and 3.0% in the placebo and mirabegron 50 and 100 mg groups, respectively. Discontinuation rates due to adverse events were 3.8%, 4.1%, and 4.4% in the placebo and mirabegron 50 and 100 mg groups.

A recent trial evaluated the effect of mirabegron on intraocular pressure (IOP) and ocular safety since beta-2 adrenoreceptor stimulation can worsen closed-angle glaucoma and increase the risk of vision loss.¹⁸ Although mirabegron is beta-3 adrenoreceptor-selective, its effect on intraocular pressure was investigated in 305 normotensive subjects randomized to receive either oral mirabegron 100 mg or placebo once daily for 56 days. Mean IOP at baseline was

15.3 (0.16) mmHg for mirabegron and 15.4 (0.16) mmHg for the placebo group. Values at day 56 were 15.0 (0.16) mmHg and 15.2 (0.17) mmHg respectively. Adjusted mean IOP change from baseline to day 56 was -0.3 mmHg for mirabegron and -0.2 mmHg for placebo (-0.1 mmHg difference [95% CI -0.4 – 0.3]). No subject discontinued the study due to increased IOP. Visual acuity and biomicroscopy data were reported as unremarkable, and no episodes of glaucoma were reported. The study demonstrated that mirabegron was not inferior to placebo with regard to effect on IOP.

The primary safety variable from the year-long study¹⁶ was the incidence and severity of treatment-emergent adverse events. Discontinuations due to adverse events were 6.4%, 5.9%, and 6.0% in the mirabegron 50 mg and 100 mg and tolterodine 4 mg groups, respectively. Treatment emergent adverse events were primarily reported as mild to moderate and were 59.7%, 61.3%, and 62.3% for the mirabegron 50 mg and 100 mg and tolterodine 4 mg groups, respectively. The most common adverse events included hypertension, urinary tract infection, and nasopharyngitis. Incidence of constipation was 2.8%, 3.0%, and 2.7% for the mirabegron 50 mg and 100 mg and tolterodine 4 mg groups, respectively, and incidence of dry mouth was 2.8%, 2.3% and 8.6% for the mirabegron 50 mg and 100 mg and tolterodine 4 mg groups, respectively. Over the 52-week follow-up, a total of 5 deaths were reported, including 3 in the mirabegron 50 mg group and 2 in the tolterodine group. The investigators concluded that the safety and tolerability of mirabegron and tolterodine in this study were similar but noted that the incidence of dry mouth was higher in the tolterodine group.

Conclusion, place in therapy

Available evidence appears to favor mirabegron as a new treatment for OAB symptoms. Mirabegron has been approved in Japan for the indication of urgency, urinary frequency, and urge urinary incontinence associated with OAB, and was recently submitted for approval to US and European authorities for the same indication.¹⁹ Mirabegron may adversely interact with CYP2D6 substrates, and studies examining drug–drug interaction studies are currently underway. Mirabegron increases pulse rate and blood pressure from baseline; however, these increases are minor and comparable to those seen with tolterodine. It has been proposed that mirabegron at a 50 mg dose can be used clinically, representing a new approach for treating OAB.

Disclosure

The authors declare that in the past they have consulted and received paid travel expenses from Astellas Pharma, Inc. VK is principal investigator on phase 3 study Mirabegron versus placebo.

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