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REVIEW ARTICLE

Use of mirabegron in treating overactive bladder

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Abstract The lack of an alternative to antimuscarinics has led to the search for new drug targets for overactive bladder (OAB) symptoms. The presence of β-3 adrenoreceptors in the bladder has been confirmed, and they are known to have a role in bladder relaxation. Targeting these receptors improves bladder compliance on filling and increases bladder capacity. MEDLINE literature search on efficacy and safety of mirabegron was performed. The US Food and Drug Administration Web site, clinicaltrials.gov, and controlled-trials.com online trial registries were searched for English-language articles containing the term "mirabegron". Finally, abstracts from recent International scientific meetings were searched for randomised controlled trials (RCTs). Studies show that mirabegron reduces the number of micturitions and incontinence episodes in a 24-h period compared with placebo. Dry mouth and gastrointestinal disturbances are the most common side effects, but these have been rated as mild to moderate. A small rise in mean heart rate and blood pressure has been shown. Further investigations are ongoing and results are awaited. Although mirabegron is metabolised by CYP2D6, it is also thought to inhibit the activity of this enzyme. Therefore, potential drug interactions with other CYP2D6 substrates need to be further studied. Mirabegron is a promising alternative to antimuscarinics. Further information on its long-term use in terms of efficacy, safety, and tolerability is awaited.

Keywords Mirabegron · Overactive bladder · β-3 adrenoreceptors · Efficacy · Safety

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Introduction

The urothelium has emerged as a new target for drug therapy in patients with overactive bladder (OAB) [1]. It consists of three layers: an apical cell layer, an intermediate layer, and a basal cell layer that interacts with the suburothelium for structural support. Numerous urothelium receptors that are in close physical association with suburothelium afferent nerves release chemical mediators, such as adenosine triphosphatase (ATP) and acetylcholine (ACH), thus playing an important role in the pathogenesis of OAB symptoms [2, 3]. β-1, 2 and 3 adrenoreceptors have been recently confirmed in human urothelium and detrusor muscle [1]. It has been shown that stimulation of human β-2 and β-3 adrenoreceptors results in direct relaxation of detrusor smooth muscle via activation of G proteins and adenyl cyclase, which increases the levels of cyclic adenosine monophosphate (AMP). It is thought that the β-3 adrenoreceptor subtype predominantly mediates human bladder smooth muscle relaxation [4–6]. Therefore, based on the principle that activation of β-3 adrenoreceptors causes detrusor muscle relaxation, they have been proposed as a potential target to treat OAB symptoms. Mirabegron is an orally administered active selective β-3 adrenoreceptor agonist tjat has been widely studied in animals and shown to decrease the frequency of rhythmic bladder contractions during the filling phase without suppressing the amplitude of bladder contraction during micturition [7].

Pharmacodynamics

Mirabegron is a lipophilic compound that undergoes hepatic metabolism. It acts as a substrate and is metabolised by cytochrome P450 3A4 (CYP3A4) and 2D6 (CYP2D6). CYP2D6 shows phenotypical variability due to genetic

polymorphism; thus, a particular individual may be described as either a poor (PM) or an extensive (EM) metaboliser. The incidence of PM phenotypes in Caucasians is approximately 5–10%. Van Gelderen et al. [8] compared single-dose pharmacokinetics of mirabegron in CYP2D6 PM and EM. In their phase 1 study, patients received a single oral dose of 160 mg mirabegron under fasted conditions. Plasma and urine samples were collected and safety parameters recorded for 72 h after dosing. Results showed that the percentage of the dose excreted unchanged in the urine was higher in PMs (15.4 ± 4.2%) compared with EM (11.7 ± 3.0%). This led to the study of mirabegron in patients with mild, moderate, and severe renal impairment (NCT00750620; 178-CL-038). It would seem appropriate that poor hepatic metabolisation of mirabegron would result in a higher urinary fraction. T_{max} was similar in EMs and PMs, and its respective half-life was 23 and 25 h. Mean C_{max} and mean area under the curve (AUC) were slightly higher in PMs than in EMs. Results of the effect of food and administration route (oral vs. intravenous) on mirabegron pharmacokinetics are awaited (NCT00940121).

Clinical efficacy

Data are now available from phase II and III trials on the role of mirabegron in treating OAB. The first report comes from a phase IIa dose-finding study [9]. This study was a randomised, double-blind, parallel group, proof of concept study to evaluate the efficacy of YM178 compared with placebo and tolterodine. It was performed in six European countries at 31 sites: 260 patients were enrolled into a single-blind, 2-week, placebo run-in period, after which they were randomised to four groups; placebo (n=66), mirabegron 100 mg twice daily (n=65), mirabegron 150 mg twice daily (n=65), and tolterodine 4 mg four times daily (n=64) for a 4-week period. The primary endpoint was to evaluate efficacy, and the primary efficacy variable was the change in mean number of micturitions per 24 h, as recorded on a micturition diary. Both doses of mirabegron showed a statistically significant reduction of mean micturition frequency by 17% and 18% at 100 and 150 mg of mirabegron, respectively, compared with 9% for placebo and 11% for tolterodine. Analysis of secondary efficacy variables showed that mirabegron was better than placebo with regard to mean volume voided per micturition, mean number of incontinence episodes, nocturia episodes, urge urinary incontinence (UUI) episodes and urgency in a 24-h period.

The following phase IIb trial was a dose-ranging study [10] carried out in Europe aiming to determine the efficacy and safety of mirabegron once daily in patients with OAB. A total of 919 patients were randomly assigned to five groups: placebo, and mirabegron 25 mg, 50 mg, 100 mg and 200 mg for a 12-week period. Efficacy was evaluated using patient micturition diaries. Analysis showed statistically significant dose-dependent reductions in mean number of micturitions per 24 h for mirabegron 50, 100 and 200 mg groups compared with placebo (−2.1, −2.1 and −2.2, respectively, $p<0.05$). It was also seen that mirabegron caused a dose-dependent increase in mean urine volume voided in each micturition compared with placebo (27.3, 25.6 and 33.3 for 50, 100 and 200 mg, respectively, $p<0.05$). Mirabegron also decreased the number of incontinence episodes (–0.5, –1.2, –1.1 and –1.1 for placebo and 50, 100 and 200 mg mirabegron, respectively, $p<0.05$), number of UUI episodes (−0.4, −1.1, −1.2 and −1.2 for placebo and 50, 100 and 200 mg mirabegron, respectively, $p<0.05$) and the number of urgency episodes (−1.1, −1.7, −2.3 and −2.5 for placebo and 50, 100 and 200 mg mirabegron, respectively, $p<0.05$) compared to placebo. Results are awaited from a phase II trial to evaluate mirabegron and solifenacin alone and in combination for treating OAB (NCT01340027).

Khullar et al. [11] conducted a phase III trial in Europe and Australia and reported on the efficacy and tolerability data for mirabegron in patients with OAB. This was a multicentre, randomised, double-blind, parallel-group, placebo and active controlled trial. Patients >18 years with OAB were enrolled into a 2-week placebo run and then randomised to receive either placebo, mirabegron 50 mg, mirabegron 100 mg or tolterodine extended-release (ER) 4 mg once daily for 4 weeks. The primary end points were number of incontinence episodes in 24 h and number of micturitions in 24 h. Efficacy was assessed according to patient micturition diaries in 1,978 randomised patients. Results showed both mirabegron groups to have a statistically significant reduction in number of incontinence episodes/24 h (−1.57 for 50 mg, −1.46 for 100 mg) and number of micturitions/24 h (−1.93, −1.77, respectively) from baseline compared with placebo.

Phase III data from North America again looked at efficacy and tolerability [12]. This was a 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled trial with patients receiving either placebo or 50 or 100 mg mirabegron; 1,328 patients participated. Again, similar results were seen with both mirabegron groups, showing statistically significant improvement in the number of incontinence episodes in 24 h (−1.13, −1.47 and −1.63 for placebo, mirabegron 50 mg and 100 mg, respectively; $p<0.05$) and in the number of micturitions in 24 h (–1.05, –1.66 and –1.75 for placebo, mirabegron 50 mg and 100 mg, respectively; $p<0.05$). Statistically significant improvements were evident at the first measured time point (week 4) for incontinence episodes and micturitions.

The results of these phase III trials are encouraging for the possibility of mirabegron having a key role in the pharmacological management of OAB. Results are awaited from

further phase III trials investigating effects of long-term mirabegron use in OAB (52 weeks) (NCT00688688).

Safety and tolerability

In the Beta3-adrenoceptor agonist in Lowering OAB Symptoms Study compared to Oral anti-Muscarinic (BLOSSOM) proof of concept study [9], the incidence of adverse effects was 39.2% compared with 36.4% for the placebo group and 48.4% in the tolterodine group. The most common side effect reported with mirabegron in that study was headache (6.9%) and gastrointestinal upset (13.8%), but this was lower than tolterodine (9.4% and 23.4%, respectively). There were no reported episodes of acute urinary retention, and adverse events were rated as either mild or moderate. The discontinuation rate due to adverse events was 4.6% and 7.7% for the in the mirabegron 100 and 150 mg groups, respectively. Discontinuation was 1.5% in the placebo group and 3.1% in the tolterodine group.

The Study of YM178 in Patients with Symptomatic Overactive Bladder (DRAGON) study [10] assessed safety of mirabegron at four different dosages (25, 50,100 and 200 mg). The incidence of one or more treatment-emergent adverse events in the mirabegron groups was between 43.8–47.9% compared with 43.2% in the placebo group. The most common adverse events in the mirabegron groups were infections and infestations (14.1%), as well as gastrointestinal disorders (12.1%). Interestingly, there was a lower incidence of dry mouth compared with that reported with antimuscarinics [13]. Most adverse events were again rated as mild to moderate in intensity. In the placebo group, 3% of patients discontinued treatment due to adverse events compared with 2.4–5.3% in the mirabegron groups. Electrocardiogram (ECG) parameters remained unchanged in all treatment groups. Higher doses of mirabegron (100 and 200 mg) were associated with a mean increase in heart rate from baseline of 1.6 to 4.1 b[,. but this was not associated with increased incidence of cardiovascular adverse events. There was also a <1.5 mmHg change in blood pressure from baseline in the mirabegron group compared with placebo.

The European–Australian study [11], the largest phase III RCT conducted to date, showed a similar incidence of adverse events. Overall adverse events reported were 43.3%, 46.7%, 42.8% and 40.1% for the placebo, tolterodine ER, mirabegron 50 and 100 mg groups, respectively. The incidence of hypertension was 7.7%, 8.1%, 5.9% and 5.4%; dry mouth 2.6%, 10.1%, 2.8% and 2.8%; and headache 2.8%, 3.6%, 3.7% and 1.8% for the above stated groups, respectively. Data from the North American phase III trial [12] showed a similar incidence of adverse events across placebo, mirabegron 50 and 100 mg groups. In that study, overall adverse event rates reported were 50.1%, 51.6% and 46.9%, respectively. The incidence of hypertension was 6.6%, 6.1% and 4.9%, and headache 2.0%, 3.2% and 3.0% across the placebo, mirabegron 50 and 100 mg groups, respectively. Discontinuation rates due to adverse events were 3.8%, 4.1% and 4.4% in the placebo, mirabegron 50 and 100 mg groups.

Special populations and drug interactions

A phase I open-label crossover study evaluated the effect of multiple doses of mirabegron on desipramine metabolism, a tricyclic antidepressant, and CYP2D6 substrate [14]. Twenty-eight healthy individuals (14 men and 14 women) who were all genotyped as extensive CYP2D6 metabolisers received a single dose of desipramine 50 mg on days 1,18 and 38, in addition to mirabegron 100 mg from day 5 to day 23. The study reported that the combination of mirabegron resulted in a longer half life of desipramine with a 1.8 increase in C_{max} and 3.4-fold increase in AUC. Veltkamp et al. [15] carried out another phase I trial looking at potential drug interactions between mirabegron and metformin. Sixteen healthy men (aged 18–54 years) were enrolled in a one-sequence crossover study to receive an oral dose of metformin 500 mg twice daily for 5 days, followed by 11 days of double-blind combination therapy orally (metformin 500 mg twice daily and mirabegron 160 mg or placebo). Results showed no clinically relevant pharmacokinetic, pharmacodynamic or safety interactions. On the basis of their results, the authors concluded that mirabegron can be used safely in type 2 diabetes patients treated with metformin. Further phase I studies looking at interactions between mirabegron and rifampicin, warfarin and the oral contraceptive pill are awaited.

Conclusion

The published evidence appears to favour mirabegron as a new effective and well-tolerated class of drug for patients with OAB symptoms. However, in comparison with antimuscarinics, only a relatively small number of patients have been studied so far. In view of its pharmacokinetics, mirabegron has the potential for adverse drug interactions with other CYP2D6 substrates. This, in addition to the effect on the cardiovascular system, needs careful evaluation, especially in the elderly population. Discontinuation rate varies from 4.1% to 7.7%, which is slightly higher than placebo (2%) but similar to antimuscarinics (4–6%). Discontinuations were mainly due to treatment-emergent adverse events. Although long-term data are still pending, mirabegron can be considered an attractive alternative to antimuscarinics.

Conflicts of interest 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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