Mirabegron use in the treatment of overactive bladder symptoms

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Beta-3 adrenoreceptors have been proposed as a target in the treatment of OAB due to their role in the mediation of bladder smooth muscle relaxation. Mirabegron is an oral medication that selectively targets beta-3 adrenoreceptors and has been shown to reduce rhythmic abnormal detrusor contractions in animal models. In this Drug profile the authors present the clinical data relating to its efficacy and adverse effects and discuss its potential place in the treatment of OAB.

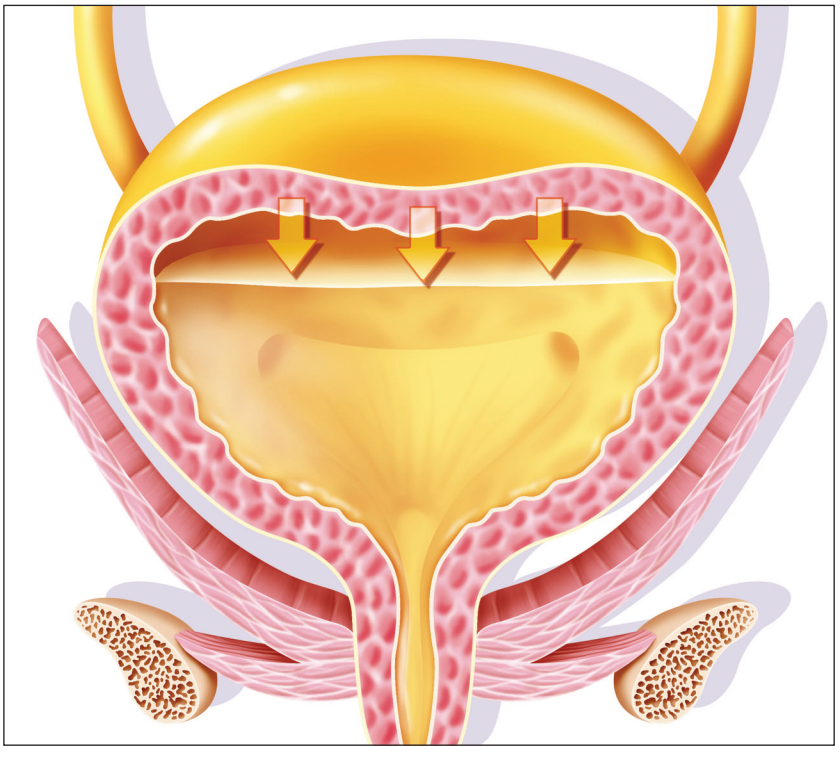

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Figure 1. Mirabegron selectively targets beta-3 adrenoreceptors and has been shown in animal models to decrease the frequency of rhythmic abnormal detrusor contractions during the filling phase without decreasing the amplitude of detrusor contraction during micturition

The presence of beta-1, beta-2 and beta-3 adrenoreceptors has been described in human urothelium and detrusor muscle.[1–3] Several studies have demonstrated that stimulation of human beta-2 and beta-3 adrenoreceptors leads to direct relaxation of detrusor smooth muscle. More recent studies have confirmed that bladder smooth muscle relaxation is mainly mediated by the beta-3 adrenoreceptor subtype.[4–6] Based on the above evidence, beta-3 adrenoreceptors have been proposed as a target to treat overactive bladder (OAB) symptoms.

Mirabegron is an oral medication that actively selects beta-3 adrenoreceptors. It is a lipophilic compound that acts as a substrate and it is metabolised in the liver by cytochrome P450 3A4 (CYP3A4) and 2D6 (CYP2D6) to form its active compound.

Animal studies have clearly demonstrated its capacity to decrease the frequency of rhythmic abnormal detrusor contractions during the filling phase without decreasing the amplitude of detrusor contraction during micturition.[4]

Clinical trials

A dose-finding phase 2a study (BLOSSOM) was published in 2008.[8] This was a randomised double-blind parallel-group proof-of-concept study to evaluate the efficacy of mirabegron compared to a placebo and tolterodine (Detrusitol). The primary endpoint was to evaluate the efficacy of mirabegron, which was measured in the mean reduction of number of micturitions in a 24-hour period, as recorded on a bladder diary. A total of 260 patients were enrolled from 31 countries. After a placebo run-in phase patients were randomised into four groups: placebo, mirabegron 100mg twice daily, mirabegron 160mg twice daily and tolterodine 4mg four times daily for four weeks.

Study	Regimen	Duration	% change in or number of micturitions/24 hours	Number of incontinence episodes/24 hours
Chapple et al 2008[8]	placebo	4 weeks	-9%	-1.01
	mirabegron 100mg bd		-17%	-2.17[a]
	mirabegron 150mg bd		-18%	-1.58[a]
	tolterodine 4mg qds		-11%	-1.65[a]
Chapple et al 2010[9]	placebo	12 weeks	-1.4	-0.5
	mirabegron 25mg qds		-1.9	-1.4*
	mirabegron 50mg qds		-2.1*	-1.2*
	mirabegron 100mg qds		-2.1*	-1.1
	mirabegron 200mg qds		-2.2*	-1.1
Khullar et al 2010[10]	placebo	12 weeks	-1.34	-1.17
	mirabegron 50mg od		-1.93[a]	-1.57[a]
	mirabegron 100mg od		-1.77[a]	-1.46[a]
	tolterodine SR 4mg od		-1.58[b]	-1.27[b]
Nitti et al 2011[11]	placebo	12 weeks	-1.05	-1.13
	mirabegron 50mg od		-1.66[a]	-1.47[a]
	mirabegron 100mg od		-1.75[a]	-1.63[a]

[a]=$p<0.05$ *vs* placebo [b]= not statistically significant

Table 1. Summary of published trials relating to the efficacy of mirabegron

Mirabegron showed a reduction in the mean number of micturition episodes at both 100mg (-17%) and 150mg (-18%). The placebo showed a reduction of mean number of micturition episodes of -9% and tolterodine a reduction of -11%. Mirabegron was also found to be better than placebo with regard to increase of mean volume voided per micturition, reduction of mean number of incontinence episodes, nocturia episodes, urgency and urgency urinary incontinence (UUI) episodes in a 24-hour period.

A phase 2b dose-ranging study (DRAGON)[9] was also carried out to determine the efficacy and safety of once-daily mirabegron in patients with OAB. A total of 919 patients were randomly assigned to five groups: placebo and mirabegron 25mg, 50mg, 100mg and 200mg for a 12-week period. Bladder diaries were used to determine the efficacy. The authors reported a significant dose-dependent reduction in mean number of micturitions for mirabegron 50mg, 100mg and 200mg compared with placebo, a dose-dependent increase in the mean volume voided/micturition, and a decrease in the number of incontinence episodes, number of UUI and urgency episodes.

Results for the phase 2 trial to evaluate the efficacy of mirabegron and solifenacin (Vesicare) alone and in combination for treating OAB symptoms are still awaited.

Phase 3 trial

A phase 3 randomised double-blind parallel-group placebo-controlled trial conducted in Europe and Australia looked at the efficacy and tolerability of mirabegron in patients with OAB symptoms.[10] Patients over 18 years with OAB symptoms were enrolled in a two-week placebo run-in period then randomised to receive either placebo, mirabegron 50mg, mirabegron 100mg or tolterodine sustained-release (SR) 4mg once daily for twelve weeks. The primary end-points were the reduction of number of urinary incontinence episodes and number of micturitions in 24 hours accordingly to a bladder diary.

A total of 1978 randomised patients were recruited. Results showed that there was a significant reduction in the number of incontinence episodes (-1.57 for 50mg and -1.46 for 100mg) and

number of micturitions (-1.93 for 50mg and -1.77 for 100mg) over a 24-hour period compared to placebo.

Although improvements in both co-primary end-points were also observed with tolterodine SR, these did not reach statistical significance *vs* placebo (number of micturitions -1.58 for tolterodine and -1.34 for placebo; incontinence episodes -1.27 for tolterodine and -1.17 for placebo)

A phase 3 trial conducted in America also looked at efficacy and tolerability of mirabegron.[11] The authors demonstrated a similar improvement in the number of micturitions and incontinence episodes for both mirabegron doses. Results are awaited for phase 3 trials investigating the long-term efficacy (52 weeks) of mirabegron in the treatment of OAB symptoms. However, results to date are encouraging for the use of mirabegron in the management of OAB symptoms.

Finally, the efficacy of mirabegron has been examined in a pooled analysis across phase 3 studies in patients with OAB symptoms (both naive and refractory OAB symptoms). This pool analysis was presented at the 37th Annual IUGA Meeting in Brisbane 2012.[12]

A total of 3542 patients were included in the full analysis set (FAS); 79% were female and the mean age was 59 years. Approximately half had previously used antimuscarinics (n=1852), but discontinued due to insufficient effect. Placebo was given to 704 patients, mirabegron 50mg to 688 patients and mirabegron 100mg to 460 patients.

All patients in the FAS who had at least one episode of incontinence were included in the FAS – Incontinence (FAS-I). Of the 2317 patients in the FAS-I group 1360 had previously used antimuscarinics; placebo = 518, mirabegron 50mg = 506 and mirabegron 100mg = 336. Patient demographics were comparable across the placebo and mirabegron groups.

The mean number of incontinence episodes and number of micturitions were demonstrably lower with 50mg and 100mg doses in both patients who had never taken antimuscarinics (-0.15 and -0.33) and those who had previously been treated (-0.57 and -0.74).[12] The efficacy results published in the literature to date are outlined in Table 1.

Safety

In the BLOSSOM study[8] mirabegron was compared to tolterodine and placebo. The incidence of adverse effects was 39.2% for mirabegron compared with 36.4% for the placebo group and 48.4% in the tolterodine group. Reported side-effects in the mirabegron group were lower than in the tolterodine group. The most reported side-effects in the mirabegron group were headache (6.9%) and gastrointestinal upset (13.8%) compared with 9.4% and 23.4% respectively in the tolterodine group. There were no reported episodes of acute urinary

Study	Regimen	Duration	Overall adverse event	Headache	Dry mouth	Hypertension	GI upset	Infections and infestations
Chapple et al 2008[8]	Placebo Mirabegron 100mg and 150mg bd Tolterodine 4mg qds	4 weeks	36.4 39.2 48.4	3 6.9 9.4			3 13.8 23.4	
Chapple et al 2010[9]	Placebo Mirabegron 25mg, 50mg, 100mg and 200mg qds	12 weeks	43.2 43.8-47.9				12.1	14.1
Khullar et al 2010[10]	Placebo Mirabegron 50mg od Mirabegron 100mg od Tolterodine SR 4mg od	12 weeks	43.3 42.8 40.1 46.7	2.8 3.7 1.8 3.6	2.6 2.8 2.8 10.1	7.7 5.9 5.4 8.1		
All numbers expressed as percentages								

Table 2. Summary of adverse events with mirabegron recorded in published trials

retention. The adverse events were described as mild or moderate.

Mirabegron was given in doses of 100mg and 150mg and discontinuation rates due to adverse events were 4.6% and 7.7%, respectively. In the placebo and tolterodine group discontinuation rates were 1.5% and 3.1%, respectively.

The DRAGON study[9] also assessed the safety of mirabegron at four different doses (25, 50, 100 and 200mg). The incidence of one or more treatment emergent adverse effects in the mirabegron group was between 43.8–47.9% compared with 43.2% in the placebo group. The most common adverse events in the mirabegron group were infections in 14.1% and gastrointestinal disorders in 12.1%. However, the incidence of dry mouth was lower than in the antimuscarinic group.

Adverse events were again reported as mild to moderate with a discontinuation rate of 3% in the placebo group compared with 2.4–5.3% in the mirabegron group. ECG parameters remained unchanged in all treatment groups.

There was a small mean increase in heart rate (1.6 to 4.1 bpm) and blood pressure (<1.5mmHg) from baseline in higher doses (100 and 200mg) of mirabegron than in the placebo group. There was, however, no increase in the incidence of cardiovascular adverse events.

The European-Australian study is the largest RCT conducted to date and showed similar incidence in adverse events.[10] The American study also showed similar results in adverse events in mirabegron 50mg, 100mg and placebo groups.[11]

The safety results published in the literature to date are outlined in Table 2.

Conclusion

The published evidence to date appears to support mirabegron as an alternative to antimuscarinics for patients with OAB symptoms. Recently, based on the reported data the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion, recommending the granting of a marketing authorisation for mirabegron for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in adult patients with OAB syndrome.

However, only a small number of patients have been studied to date in comparison to antimuscarinics and long-term data are still awaited. There is the potential for interactions with other CYP2D6 substrates as well as a potential effect on the cardiovascular system. Discontinuation rates vary from 4.1% to 7.7%, which is slightly higher than the placebo group (2%) but similar to antimuscarinics (4–6%). This discontinuation was mainly due to treatment emergent adverse events.

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Declaration of interests

Drs Khullar and Digesu have consulted for and/or received travel expenses from several pharmaceutical companies. Dr Khullar was the principal investigator on the phase 3 study for mirabegron *vs* placebo. Drs Khullar and Digesu have been co-authors and co-investigators in some of the clinical trials for mirabegron. Michelle Gore does not have any conflict of interests to declare.