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REAL-WORLD CARDIOVASCULAR ASSESSMENT OF MIRABEGRON TREATMENT IN PATIENTS WITH OVERACTIVE BLADDER AND CONCOMITANT CARDIOVASCULAR DISEASE: RESULTS OF A JAPANESE POST-MARKETING STUDY

Hypothesis / aims of study
Mirabegron is a selective β3-adrenoceptor agonist approved for the treatment of overactive bladder (OAB), however, cross-reactivity with β1-adrenoceptors in the cardiovascular (CV) system is possible. This post-marketing study (NCT02570035) is the first study assessing CV parameters and adverse drug reactions (ADRs) in real-world patients in Japan with OAB and concomitant CV disease who initiated treatment with mirabegron.

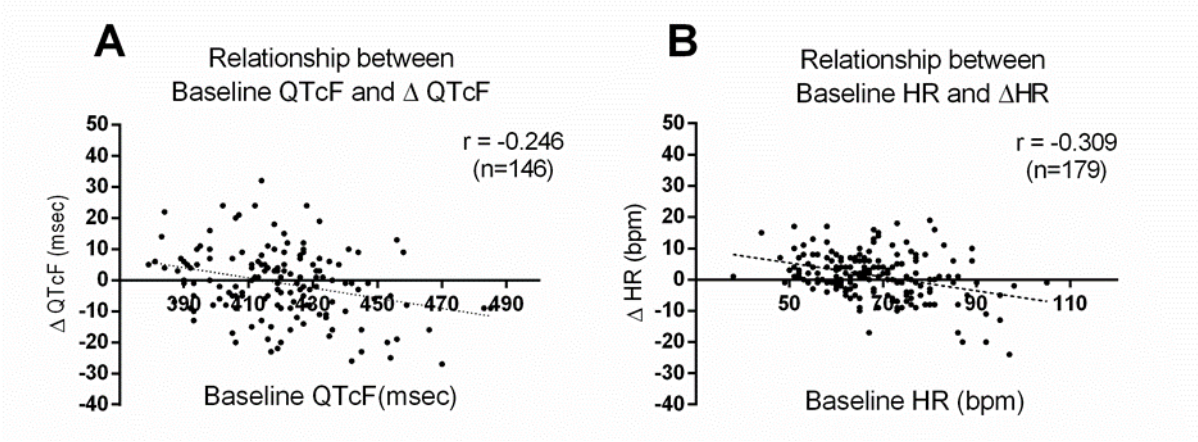
Study design, materials and methods
Participants were patients with OAB who had either a history of, or coexisting, CV disease (including both CV disease and surgery), had recently initiated mirabegron (25 or 50 mg daily) treatment and had a 12-lead ECG performed within 7 days prior to initiation of mirabegron. Patients with "serious CV disease" (significant abnormalities in the baseline ECG including QTc >500 msec) were excluded. Physicians provided patient demographics, physical characteristics, CV disease history, and OAB symptom characteristics at registration (Baseline [BL]). After 4 weeks' treatment, patients underwent a second ECG assessment including RR, PR, QRS intervals, Fridericia's corrected QT [QTcF], and heart rate [HR]. The incidence of CV ADRs and change from BL in ECG parameters at 4 weeks were assessed. Data were collected between 4 December 2012 and 10 July 2014.

Results
Of 316 patients, 236 met registration criteria (38 excluded for "serious CV disorders" and 31 failed to visit their medical institutions after first mirabegron dose) and had BL and post-dose ECG data. Of these, 61.9% were male; 60.2% ≥75 years old; and 93.6% with coexisting CV disease, notably, arrhythmia (67.8%), and angina pectoris (19.1%). In addition, 54.2% of patients had concurrent hypertension, 17.8% had hyperlipidemia and 16.9%, diabetes mellitus. At start of treatment, patients received daily mirabegron 25 mg (19.9%) or 50 mg (80.1%). During treatment, the incidence of CV ADRs (including disorders and investigations) was 5.51% (n=13), including supraventricular extrasystoles (1.27%; n=3), prolonged QT (1.27%; n=3), arrhythmia supraventricular (0.85%; n=2) and ventricular extrasystoles (0.85%; n=2). After 4 weeks' treatment (all doses), the mean increase in HR was 1.24 bpm and RR was shortened by 18.38 msec. Although these results were statistically significant, the changes were small and not clinically relevant. Specifically, the change in HR was similar to that reported in mirabegron registration trials (1,2). No statistically significant changes were observed in PR, QRS or QTcF. To examine the possibility of latent QT prolongation, the correlation between the value of QTcF or HR at BL and the change from BL (ΔQTcF or ΔHR) after mirabegron treatment was determined. The correlation coefficients (r) between QTcF or HR at BL and ΔQTcF and ΔHR were -0.246 and -0.309, respectively and thus do not support any particular trend in the response to mirabegron. Further analyses were performed on subgroup populations defined by age or sex. The results do not suggest that the effect of mirabegron on QTcF is influenced by either the patients' age (<75 or ≥75 years, r = -0.351 and -0.157, respectively) or patients' sex (male or female, r = -0.198 and -0.309, respectively). Similarly, the correlation coefficients calculated for HR do not suggest that either age (<75 and ≥75 years, r = -0.377 and -0.254, respectively) or sex (male or female, r = -0.262 and -0.338, respectively) are factors influencing the effect of mirabegron on HR.

Interpretation of results
The incidence of CV ADRs was 5.51% in this real-world, clinical population of patients receiving mirabegron treatment for OAB, in which patients were predominantly elderly (60.2% ≥75 years) and had coexisting CV disease (93.6%). Consistent with mirabegron registration trials, no significant differences in ECG parameters were revealed by mirabegron treatment, with the exception of a small, clinically acceptable increase in HR (1,2). Furthermore, analyses did not reveal any correlation between BL QTcF or HR and change in QTcF or HR during mirabegron treatment, either for the total population or age/sex stratified subgroups.

Concluding message
Mirabegron was well tolerated in Japanese patients with OAB and a history of/or coexisting CV disease and no additional CV safety concerns were observed.

Figure. Correlation* between Baseline and change from Baseline after mirabegron treatment (Δ), for QTcF and HR in patients for whom Baseline and post-treatment ECG data were available



C Correlation between Baseline value and change from Baseline value (Δ) of QTcF and HR in patient subgroups stratified by age or by sex.

	Total	<75 years	≥75 years	Male	Female
QTcF vs Δ QTcF	-0.246	-0.351	-0.157	-0.198	-0.309
Population, n	146	67	79	85	61
HR vs Δ HR	-0.309	-0.377	-0.254	-0.262	-0.338
Population, n	179	76	103	112	67

*Spearman's rank-correlation coefficient

References

1. Yamaguchi O, Marui E, Kakizaki H et al. Phase III, randomised, double-blind, placebo-controlled study of the beta3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. BJU Int 2014; 113: 951-960
2. Yamaguchi O, Ikeda Y, Ohkawa S. Phase III study to assess long-term (52-week) safety and efficacy of mirabegron, a??3-adrenoceptor agonist, in Japanese patients with overactive bladder. LUTS: Lower Urinary Tract Symptoms. 2015; doi: 10.1111/luts.12107

Disclosures

Funding: Astellas Pharma Inc **Clinical Trial:** Yes **Registration Number:** Clinical Trials.Gov, NCT02570035 **RCT:** No **Subjects:** HUMAN **Ethics not Req'd:** Prospective Study. The study protocol was approved by the Ministry of Health, Labor and Welfare (MHLW), was performed in accordance with the standards for Good Post-Marketing Study Practice (GPSP) provided by the MHLW in Japan **Helsinki:** Yes **Informed Consent:** No