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Kato D[1], Nozawa Y[1], Tabuchi H[1], Kuroishi K[1]
1. *Astellas Pharma Inc*

FACTORS ASSOCIATED WITH THE INCIDENCE OF ADVERSE DRUG REACTIONS (ADRS) IN PATIENTS WITH OVERACTIVE BLADDER (OAB) TREATED WITH MIRABEGRON: A JAPANESE POST-MARKETING STUDY

Hypothesis / aims of study
The β3-adrenoceptor agonist mirabegron was first approved in Japan in 2011 for treatment of OAB symptoms. This post-marketing study (NCT01919047) of Japanese patients initiating mirabegron treatment examined real-world incidence of ADRs and assessed the association of factors including age, concurrent diseases, mirabegron administration period, OAB duration, prior OAB medications, medical history, and concomitant drug use, on treatment efficacy and incidence of ADRs.

Study design, materials and methods
Complete medical histories, including prior and concomitant drug use, were collected before initiating mirabegron treatment. After 12 weeks daily mirabegron, physicians judged treatment as “effective”, “ineffective”, or “non-judgement”, and residual urine volume, and incidence of ADRs were assessed. At Baseline (BL) and after 12 weeks treatment, patients completed the OAB Symptom Score (OABSS) and the International Prostate Symptom Score-Quality of Life (I-PSS QoL) surveys. The influence of patient characteristics at BL (detailed below) on the proportion of patients achieving the minimal clinically important change (MCIC) in total OABSS and the incidence of ADRs, was assessed by multivariate logistic analysis. Model building proceeded in two steps. First, univariate models were conducted. Second, univariate models with p-value <0.20 and with fewer than 20% missing data were included in the multivariate logistic analysis. This survey collected data on patients treated with mirabegron between April 2012 and July 2014.

Results
Of the 9795 patients assessed (safety analysis set, SAF), 46.8% were male; 80.8% ≥65 years, and 71.7% had coexisting disease, notably prostatic hyperplasia (32.4%), hypertension (31.9%), diabetes (9.4%), and CV disease (6.9%). Overall, 53.4% of patients reported concomitant drug use, including α_1-antagonists (27.8%) and anticholinergic agents (6.3%). At BL, 85.5% of patients received mirabegron 50 mg, while 14.5% and ≤0.1% received 25 mg or 100 mg (off-license dosage), respectively. After 12 weeks, mirabegron was judged “effective” in 80.7% of patients. Of patients completing mirabegron treatment and for whom all OABSS scores were complete (OABSS population, n=4153), 63.6% achieved the MCIC from BL in mean OABSS score. Overall incidence of ADRs and serious ADRs was 6.07% and 0.21%, respectively. No unexpected ADRs were identified.
Multivariate logistic analyses of data from 3418 of 4153 patients in the OABSS population revealed that factors predictive of the rate of achieving the OABSS MCIC included age (<75 vs ≥75 years), sex, co-existing arrhythmia or diabetes mellitus, DRY/WET OAB status, medical history, prior OAB therapy, concomitant α_1-antagonist usage, severity of OAB symptoms (“mild” vs “moderate” or “severe”) and duration of OAB (“<3 months” vs “≥1 year and <3 years” or “≥3 years”) (Table, upper panel). Multivariate logistic analyses of data from 6779 of 9795 patients in the SAF, revealed that the incidence of ADRs with mirabegron treatment increased significantly with age (<75 vs ≥75 years), with co-existing glaucoma, angina pectoris or diabetes mellitus, or with medical history. The incidence of ADRs also increased with concurrent diseases excluded for OAB diagnosis, prior OAB treatment or use of α_1-antagonists but decreased with increased administration period (Table, lower panel). However, analyses for the major reported ADRs (constipation, residual urine volume, increased thirst and dysuria) found no relationship to the patient characteristics.

Interpretation of results
Mirabegron is an effective treatment for Japanese patients with OAB in a clinical setting and is well tolerated. Patient characteristics at BL such as age, sex, coexisting disease (arrhythmia or diabetes mellitus), DRY/WET OAB status, medical history, prior OAB therapy, concomitant α_1-antagonists use, OAB severity and OAB disease duration, influenced the proportion of patients achieving the OABSS MCIC. Incidence of ADRs was found to increase with age and decrease with increased administration period.

Concluding message
In a real-world clinical setting where a wide variety of patients with OAB are treated with mirabegron (notably the elderly or those with concomitant diseases/drug use), mirabegron treatment is effective and well tolerated, although influenced by patient BL characteristics

Table. Factors predictive of efficacy and incidence of adverse drug reactions in Japanese patients receiving mirabegron therapy in the clinical setting

Patient baseline characteristics predictive of OABSS MCIC achievement: adjusted multivariate logistic regression analysis*				
		Baseline, n (%)	MCIC Achieved, n (%)	p-value; odds ratio (95% CIs)
Patients in OABSS analysis set		4153 (100)	2641(63.6)	
Age	<75 yrs	2195 (52.9)	1447(65.9)	-
	>75 yrs	1958 (47.1)	1194 (61.0)	**p<0.048**; 0.860 (0.741, 0.999)
Sex	Male	1796 (43.2)	1041 (58.0)	-
	Female	2357 (56.8)	1600(67.9)	**p=0.010**; 1.284 (1.062,1.553)
Arrhythmia	No	3988 (96.0)	2552 (64.0)	-
	Yes	118 (2.8)	61 (51.7)	**p=0.018**; 0.588 (0.379, 0.913)
Diabetes mellitus	No	3704 (89.2)	2381 (64.3)	-
	Yes	402 (9.7)	232 (57.7)	**p=0.013**; 0.732 (0.572, 0.936)
DRY/WET classification	No	833 (20.1)	442 (53.1)	-
	Yes	3320 (79.9)	2199 (66.2)	**p=0.001**; 1.369 (1.128, 1.661)
Medical history	No	2681 (64.6)	1782 (66.5)	-
	Yes	1064 (25.6)	627 (58.9)	**p<0.001**; 0.728 (06.19, 0.856)
Prior OAB therapy	No	3432 (82.6)	2253 (65.6)	-
	Yes	606 (14.6)	306 (50.5)	**p<0.001**; 0.650 (0.533, 0.793)
Concomitant α_1-antagonists	No	2890 (69.6)	1923 (66.5)	-
	Yes	1144 (27.5)	641 (56.0)	**p=0.034**; 0.799 (0.649, 984)
OAB severity	Mild	322 (7.8)	124 (38.5)	**-**
	Moderate	3057 (73.6)	1964(64.2)	**p<0.001**; 2.757 (2.082, 3.649)
	Severe	774 (18.6)	553 (71.4)	**p<0.001**; 3.941 (2.811, 5.523)
OAB Disease duration	<3 mos	837 (20.2)	583 (69.7)	-
	>3 mos <1 yr	921 (22.2)	650 (70.6)	**p=0.133**;1.188 (0.949, 1.488)
	>1 yrs	1096 (26.4)	674 (61.5)	**p=0.005**; 0.742 (0.601, 0.915)
	>3 yrs	981 (23.6)	536 (54.6)	**p<0.001**; 0.589 (0.475, 0.730)
Patient baseline characteristics predictive of incidence of ADRs: adjusted multivariate logistic regression analysis*				
		Baseline, n (%)	ADRs, n (%)	p-value; odds ratio (95% CIs)
Patients in SAF		9795 (100)	595 (6.07)	
Age	<75 yrs	5011 (51.2)	260 (5.19)	-
	>75 yrs	4784 (48.8)	335 (7.00)	**p<0.001**; 1.758 (1.372, 2.253)
Glaucoma	No	9330 (95.3)	559 (5.99)	-
	Yes	309 (3.2)	28 (9.06)	**p=0.014**; 2.064 (1.158, 3.679)
Angina pectoris	No	9342 (95.4)	550 (5.89)	-
	Yes	297 (3.0)	37 (12.46)	**p=0.003**; 2.482 (1.348, 4.568)
Diabetes mellitus	No	8714 (89.0)	521 (5.98)	-
	Yes	925 (9.4)	66 7.14)	**p=0.015**; 1.600 (1.095, 2.340)
Concurrent diseases excluded for OAB diagnosis	No	9271 (94.7)	552 (5.95)	-
	Yes	524 (5.3)	43 (8.21)	**p=0.022;** 1.736 (1.081, 2.788)
Medical history	No	6093 (62.2)	324 (5.32)	-
	Yes	2619 (26.7)	196 (7.48)	**p=0.011**; 1.391 (1.078, 1.795)
Prior OAB therapy	No	7999 (81.7)	464 (5.80)	-
	Yes	1491 (15.2)	107 (7.18)	**p=0.011**; 1.519 (1.101, 2.095)
Concomitant α_1-antagonists	No	6775 (69.2)	393 (5.80)	-
	Yes	2720 (27.8)	182 (6.69)	**p<0.001**; 1.694 (1.290, 2.224)
Administration period	<7 days	164 (1.7)	119 (72.56)	-
	7-13 days	271 (2.8)	86 (31.73)	**p<0.001**; 0.176 (0.102, 0.305)
	14-27 days	789 (8.1)	106 (13.43)	**p<0.001**; 0.058 (0.035, 0.097)
	28-55 days	1119 (11.4)	131 (11.71)	**p<0.001**; 0.045 (0.027, 0.074)
	56-83 days	580 (5.9)	76 (13.10)	**p<0.001**; 0.053 (0.031, 0.089)
	≥84 days	6826 (69.9)	32 (0.47)	**p<0.001**; 0.001 (<0.001, 0.002)

*Forward and backward methods were used for sequential selection. OABSS=overactive bladder symptom score; MCIC=minimal clinically important change; OAB=overactive bladder; ADRs=adverse drug reactions

Disclosures
Funding: Astellas Pharma Inc **Clinical Trial:** Yes **Registration Number:** cvb **RCT:** No **Subjects:** HUMAN **Ethics not Req'd:** The study protocol was performed in accordance with the standards for Good Post-Marketing Study Practice (GPSP of the Japanese Ministry of Health, Labour and Welfare) **Helsinki:** Yes **Informed Consent:** No