9

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LONG-TERM ANTICHOLINERGIC ADD-ON THERAPY IN OVERACTIVE BLADDER (OAB) PATIENTS REFRACTORY TO MIRABEGRON MONOTHERAPY: A MULTICENTRE, RANDOMIZED STUDY (MILAI II STUDY)

Hypothesis / aims of study

Recently, the β3-adrenoceptor agonist mirabegron has been used as a first-line treatment in OAB. However, some patients may not respond well to mirabegron; therefore the present study evaluated efficacy and safety of antimuscarinic add-on therapy in OAB patients receiving mirabegron.

Study design, materials and methods

Study duration was 54 weeks, with a 2-week screening period and 52-weeks treatment. Patients ≥20 years who had been treated with mirabegron 50 mg for ≥6 weeks and with residual OAB symptoms based on Overactive Bladder Symptom Score (OABSS) were enrolled. They initially received mirabegron 50 mg once daily for 2 weeks and were randomized 1:1:1:1 to 52 weeks treatment with mirabegron 50 mg once daily plus solifenacin 5 mg, propiverine 20 mg, imidafenacin 0.2 mg, or tolterodine 4 mg. At week 8, dosage of each anticholinergic agent except for tolterodine could be doubled if, based on investigator's opinion, anticholinergics were insufficiently effective and there were no safety concerns.

Results

At baseline, 88.1% and 11.9% of participants (n=647) were women and men, respectively, with 53.9% ≥65 years of age. Micturitions, urgency, incontinence, urgency incontinence, mean volume voided (MVV) and night-time frequency significantly improved from baseline to endpoint in all groups ($P<0.001$, Table 1). Adverse drug reactions (ADRs) were generally reported at similar rates for all groups; the most frequently reported were constipation and dry mouth (Table 2). Mean change (SD) in PVR (mL) was 8.17±39.42, 6.83±32.20, 4.52±23.51 and 5.94±35.83 for the solifenacin, propiverine, imidafenacin, and tolterodine add-on groups, respectively. In general, across all groups there were slight increases in pulse rate, and slight decreases in diastolic blood pressure (DBP) and systolic blood pressure (SBP) from baseline to end of treatment (EoT). Mean change in QTcF interval was at most 3 msec (in the tolterodine add-on group; Table 3).

Interpretation of results

Anticholinergic add-on therapy was effective and well tolerated in all groups, with improvements from baseline to endpoint and no unexpected ADRs. Changes in QTcF interval were not clinically significant.

Concluding message

In OAB patients refractory to mirabegron monotherapy, anticholinergic add-on therapy is well tolerated and effective, and thereby a useful treatment option.

Table 1: Efficacy

Values, mean (standard deviation)	Mirabegron+ solifenacin	Mirabegron+ propiverine	Mirabegron+ imidafenacin	Mirabegron+ tolterodine
Micturitions/24 h	**n=166**	**n=161**	**n=161**	**n=159**
Baseline	10.06 (2.59)	10.37 (2.65)	10.13 (2.92)	10.20 (2.62)
Baseline to EoT change	-2.18 (1.96)*	-1.89 (2.08)*	-1.75 (2.09)*	-1.91 (2.22)*
Urgency episodes/24 h	**n=153**	**n=148**	**n=150**	**n=148**
Baseline	3.23 (2.48)	3.10 (2.66)	3.25 (2.22)	3.14 (2.55)
Baseline to EoT change	-2.03 (2.55)*	-2.24 (2.41)*	-2.04 (2.19)*	-2.07 (2.23)*
Incontinence/24 h	**n=91**	**n=94**	**n=102**	**n=95**
Baseline	1.60 (1.63)	1.59 (1.83)	1.45 (1.35)	1.56 (1.77)
Baseline to EoT change	-1.25 (1.48)*	-1.18 (1.59)*	-1.03 (1.08)*	-1.15 (1.52)*
Urgency incontinence episodes/24 h	**n=80**	**n=82**	**n=85**	**n=84**
Baseline	1.53 (1.48)	1.37 (1.44)	1.29 (1.18)	1.32 (1.62)
Baseline to EoT change	-1.20 (1.32)*	-1.12 (1.33)*	-0.91 (0.93)*	-1.05 (1.59)*
MVV/micturition	**n=166**	**n=161**	**n=161**	**n=159**
Baseline	168.833 (50.266)	171.742 (63.125)	172.155 (48.957)	169.882 (55.610)
Baseline to EoT change	38.313 (44.592)*	37.844 (45.504)*	30.962 (43.671)*	38.439 (45.564)*
Night-time frequency/24 h	**n=144**	**n=137**	**n=143**	**n=134**
Baseline	1.59 (0.99)	1.74 (1.10)	1.68 (1.31)	1.73 (1.06)
Baseline to EoT change	-0.47 (0.91)*	-0.38 (0.88)*	-0.48 (0.93)*	-0.48 (0.88)*

*P<0.001 (one sample t-test vs Baseline), n=number of patients at baseline.

Table 2: ADRs

	Mirabegron+ solifenacin	Mirabegron+ propiverine	Mirabegron+ imidafenacin	Mirabegron+ tolterodine
n	**166**	**161**	**161**	**159**
ADRs, n (%)	76 (45.8)	81 (50.3)	72 (44.7)	74 (46.5)
Common ADRs (≥2% in any treatment group), n (%)				
Abdominal discomfort	5 (3.0)	2 (1.2)	3 (1.9)	2 (1.3)
Constipation	33 (19.9)	26 (16.1)	23 (14.3)	18 (11.3)
Dry mouth	31 (18.7)	51 (31.7)	40 (24.8)	40 (25.2)
Cystitis	0	0	4 (2.5)	0
Electrocardiogram QT prolonged	1 (0.6)	2 (1.2)	4 (2.5)	1 (0.6)
Residual urine volume increased	6 (3.6)	7 (4.3)	1 (0.6)	2 (1.3)
Dysuria	8 (4.8)	4 (2.5)	3 (1.9)	7 (4.4)

Table 3: Vital signs

Values, mean (standard deviation)	Mirabegron+ solifenacin	Mirabegron+ propiverine	Mirabegron+ imidafenacin	Mirabegron+ tolterodine
Pulse rate, morning	**n=166**	**n=161**	**n=160**	**n=159**
Baseline bpm	70.07 (8.15)	69.15 (8.19)	69.17 (7.25)	68.51 (8.15)
Baseline to EoT change	0.68 (4.95)	3.19 (6.54)	0.09 (5.74)	2.11 (5.20)
Pulse rate, afternoon	**n=166**	**n=160**	**n=161**	**n=159**
Baseline	74.91 (8.80)	73.87 (9.16)	74.56 (8.08)	74.09 (8.68)
Baseline to EoT change	0.17 (6.25)	2.86 (6.62)	-1.27 (6.67)	3.40 (6.86)
SBP, morning	**n=166**	**n=161**	**n=160**	**n=159**
Baseline bpm	128.91 (16.03)	129.75 (17.22)	127.21 (16.34)	129.22 (16.41)
Baseline to EoT change	-1.60 (11.56)	-2.88 (9.08)	-0.86 (9.64)	-2.31 (10.14)
SBP, afternoon	**n=166**	**n=160**	**n=161**	**n=159**
Baseline	125.45 (13.52)	125.44 (13.99)	125.20 (14.35)	127.15 (13.74)
Baseline to EoT change	-0.46 (10.53)	-1.55 (9.27)	-1.64 (9.23)	-2.35 (9.86)
DBP, morning	**n=166**	**n=161**	**n=160**	**n=159**
Baseline bpm	80.65 (9.14)	80.45 (10.36)	79.08 (10.04)	79.40 (9.82)
Baseline to EoT change	-0.90 (6.48)	-1.00 (6.07)	-0.64 (6.31)	-0.54 (6.81)
DBP, afternoon	**n=166**	**n=160**	**n=161**	**n=159**
Baseline	78.03 (8.38)	77.67 (9.23)	77.30 (9.32)	77.85 (8.76)
Baseline to EoT change	-0.54 (6.48)	-0.56 (6.25)	-1.79 (5.92)	0.33 (7.17)
QTcF interval	**n=164**	**n=161**	**n=160**	**n=158**
Screening msec	418.5 (17.4)	419.2 (16.9)	416.4 (17.3)	415.4 (15.6)
Screening to EoT change	1.8 (11.6)	-1.2 (10.8)	-0.4 (12.8)	3.0 (10.6)

n=number of patients at baseline.

Disclosures

Funding: Astellas Pharma Inc **Clinical Trial:** Yes **Registration Number:** Clinicaltrial.gov NCT02294396 **RCT:** No **Subjects:** HUMAN **Ethics Committee:** International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, applicable local laws/regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki **Helsinki:** Yes **Informed Consent:** Yes