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PATIENTS REPORTING SEVERE OVERACTIVE BLADDER SYMPTOMS: EFFECTS OF SOLIFENACIN TREATMENT ON OBJECTIVE MEASURES AND PATIENT-REPORTED OUTCOMES

Hypothesis / aims of study

The efficacy of antimuscarinic therapy in patients considered to have severe symptoms of overactive bladder (OAB) has not been adequately explored. We analyzed data from **V**ESIcare **E**fficacy and Safety in Patie**N**ts with **U**rgency **S**tudy (VENUS), which measured urgency as the primary endpoint. Micturition diary outcomes (frequency, urgency, and incontinence) were measured alongside patient-reported outcomes (PROs) that assess key aspects of OAB such as symptom bother, health-related quality of life (HRQoL), and warning time (WT, time between first sensation of urgency to voiding/incontinence). Here we report data from a post-hoc analysis of VENUS, featuring data from patients with severe OAB symptoms.

Study design, materials and methods

VENUS was a randomized, double blind, placebo-controlled, 12-week study that measured urinary urgency as the primary endpoint using both objective and subjective measures. We conducted a subanalysis of this data set to determine effects of treatment in patients with severe symptoms, defined at baseline by a score of 5 or above on the Patient Perception of Bladder Condition (PPBC) scale (6 point scale: 1 indicates bladder condition causes no problems, 6 indicates many severe problems). OAB patients with at least 1 urinary urgency episode/day, with or without urinary incontinence began taking solifenacin 5 mg/day or placebo. At Weeks 4 and 8, the dose of solifenacin could be titrated as clinically indicated to 10 mg (Weeks 4 and 8), or back to 5 mg (Week 8). Primary endpoint was mean change from baseline to study end (Week 12) in urgency episodes/day assessed by 3-day micturition diary. Secondary endpoints included mean changes in daily micturitions, incontinence episodes, nocturia episodes and nocturnal voids, and median change from baseline to study end in WT. Secondary efficacy analyses were also performed on multiple PRO measures (specific to symptom bother and HRQoL) and included mean changes from baseline to study end in the PPBC scale, Indevus Urgency Severity Scale (IUSS), Urgency Perception Scale (UPS), and Overactive Bladder Questionnaire (OAB-q). Results for the VENUS severe subgroup are compared with the full VENUS population.

Results

In total, 22.3% of patients in the full VENUS population (n=707) qualified as having severe OAB symptoms (n=158). These patients had a mean age of 57.2 years (34.2% age 65 or older) and were mostly female (85.4%), demographics which are comparable for patients in the full VENUS population. At study end, 37 patients (41.5%) in the severe-symptom group were taking 5 mg solifenacin and the same number of patients were taking 10 mg solifenacin; 4 patients (4.5%) discontinued drug. For placebo, 15 patients (19.5%) were in the 5-mg group; 48 (62.3%) were in the 10-mg group, and 7 patients (9.1%) discontinued. For severe patients, mean number of urgency episodes/day at baseline was 7.88 among solifenacin-treated subjects versus 7.94 in the placebo group. At study end, solifenacin-treated severe patients reported 3.33 urgency episodes/day versus 4.86 in the placebo group; a reduction of 4.56 episodes/day in the solifenacin group versus 3.08 in the placebo group. This followed the trend shown in the full VENUS population where solifenacin significantly reduced urgency episodes versus placebo (P<0.0001). Patients with severe OAB symptoms also showed similar reductions in daily micturitions and incontinence episodes versus placebo to the significant reductions seen in the full VENUS population (Table). Overall, 94.8% of solifenacin-treated patients with severe OAB symptoms reported PPBC score improvements relative to baseline versus 68.8% of placebo-treated patients. For the severe subgroup receiving solifenacin, the mean PPBC score was 5.2 at baseline (indicating 'severe' to 'many severe' problems). After 12 weeks of treatment with solifenacin, PPBC score was 3.1 (indicating 'minor to moderate' problems at study end). By comparison, for the placebo group, PPBC improved from 5.8 at baseline to 3.8 at study end. This followed the trend seen in the full VENUS population, where PPBC improved significantly in solifenacin-treated patients versus those on placebo (P<0.0001). Improvements in WT, IUSS, and UPS in the severe solifenacin-treated group versus placebo were consistent with the significant improvements versus placebo in the full VENUS population. Median WT for the solifenacin-treated severe subgroup improved (23-second increase), compared to a 9-second increase in the placebo group. Mean IUSS score for the solifenacin-treated severe subgroup improved from 2.4 at baseline (indicating 'moderate' to 'severe' urgency) to 1.2 at study end (indicating 'mild' to 'moderate' urgency). For the placebo group, scores were 2.5 and 1.7 at baseline and study end, respectively. Mean UPS score for the solifenacin-treated severe subgroup improved from 1.8 at baseline (indicating 'not usually able to hold urine'/'able to hold if go to toilet immediately') to 2.2 at study end (indicating 'able to hold if go to toilet immediately'). For the placebo group, scores were 1.6 and 2.1 at baseline and study end, respectively. Improvements on all OAB-q domains except social interaction also supported the significant results seen in solifenacin patients in the full VENUS population (Table). Treatment-emergent adverse events were mostly mild or moderate and resulted in few discontinuations (severe subgroup 4.5%, full VENUS population 6.5%).

	Severe subset (n=158)		Full VENUS population (n=707)		
Parameter (mean)	Solifenacin Baseline (Change*) n=84	Placebo Baseline (Change*) n=74	Solifenacin Baseline (Change*) n=357	Placebo Baseline (Change*) n=350	*P*-value (between groups)‡
Urgency episodes/day†	7.88 (–4.56)	7.94 (−3.08)	6.15 (–3.91)	6.03 (−2.73)	<0.0001
Micturitions/day†	12.11 (–2.91)	12.69 (−2.40)	11.65 (–2.67)	11.70 (−1.94)	0.001
Incontinence episodes/day†	4.52 (–3.26)	4.21 (−2.13)	2.82 (–2.10)	2.56 (−1.24)	<0.0001
Nocturia episodes/day†	1.82 (–0.62)	1.94 (-0.76)	1.67 (–0.64)	1.60 (−0.49)	0.208
Nocturnal voids/day†	2.21 (–0.69)	2.52 (-0.87)	2.02 (–0.72)	2.02 (−0.59)	0.191

Median WT (sec)	99.0 (23.0)	52.0 (9.0)	67.75 (31.50)	65.0 (12.0)	<0.01
IUSS score*	2.4 (–1.2)	2.5 (–0.8)	2.0 (–0.9)	2.0 (–0.5)	<0.0001
UPS score	1.8 (0.5)	1.6 (0.4)	2.0 (0.4)	2.0 (0.2)	0.002
PPBC scale score†	5.2 (–2.1)	5.2 (–1.3)	3.8 (–1.0)	3.9 (–0.6)	<0.0001
OAB-q domain score					
Bother†	69.5 (–41.1)	71.3 (−25.5)	52.4 (–28.0)	51.5 (−18.5)	<0.0001
Coping	33.5 (38.7)	32.3 (28.2)	56.1 (24.9)	55.9 (19.4)	<0.001
Concern	29.8 (45.3)	27.5 (30.3)	54.5 (28.4)	55.2 (20.3)	<0.0001
Sleep	44.4 (29.5)	36.9 (23.0)	54.6 (22.2)	54.2 (16.8)	<0.05
Social interaction	64.6 (23.2)	65.1 (15.4)	81.5 (11.0)	81.4 (9.7)	0.2362
Overall HRQoL	40.9 (35.6)	38.4 (25.2)	60.4 (22.6)	60.5 (17.2)	<0.001

*Adjusted mean change from baseline; †Negative score change indicates improvement. Improvements in all other domains are indicated by positive score changes; ‡Between solifenacin and placebo in the full VENUS population. *P*-values not reported for the severe subset due to the post-hoc nature of the analysis and small sample size.

Interpretation of results

After 12 weeks of treatment with solifenacin, patients with severe OAB symptoms experienced improvements in urgency, micturitions, and incontinence versus placebo (recorded by 3-day diaries) and in WT (recorded by stopwatch diary). These patients also reported improvements from baseline versus placebo in urgency severity, symptom bother, and HRQoL, as measured by the IUSS, UPS, PPBC, and OAB-q.

Concluding message

In patients with severe OAB symptoms, flexibly dosed solifenacin reduced OAB symptoms and improved symptom bother and health-related quality of life. These results were similar to the significant improvements observed in the full VENUS study population.

Specify source of funding or grant	**This study was sponsored by Astellas Pharma US, Inc. and GlaxoSmithKline**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**The trial registry number is NCT00454896**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**This study was conducted in accordance with Good Clinical Practice and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and FDA regulations**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**