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EFFECTS OF 12 WEEKS TREATMENT WITH SOLIFENACIN ON BLADDER WALL THICKNESS (BWT) AND CLINICAL OUTCOMES: RESULTS FROM THE PLACEBO-CONTROLLED SHRINK STUDY

Hypothesis / aims of study

Few studies have explored the link between ultrasound derived bladder wall thickness (BWT) and bladder diary variables, such as the frequency of micturitions and incontinence episodes and the corresponding feeling of urgency. The SHRINK study (clinicaltrials.gov identifier: NCT01093534) investigated the effect of solifenacin on BWT in women with overactive bladder (OAB) and a urodynamic diagnosis of detrusor overactivity, and this evaluation aimed to determine the relationships between BWT, OAB symptoms and patient satisfaction, both at baseline and throughout the study.

Study design, materials and methods

SHRINK was a phase 4, randomised, blinded placebo-controlled trial. A total of 547 patients were randomised in a ratio 1:1:1 to placebo, solifenacin 5 mg or solifenacin 10 mg for 12 weeks. BWT was measured by the assessment of images from each visit (baseline, week 6 and week 12 or end of treatment) by two blinded central readers at three locations (anterior, dome and trigone), and a mean BWT was derived per subject. Images were assessed by a blinded third reader in cases of significant variability between the two readers ($p<0.05$, based on Bland-Altman limits of agreement)(1). At each visit patients completed the patient perception of bladder condition (PPBC) questionnaire, the patient assessment of urgency bother and treatment satisfaction using visual analogue (VAS) scales (UB-VAS and TS-VAS) and the overactive bladder questionnaire (OAB-q). In addition, patients completed a 3-day micturition diary prior to each visit.

Results

Of 547 randomised women, 501 were included in BWT analyses at baseline (change from baseline could be calculated for 478 women). Reductions in BWT from baseline to end of treatment were seen in both 5 mg and 10 mg groups versus placebo, but did not reach statistical significance for the 10 mg dose (5 mg: -0.254 mm [p=0.030] versus placebo; 10 mg: -0.084 mm [p=0.477] versus placebo). Improvements from baseline to end of treatment compared to placebo were seen in clinical outcomes in both solifenacin treatment arms (Table).

Interpretation of results

Both doses of solifenacin improved clinical outcome variables after 12 weeks of treatment compared to placebo. Reductions in BWT were observed with both solifenacin doses, and reached statistical significance for the 5 mg dose versus placebo, but not for the 10 mg dose. At baseline (data not shown) the 10 mg dose group had fewer micturitions and urgency episodes and lower OAB-q symptom severity score compared with the 5 mg dose group, suggesting this group was less severe. The study was powered for a comparison of the pooled solifenacin doses versus placebo, assuming an average treatment difference of 0.5 mm and a standard deviation of 1.65 mm. The power for finding a statistical significant difference versus placebo is about 76% for each solifenacin dose; however the power for seeing such a significant difference for both doses in the same trial is lower.

Concluding message

Treatment with solifenacin can significantly reduce BWT compared with placebo. Clinical outcome results show improvement in both solifenacin doses; however, the study is inconclusive whether there is a dose effect of solifenacin treatment on the reduction of BWT.

Table: Mean change from baseline to week 12 (LOCF) in BWT and selected clinical outcomes.

	Placebo	**Solifenacin 5 mg**	**Solifenacin 10 mg**
Mean BWT (mm) Mean difference vs. Placebo (95% CI)	-0.162	-0.416 -0.254 * (-0.484, - 0.025)	-0.246 -0.084 (-0.318, 0.149)
Micturitions/24 h	-1.23	-1.65	-1.78*
Urgency micturitions/24 h with PPIUS grade 3 or 4	-1.41	-1.86*	-1.69
Incontinence episodes/24 h	-0.74	-1.34*	-0.96
OAB-q symptom severity	-14.90	-22.32 ***	-22.91 ***
OAB-q symptom bother VAS	-12.0	-24.5 ***	-26.9 ***
PPBC: improvement by ≥1 category	50.5%	70.2% ***	74.0% ***
Treatment satisfaction VAS	16.5	24.1*	28.3 ***

Percentages are calculated from raw data. Mean values are estimated as LS mean values, adjusted for baseline (ANCOVA model). *p<0.05, ***p<0.001 versus placebo. ANCOVA model included treatment and geographic region as fixed effects and

baseline as covariate. Logistic regression for PPBC included treatment and baseline PPBC score. VAS = Visual analogue scale score, range 0 to 100.

References
1. Lancet, 1986; 327: 307-10.

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