

A MULTI-CENTRE, RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP STUDY TO EVALUATE WHETHER TOLTERODINE EXTENDED RELEASE CAN REVERSE THE INCREASED BLADDER WALL THICKNESS IN WOMEN WITH OVERACTIVE BLADDER

Hypothesis / aims of study

Overactive bladder (OAB) is a syndrome consisting of urgency, with or without urgency urinary incontinence, usually with frequency and nocturia. It is a common and distressing condition, and the prevalence increases with age. OAB symptoms are often the result of detrusor overactivity (DO), which in turn, causes detrusor muscle hypertrophy and a thickening of the bladder wall. Transvaginal ultrasound (TVUS) is a reliable tool to measure bladder wall thickness of the empty bladder and may be diagnostic of DO.^{1,2} Because antimuscarinics such as tolterodine have proven efficacy for improving OAB symptoms, this study aimed to evaluate the effect of tolterodine extended release (TER) on the thickened bladder wall in patients with OAB. Results from a previous study showed that bladder wall thickness is ~5 mm in normal women and ~6.3 mm in women with OAB.³ The study hypothesis was that treatment with TER would normalize patients' bladder wall thickness.

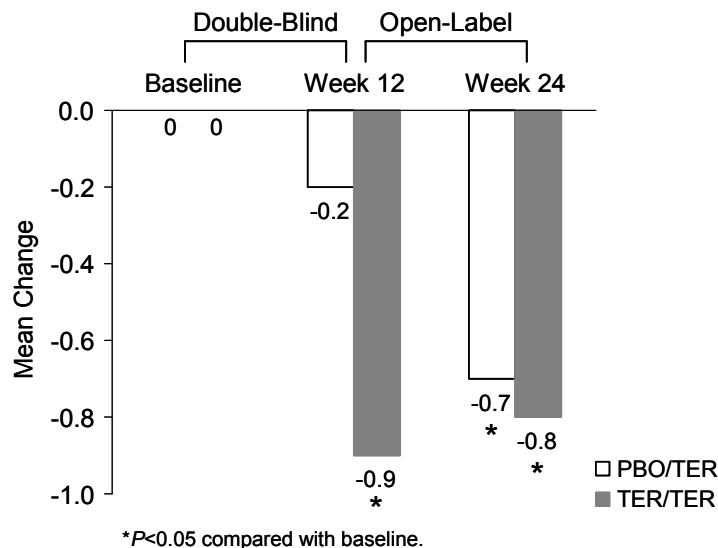
Study design, materials and methods

The study comprised a 12-week double-blind phase followed by a 12-week open-label phase and was conducted at 11 hospital-based sites in the United Kingdom. Eligible women (aged ≥ 18 y) had OAB symptoms for ≥ 6 months and a mean detrusor muscle thickness ≥ 5.0 mm as determined by TVUS at screening (visit 1). At baseline (visit 2), patients were randomized (1:1) to receive once-daily TER (4 mg) or placebo (PBO) for 12 weeks. At week 12 (visit 4), all patients received TER for 12 weeks. TVUS was performed at the end of week 12 (visit 4) and at the end of open-label treatment (week 24, visit 6), or at discontinuation from the study. The primary endpoint was the change from baseline to week 12 in bladder wall thickness in patients who received TER vs placebo. Based on previous findings, a decrease in the mean bladder wall thickness of ≥ 1.3 mm was used in this study for sample size estimation. Data were evaluated using an analysis of covariance, with treatment and centre as factors and baseline bladder wall thickness as a covariate. Treatment differences are reported as least squares (LS) means and 95% confidence intervals (CIs). For early discontinuations, post-baseline values were imputed using the last observation carried forward.

Results

Of the 134 patients screened, 79 were randomised to TER (n=37) or PBO (n=42). 82% of patients completed the 24-week study. Six patients discontinued from TER treatment and 8 discontinued from PBO. One discontinuation from each group was considered treatment related. Mean age was similar: 47 years (range, 20–72 y) for TER and 47 years (range, 21–72 y) for PBO. Mean duration since OAB diagnosis was also similar: 6.1 years (range, 0–31 y) and 5.0 years (range, 0.2–25 y), respectively. Median duration of treatment was 170 days for TER and 166 days for PBO. 73% of TER- and 82% of PBO-treated patients were compliant (ie, patients took 80%–120% of their medication). At baseline, mean (standard deviation [SD]) bladder wall thickness was 6.7 (1.5) mm in the TER group and 6.2 (0.8) mm in the PBO group. The change from baseline to week 12 in mean (SD) bladder wall thickness was statistically significant in the TER group ($P < 0.05$) but not in the PBO group ($P = 0.54$; Figure). The LS mean (95% CI) for the treatment difference was -0.4 (-1.2 to 0.3) and was not statistically significant ($P = 0.25$). During open-label treatment with TER, there were no further reductions in bladder wall thickness among those who received TER during the double-blind phase; however, there was a statistically significant reduction in bladder wall thickness among patients who received PBO during the double-blind phase ($P < 0.05$; Figure).

Figure. Changes in Bladder Wall Thickness



Interpretation of results

Although TER treatment was associated with a statistically significant decrease in bladder wall thickness from baseline to week 12, the between-group difference in the change from baseline did not reach statistical significance. Nevertheless, there was a clear trend in the effect of TER on bladder wall thickness, suggesting that tolterodine may change the bladder wall structure or even reduce hypertrophy. Interestingly, reductions in bladder wall thickness in the PBO group remained small, suggesting that this may be a useful objective measure of antimuscarinic efficacy for OAB. The results also suggest that TER-related reductions in bladder wall thickness were maximized after 12 weeks, as there were no further reductions between weeks 12 and 24 of TER treatment. In addition, patients in the PBO group demonstrated comparable reductions in bladder wall thickness after switching to open-label TER for 12 weeks.

It is likely that the predicted change of 1.3 mm was not achieved because the sample size was determined based on the results of a previous study³ that performed a within- but not between-group analysis of the data, as was done in this study. The current study provides a basis for a more accurate calculation of sample size calculation for a larger future study.

Concluding message

The results of this study suggest that TER has a direct effect on bladder wall thickness in women with OAB. TER may change bladder wall structure and reduce, or even reverse, bladder wall hypertrophy. Bladder wall thickness might be used as an objective measure of antimuscarinic efficacy for OAB. Larger studies are warranted to further investigate this treatment effect and to examine the potential relationship between treatment-related improvements in OAB symptoms and in bladder wall thickness.

References

1. Br J Obstet Gynaecol (1996) 103; 904-908.
2. Neurourol Urodyn (2002) 21; 284-285.
3. Int Urogynecol J (1994) 5; 327.

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CLINICAL TRIAL REGISTRATION: Clinical Trials Registry: NCT00137397

HUMAN SUBJECTS: This study was approved by the Northwest Multi-Centre Research and followed the Declaration of Helsinki Informed consent was obtained from the patients.