

## REFRACTORY URGE URINARY INCONTINENCE AND BOTULINUM A TOXIN INJECTION TRIAL

### Hypothesis / aims of study

This trial compares the effect of 200 units of intra-detrusor botulinum toxin A (Botox®) versus placebo on urinary symptoms and adverse events in neurologically normal women with detrusor overactivity incontinence (DOI) refractory to at least two first-line urge incontinence treatments.

### Study design, materials and methods

This study complies with the recommendations of the CONSORT group. Participants in this multi-center randomized masked trial had refractory urge incontinence,  $\geq$  six urge incontinence episodes on a 3-day diary and documented urodynamic DOI. Participants were randomized (2:1 Botox®:placebo) on injection day. Investigators injected a total of 6 cc of masked substance into approximately 15-20 different detrusor muscle sites under direct visualization, sparing the bladder trigone and ureteral orifices. The primary outcome measurement was time to failure after injection defined by a Patient Global Impression of Improvement (PGI-I) score  $\geq$  4 (no change or worsening of symptoms) two or more months after the injection or new or increased treatment for DOI at any time after the injection. Safety data, including urinary retention and urinary tract infections (UTI), were monitored. We planned to accrue 210 subjects in order to have 80% power to identify a difference between 50% vs. 30% success rates.

### Results

After 43 women were injected (28 Botox®, 15 placebo), rates of urinary retention and UTI exceeded expected ranges and further injections were stopped. Urinary retention (defined as catheterization beyond 4 weeks after injection or PVR >200cc before or at the 4 week visit) occurred exclusively in the Botox® group, affecting 12 (42%) women in that group. Retention was diagnosed based on symptoms before the 4-week visit (3 subjects) or by PVR at the 4-week study visit (9 cases) and resolved 32-206 days after injection (median 73.5 days). Sixteen women reported UTIs; these were more common in those who catheterized (10/12, 83%) vs. others (6/31, 19%). Median failure times for Botox® and placebo were 160 and 62 days, (i.e., at first PGI-I), respectively ( $p=0.002$  log-rank test adjusted for DOI medications). Two months after injection 12/15 (80%) women in the placebo and 10/28 (35%) in the Botox® group ( $p=0.01$ ) reported no benefit. The median benefit of Botox® responders was at least 6 months (follow up is continuing).

### Interpretation of results

Botox® was effective in most women, although urinary tract infections and transient urinary retention were higher than previously reports of intra-detrusor injection of 200 units of Botox®. Urinary retention may not be clinically obvious and was found only by PVR surveillance in 75% of the affected subjects.

### Concluding message

Close surveillance for urinary retention and urinary tract infections are warranted following treatment of Botox 200 units in women with refractory urge urinary incontinence secondary for idiopathic detrusor overactivity incontinence.

**FUNDING:** Supported by grants from the National Institute of Child Health and Human Development (2U01 HD41249, 2U10 HD41250, 2U10 HD41261, 2U10 HD41267, 1U10 HD54136, 1U10 HD54214, 1U10 HD54215, 1U10 HD54241).

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov NCT00373789

**HUMAN SUBJECTS:** This study was approved by the Principal Investigator - Loyola University LU# 108719 and all enrolling sites, including data coordinating center IRB approved. and followed the Declaration of Helsinki Informed consent was obtained from the patients.