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ONABOTULINUMTOXINA IMPROVES URODYNAMIC OUTCOMES IN PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY

Hypothesis / aims of study

To evaluate the effects of onabotulinumtoxinA 200U and 300U compared with placebo on urodynamic outcomes in patients with urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO).

Study design, materials and methods

Here we present the results of a pooled analysis of two pivotal, multicenter, double-blind, randomized, placebo-controlled Phase 3 studies that were identical in study design (ClinicalTrials.gov identifiers NCT00311376 and NCT00461292), except for the UI retreatment threshold. Eligible patients had NDO due to multiple sclerosis (MS) or spinal cord injury (SCI) with ≥14 UI episodes/week and were not adequately managed by anticholinergics, though the continued use of anticholinergics was permitted throughout the study. Patients received 30 intradetrusor injections of placebo, onabotulinumtoxinA 200U, or onabotulinumtoxinA 300U, administered cystoscopically, avoiding the trigone. The primary efficacy endpoint in both studies was change from baseline in number of UI episodes at week 6 following the first treatment. Secondary endpoints included urodynamic outcomes (changes from baseline in maximum cystometric capacity [MCC] and maximum detrusor pressure [MDP] during first intradetrusor contraction [IDC]) at week 6. Bladder compliance and volume at first IDC were also assessed. Patients could request a second treatment from 12 weeks post first treatment onward. Retreatment required the patient to have a <50% (study 1) or <30% (study 2) reduction from baseline in weekly UI episodes. The placebo-controlled comparison focuses on the first 12 weeks post treatment 1, prior to possible retreatment. Study 1 was designed to provide 90% power to detect a 7.5 episode difference in change from baseline in frequency of UI between onabotulinumtoxinA and placebo, with a two-sided type I error of 0.025. The common standard deviation is assumed to be 15 episodes. Study 2 was powered for 80% under the same assumptions as in study 1.

Results

A total of 691 patients were analyzed in the pooled studies. Overall baseline characteristics of the ITT population were balanced across the treatment groups (mean age 45.9 years, 57.9% female, 85.8% Caucasian, 55.1% with MS, 44.9% with SCI, 54.8% on anticholinergic therapy, mean duration of NDO of 7.7 years). Similarly, the baseline urodynamic parameters were comparable across the treatment groups (MCC of 252.0 mL, MDP during first IDC of 47.9 cm H_2O, volume at first IDC of 186.3 mL). Significant decreases in UI compared to placebo were observed in both onabotulinumtoxinA dose groups (mean reduction of -21.3 episodes per week for both dose groups compared to -10.5 in the placebo group; $P<0.001$). Both doses of onabotulinumtoxinA significantly increased MCC compared with placebo ($P<0.001$), with mean increases of +153.6 and +163.1 mL in the 200U and 300U onabotulinumtoxinA groups versus only +11.9 mL in the placebo group. A large proportion of patients were confirmed as not having an IDC at week 6 in both onabotulinumtoxinA dose groups (64.0% and 65.1% in the 200U and 300U groups, respectively) compared to 18.4% in the placebo group. Furthermore, in the subset of patients who did have an IDC, the mean MDP during the first IDC was significantly decreased in both onabotulinumtoxinA dose groups (-32.4 and -30.1 cm H_2O in the 200U and 300U groups, respectively) compared with a small increase in the placebo group (+1.1 cm H_2O; $P<0.001$). Volume at first IDC was significantly increased with onabotulinumtoxinA treatment compared with placebo ($P<0.001$), with mean increases of +183.4 and +202.4 mL in the 200U and 300U onabotulinumtoxinA groups compared with +17.5 mL in the placebo group (for patients with no IDC, MCC was imputed as the volume at first IDC). A significant mean change in bladder compliance was also seen with onabotulinumtoxinA treatment (+59.8 and +50.4 mL/cm H_2O in the 200U and 300U groups, respectively) compared with placebo (-5.2 mL/cm H_2O; $P<0.001$). These urodynamic results were consistent with the reported improvement in patient symptoms. There were no clinically meaningful differences in efficacy between onabotulinumtoxinA dosage groups, including duration of effect (median time to patient request for retreatment was 38.4 and 37.9 weeks in the 200U and 300U onabotulinumtoxinA groups, respectively, versus 13.1 weeks in the placebo group). Significant improvements were observed in both SCI and MS patients in all of the above parameters. Adverse events included dose-dependent increases in urinary tract infections and increased post-void residual urine volume in both active dose groups over placebo.

Interpretation of results

Both doses of onaboutlinumtoxinA significantly improved urodynamic outcomes as evidenced by increases in bladder capacity and decreases in bladder pressure. The urodynamic results were in line with the observed symptom improvement of decreased UI.

Concluding message

OnabotulinumtoxinA at doses of 200U or 300U significantly improved urodynamic outcomes in patients with NDO in both the SCI and MS populations as well as pooled populations. No clinically relevant difference in urodynamic outcomes was seen between the two active dose groups (onabotulinumtoxinA 200U and 300U). Urodynamic outcomes corresponded with the clinical variable of reduction in incontinence episodes.

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**ClinicalTrials.gov registration numbers NCT00311376 and NCT00461292**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**The institutional review boards or ethics committees at each participating center approved the study.**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**