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Apostolidis A[1], Mourad S[2], Thompson C[3], Yan X[3], Haag-Molkenteller C[3]
1. *Papageorgiou General Hospital,* ***2.*** *Ain-Shams University,* ***3.*** *Allergan, Inc.*

A DOSE-EXPLORATION STUDY OF THE EFFICACY AND SAFETY OF ONABOTULINUMTOXINA IN PATIENTS WITH URINARY INCONTINENCE DUE TO NEUROGENIC DETRUSOR OVERACTIVITY

Hypothesis / aims of study
To explore the dose-dependent response to intradetrusor injection of 50U, 100U and 200U of onabotulinumtoxinA or placebo in patients with urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO).

Study design, materials and methods
In this multicenter, double-blind, randomized, placebo-controlled, parallel-group study, eligible patients had NDO due to spinal cord injury (SCI; T1 level or lower) with ≥14 UI episodes/week. Patients had to have been inadequately managed by anticholinergics; however, patients who were continuing to take anticholinergics were asked to continue taking them throughout the study. Patients received 30 intradetrusor injections of one of 3 doses of onabotulinumtoxinA (50U, 100U or 200U) or placebo, administered cystoscopically, avoiding the trigone. The primary efficacy variable was the change from baseline in the number of UI episodes/week at week 6, assessed using a 7-day bladder diary. Urodynamic parameters and adverse events (AEs) were also assessed. As this was an exploratory study, the sample size was determined empirically and a sample size of 40 patients per treatment group was planned. Owing to slow patient enrolment, only 74 patients were enrolled and 73 were treated. Dose response was evaluated using a linear regression model on the mITT population (all randomized patients who received treatment) and testing the slope of the regression line. Efficacy variables were also summarized and analyzed using an ANCOVA to assess any between-group differences.

Results
A total of 73 patients received treatment: placebo (n=16), 50U (n=19), 100U (n=21), and 200U (n=17). Overall baseline demographics of the study population were similar among the treatment groups (mean age 34 years, 86% male, 74% Caucasian, median duration of NDO 36 months) and disease characteristics were comparable across the treatment groups. Almost half of the patients (47%) were using anticholinergics.
Efficacy: A significant linear dose-response in weekly UI episodes was identified at weeks 18, 30, 36, 42, and 54 ($P< 0.05$); a similar trend (P-value of 0.092) was noted at the primary time point of week 6. The largest decrease from baseline was consistently observed in the onabotulinumtoxinA 200U group. Greater mean reductions in weekly UI episodes at the primary time point of week 6 were noted for the 100U and 200U treatment groups (change from baseline in weekly UI episodes was -8.6, -7.7, -14.1, and -15.8, respectively, in placebo, 50U, 100U, and 200U onabotulinumtoxinA groups), but significance compared to placebo was not achieved, possibly due to restricted sample size. However, clinically relevant differences were observed between the onabotulinumtoxinA 200U and placebo groups at all time points and significance versus placebo was achieved at week 30, when changes from baseline in UI episodes/week were -9.3 and -23.9 for the placebo and 200U groups, respectively (P=0.024). The proportion of 'dry' patients at week 6 (100% decrease from baseline in UI episodes) was highest in the 200U dose group (7%, 6%, 15%, and 23% in the in the placebo, 50U, 100U, and 200U onabotulinumtoxinA groups, respectively. A significant dose response and significance compared to placebo for the 200U dose group was also observed in other variables eg. volume per void, maximum detrusor pressure during first involuntary detrusor contraction, and duration of effect was longer with 200U.

Safety: The AE rates were similar across all treatment groups, with 69%, 58%, 62%, and 65% of patients reporting AEs in the placebo, 50U, 100U, and 200U onabotulinumtoxinA groups, respectively. Urinary tract infection was the most commonly-reported AE in all groups, occurring in 62.5%, 36.8%, 52.4%, and 41.2% of patients in the placebo, 50U, 100U, and 200U onabotulinumtoxinA treatment groups, respectively.

Interpretation of results
A clear dose response was identified, favoring the 200U onabotulinumtoxinA dose, in the primary and several secondary efficacy parameters. Despite the limited sample size, the 200U dose of onabotulinumtoxinA provided significantly greater efficacy over placebo on key efficacy variables.

Concluding message
In this dose-exploration study of SCI patients with UI due to NDO, intradetrusor injection of 200U onabotulinumtoxinA was the most effective dose, significantly reducing NDO symptoms. OnabotulinumtoxinA had an AE profile comparable across all treatment groups, including placebo.

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Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
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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**