OnabotulinumtoxinA for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3, Randomized, Placebo Controlled Trial

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Abbreviations and Acronyms

AE = adverse event
CIC = clean intermittent catheterization
HRQOL = health related QOL
I-QOL = Incontinence QOL
ITT = intent to treat
KHQ = King's Health Questionnaire
OAB = overactive bladder
PVR = post-void residual urine volume
QOL = quality of life
TBS = treatment benefit scale
UI = urinary incontinence
UTI = urinary tract infection
UUI = urinary urgency incontinence

Purpose: Overactive bladder affects 12% to 17% of the general population and almost a third experience urinary incontinence, which may severely impact health related quality of life. Oral anticholinergics are the mainstay of pharmacological treatment but they are limited by inadequate efficacy or side effects, leading to a high discontinuation rate. We report the results of the first large (557 patients), phase 3, placebo controlled trial of onabotulinumtoxinA in patients with overactive bladder and urinary incontinence inadequately managed with anticholinergics.

Materials and Methods: Eligible patients with overactive bladder, 3 or more urgency urinary incontinence episodes in 3 days and 8 or more micturitions per day were randomized 1:1 to receive intradetrusor injection of onabotulinumtoxinA 100 U or placebo. Co-primary end points were the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a positive response on the treatment benefit scale at posttreatment week 12. Secondary end points included other overactive bladder symptoms and health related quality of life. Adverse events were assessed.

Results: OnabotulinumtoxinA significantly decreased the daily frequency of urinary incontinence episodes vs placebo (–2.65 vs –0.87, $p < 0.001$) and 22.9% vs 6.5% of patients became completely continent. A larger proportion of onabotulinumtoxinA than placebo treated patients reported a positive response on the treatment benefit scale (60.8% vs 29.2%, $p < 0.001$). All other overactive bladder symptoms improved vs placebo ($p \leq 0.05$). OnabotulinumtoxinA improved patient health related quality of life across multiple measures ($p < 0.001$). Uncomplicated urinary tract infection was the most common adverse event. A 5.4% rate of urinary retention was observed.

Conclusions: OnabotulinumtoxinA 100 U showed significant, clinically relevant improvement in all overactive bladder symptoms and health related quality of life in patients inadequately treated with anticholinergics and was well tolerated.

Key Words: urinary bladder, overactive; urinary incontinence; onabotulinumtoxinA; injections, intramuscular; botulinum toxins

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Overactive bladder affects 12% to 17% of the general population.[1–3] Approximately a third of individuals with OAB have UUI,[1,2,4,5] which increases in prevalence with advancing age and is more common in women than in men.[1,2,4,6] Currently, anticholinergic agents are the mainstay of pharmacological treatment for OAB. However, they are not always sufficiently effective and have numerous systemic side effects,[7] leading to poor patient compliance and a high discontinuation rate in clinical practice.[8]

OnabotulinumtoxinA delivered directly to the detrusor muscle may represent a new treatment paradigm in patients with OAB and UUI inadequately managed with anticholinergic therapy (inadequate efficacy or intolerable side effects) by treating only the bladder and minimizing the potential for systemic side effects.

In a placebo controlled, dose ranging trial in patients with OAB and UI the 100 U dose of onabotulinumtoxinA provided the appropriate risk-benefit balance.[9] Therefore, we further evaluated the 100 U dose in what we believe to be the first large, multicenter, placebo controlled phase 3 trial.

METHODS

Study

Participants. Patients 18 years old or older with idiopathic OAB who experienced 3 or more urgency UI episodes in a 3-day period and an average of 8 or more micturitions per day were enrolled in the study. Those with a predominance of stress incontinence were excluded. All patients were inadequately treated with prior anticholinergic therapy due to inadequate efficacy or intolerable side effects. Anticholinergic use was not permitted within 7 days of screening or throughout the study. Patients had to have a PVR of 100 ml or less and be willing to perform CIC, if required.

Design. The study was conducted at a total of 72 sites in the United States and Canada (ClinicalTrials.gov NCT00910845) in compliance with Good Clinical Practice regulations. It was approved by the institutional review board at each site and all patients provided written informed consent.

After a screening period of up to 3 weeks, all eligible patients were randomized on day 1 by an interactive voice response system to receive double-blind treatment with onabotulinumtoxinA 100 U (Botox®) reconstituted with 10 ml normal saline or placebo (10 ml normal saline) in a 1:1 ratio, stratified by site and 9 or fewer, or greater than 9 UUI episodes in the 3-day diary. Notably, units of the biological activity of onabotulinumtoxinA cannot be compared with or converted into units of any other botulinum toxin product and onabotulinumtoxinA is not interchangeable with other botulinum toxin preparations.

Treatment was administered as 20 evenly distributed intradetrusor injections of 0.5 ml per injection site using a flexible or rigid cystoscope and sparing the trigone. Injections were spaced approximately 1 cm apart and the needle was inserted approximately 2 mm into the detrusor. Local anesthesia instillation in the bladder before injection and/or sedation could be used at investigator discretion.

Followup visits occurred at weeks 2, 6 and 12, and every 6 weeks thereafter until study exit at week 24 unless re-treatment was necessary. This could occur from 12 weeks onward if the patient requested it and experienced at least 2 UUI episodes during 3 days. All patients received onabotulinumtoxinA 100 U and posttreatment followup was done according to the first treatment. Therefore, the appropriate period for placebo controlled comparison was up to week 12 because re-treatment was only permitted thereafter. Treatment cycle 1 was defined as the period between the receipt of initial treatment and re-treatment, or study exit when there was no re-treatment.

Efficacy and Safety Evaluations

A 3-day paper bladder diary was used before study visits to collect all OAB symptoms (episodes of urgency, incontinence, micturition and nocturia) and volume per void. Patients recorded their perception of treatment benefit at each posttreatment visit using the TBS,[10] rating their condition as greatly improved, improved, not changed or worsened. The impact of OAB on patient HRQOL was assessed at posttreatment week 12 using 2 validated patient questionnaires, including the I-QOL[11] and KHQ.[12] All HRQOL scores are reported on a scale of 0 to 100 points with higher scores indicating better HRQOL on the I-QOL and the reverse for the KHQ. The predefined, clinically relevant change from baseline in these HRQOL measures or the minimally important difference was an increase of 10 points or more for the I-QOL and a decrease of 5 points or greater for the KHQ.

Co-primary efficacy variables were defined as 1) the change from baseline in the daily average frequency of UI episodes and 2) the proportion of patients with a positive treatment response on the TBS (condition greatly improved or improved) at posttreatment week 12. Secondary efficacy variables were the change from baseline in the daily average frequency of micturition and urgency episodes, the I-QOL total summary score and 2 KHQ multiitem domain scores (role and social limitations). Other efficacy variables were the change from baseline in nocturia episodes, volume voided per micturition and the proportion of patients achieving a 50% or greater, or a 100% reduction in UI episodes. Co-primary, secondary and other efficacy variables were also evaluated at 2 and 6 weeks posttreatment. HRQOL outcomes were evaluated at week 12 posttreatment.