Durable Efficacy and Safety of Long-Term OnabotulinumtoxinA Treatment in Patients with Overactive Bladder Syndrome: Final Results of a 3.5-Year Study

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Purpose: These are the final results of the prospective, multicenter, long-term (3.5-year) study of the efficacy/safety of onabotulinumtoxinA for overactive bladder syndrome.

Materials and Methods: Patients who completed either of 2, 24-week phase 3 trials could enter a 3-year extension and continue treatment with onabotulinumtoxinA 100 U as needed to control overactive bladder symptoms. Data were analyzed by the treatment(s) received (up to 6) and in discrete subgroups that received 1, 2, 3, 4, 5 or 6 treatments (to evaluate the consistency of the response after repeat treatments in the same patient groups). Assessments included the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients who reported improvement/great improvement in urinary symptoms on the TBS (Treatment Benefit Scale) at week 12 as co-primary end points. Other end points were the change from baseline in I-QOL (Incontinence Quality of Life), the number of urgency and micturition episodes per day; duration of effect; the number of adverse events; and the initiation of intermittent catheterization.

Results: Consistent mean reductions in urinary incontinence were observed following continued onabotulinumtoxinA treatment, ranging from −3.1 to −3.8 in the overall population and −2.9 to −4.5 in the discrete subgroups. Durable improvements were seen in overactive bladder symptoms and quality of life. A high proportion of patients rated their condition as improved/greatly improved. The median duration of effect was 7.6 months. The most common adverse event

Abbreviations and Acronyms

AE = adverse event
CIC = clean intermittent catheterization
MID = minimally important difference
OAB = overactive bladder syndrome
PVR = post-void residual urine
QOL = quality of life
UI = urinary incontinence
UTI = urinary tract infection
UUI = urgency UI

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Studies received institutional review board/ethics committee approval at each site.

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was urinary tract infection. The rate of de novo catheterization after the first treatment was 4.0% and it ranged from 0.6% to 1.7% after subsequent treatments.

Conclusions: Long-term onabotulinumtoxinA treatment consistently decreased overactive bladder symptoms and improved quality of life with no new safety signals.

Key Words: urinary bladder, overactive; urinary incontinence; onabotulinumtoxinA; quality of life; urinary tract infections

Overactive bladder is a symptom complex characterized by urinary urgency with or without UUI, and often with urinary frequency and nocturia.[1,2] OAB is highly prevalent, affecting more than 400 million people worldwide.[3] Anticholinergic medications are considered first line pharmacotherapy for OAB[4] but effectiveness is hampered by low patient satisfaction, low persistence and bothersome side effects.[5–8] Thus, there is a need for alternative therapies.

OnabotulinumtoxinA has been approved in more than 60 countries for OAB with symptoms of UUI, urgency and frequency in patients who have an inadequate response to or are intolerant of an anticholinergic medication (U.S. indication). Approval was based on the results of 2, 24-week phase 3, randomized, double-blind, placebo controlled studies, which demonstrated that onabotulinumtoxinA 100 U significantly improved OAB symptoms and QOL vs placebo and was well tolerated in patients who were inadequately treated with 1 or more anticholinergic medications.[9,10] Because of these studies, AUA (American Urological Association) and EAU (European Association of Urology) guidelines recognize onabotulinumtoxinA as having the highest level of evidence of the third line OAB treatment options for those in whom pharmacological therapy has failed.[4,11] OnabotulinumtoxinA is the only botulinum toxin currently approved for OAB. Due to its unique manufacturing process, which determines structure and composition, and potency assay, onabotulinumtoxinA is not interchangeable with other botulinum toxins and units cannot be converted using a dose ratio.[12]

Although OAB is a chronic symptom complex requiring long-term treatment, there is a paucity of information on long-term OAB treatments. This prospective extension trial was performed to examine the long-term safety and efficacy of onabotulinumtoxinA during 3.5 years.

MATERIALS AND METHODS

Study Design and Participants

This 3-year extension study (ClinicalTrials.gov identifier NCT00915525) was performed at 131 centers in North America and Europe from March 2010 to August 2014. Patients who completed either of the 2, 24-week, phase 3 studies, in which they received onabotulinumtoxinA (Botox®) 100 U or placebo,[9,10] were eligible for the study. All patients provided written informed consent and institutional review board/ethics committee approval was received at each site.

Patients requested onabotulinumtoxinA treatment as needed to control symptoms. Upon patient fulfillment of prespecified re-treatment criteria (12 weeks or more since previous treatment, 2 or more UUI episodes during a 3-day diary and PVR volume less than 200 ml) 20 intradetrusor injections of 0.5 ml each were administered via cystoscopy, avoiding the trigone as previously described by the manufacturer.

Originally, a dose increase from 100 to 150 U was permitted at patient request from treatment 3 and thereafter. A planned interim statistical analysis showed that the 150 U dose did not provide additional efficacy and, thus, the protocol was amended to allow only the 100 U dose.

Efficacy and Safety Evaluations

The co-primary end points were the mean reduction in UI episodes per day and the proportion of patients reporting a positive response (improvement or great improvement in urinary symptoms) on TBS,[13] both at week 12. Baseline was defined as data collected prior to the first treatment in the preceding phase 3 study. Additional efficacy variables included changes from baseline in urgency episodes per day, micturition episodes per day, I-QOL total summary score[14] and duration of treatment effect (time to patient request for re-treatment).

AEs were assessed throughout the study. UTI was defined based on laboratory findings (a positive urine culture result of a bacteriuria count greater than 10^5 cfu/ml and leukocyturia greater than 5 per high power field) and did not require the patient to be symptomatic. The protocol provided guidance on PVR management and initiation of CIC, which was to be initiated if PVR was 350 ml or greater regardless of symptoms, or 200 ml or greater to less than 350 ml with symptoms deemed to be associated with incomplete emptying and requiring CIC. However, this guidance did not preclude investigators treating individuals based on clinical judgment (eg initiating CIC at PVR less than 200 ml). Serum was screened first by enzyme-linked immunosorbent assay to detect toxin binding antibodies. Positive samples were then tested for toxin neutralizing antibodies via the confirmatory mouse protection assay.[15]

Statistical Analysis

Data on patients in the long-term extension study were integrated with their data from the preceding phase