Efficacy and Safety of OnabotulinumtoxinA Therapy are Sustained Over 4 Years of Treatment in Patients With Neurogenic Detrusor Overactivity: Final Results of a Long-Term Extension Study

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Aims: To present final efficacy/safety results from a prospective, long-term extension trial of onabotulinumtoxinA for urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO); patients received treatment for up to 4 years.

Methods: Patients who completed a 52-week, phase III trial of onabotulinumtoxinA for NDO were eligible to enter a 3-year, multicenter, open-label extension study of intradetrusor onabotulinumtoxinA (200U or 300U). Patients were treated “as needed” based on their request and fulfillment of prespecified qualification criteria (≥12 weeks since previous treatment and a UI episode threshold). Assessments included change from study baseline in UI episodes/day (primary efficacy measure), volume/void, and Incontinence Quality of Life (I-QOL) total score (week 6); duration of effect; adverse events (AEs); and initiation of de novo clean intermittent catheterization (CIC). Data are presented for up to six treatments.

Results: OnabotulinumtoxinA 200U consistently reduced UI episodes/day; reductions from baseline ranged from −3.2 to −4.1 across six treatments. Volume/void consistently increased, nearly doubling after treatment. I-QOL improvements were consistently greater than twice the minimally important difference (+11 points). Overall median duration of effect was 9.0 months (200U). Results were similar for onabotulinumtoxinA 300U. Most common AEs were urinary tract infections and urinary retention. De novo CIC rates were 29.5, 3.4, and 6.0% (200U), and 43.0, 15.0, and 4.8% (300U) for treatments 1–3, respectively; de novo CIC rates were 0% for treatments 4–6. Conclusions: OnabotulinumtoxinA treatments consistently improve UI, volume/void, and QOL in patients with UI due to NDO in this 4-year study, with no new safety signals.

Key words: botulinum toxin; multiple sclerosis; neurogenic detrusor overactivity; onabotulinumtoxinA; quality of life; spinal cord injury; urinary incontinence

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Patients with neurologic disorders such as spinal cord injury (SCI) or multiple sclerosis (MS) often develop neurogenic detrusor overactivity (NDO), which can lead to urinary incontinence (UI) and complications if not well managed. Although anticholinergics are recommended as first-line pharmacologic treatment for urinary symptoms, many patients have an inadequate response to them and/or experience intolerable adverse effects. OnabotulinumtoxinA is a botulinum toxin type A formulation that is the only botulinum toxin approved for the treatment of UI due to NDO (e.g., MS or SCI) in patients who have been inadequately managed by >1 anticholinergic. Compared with placebo, onabotulinumtoxinA significantly reduced UI episodes/week and improved urodynamics parameters and quality of life (QOL) over 52 weeks as demonstrated in two phase III, randomized, multicenter, multinational studies.

Because NDO is a chronic condition, long-term treatment is required. It is thus important to assess the efficacy and safety of long-term onabotulinumtoxinA treatment in patients with UI due to NDO. We conducted a 3-year, prospective, multicenter extension study to evaluate the long-term safety and maintenance of efficacy of intradetrusor onabotulinumtoxinA. We previously reported results of an interim analysis of this trial, which demonstrated sustained improvements in incontinence episodes, volume/void, and QOL following 2.3 years of onabotulinumtoxinA treatment. Here we present final results from the study, in which patients received up to 4 years of onabotulinumtoxinA treatment (52 weeks in the phase III studies, plus up to 3 years in the extension).

MATERIALS AND METHODS

Study Design and Participants

This 3-year extension study was conducted at 117 centers in North America, Europe, Latin America, South Africa, and the Asia-Pacific region between April 2009 and September 2013. Patients with NDO due to MS or SCI who were inadequately managed by >1 anticholinergic and completed either of two 52-week phase III studies were integrated with the corresponding data from the phase III trials. OnabotulinumtoxinA treatment was individualized per patient; patients received up to two onabotulinumtoxinA treatments (200U or 300U) in the phase III studies and could receive multiple treatments during the extension study. Initially, patients in the extension study received the same onabotulinumtoxinA dose as in the phase III study (200 or 300U; administered as 30 1-ml detrusor injections via cystoscopy [sparing the trigone]). The protocol was amended in 2011 so all patients received only onabotulinumtoxinA 200U, which is the approved dose for the treatment of UI due to NDO.

Patients were treated “as needed” for control of symptoms based on their request and fulfillment of prespecified qualification criteria (>12 weeks since previous treatment and >1 UI episode within 3 days), so the total number of treatments each patient needed during the study differed. Visits continued throughout the study period at prespecified intervals. The use of anticholinergics was permitted during the extension study; dose and use modifications were permitted per investigator discretion. All patients provided written informed consent, and each investigator obtained institutional review board/ethics committee approval.

The primary efficacy endpoint was change from study baseline in UI episodes/day at week 6 after each treatment. Baseline was defined as the last value prior to the first treatment in the phase III studies. Additional efficacy variables included percent change in UI episodes, the proportions of patients with ≥50% and 100% reductions from baseline in UI episodes/day, changes from baseline in volume/void, and baseline in UI episodes/day at week 6 after each treatment.

Study Assessments

Efficacy and safety analyses were conducted using the onabotulinumtoxinA-treated population (all patients who received ≥1 onabotulinumtoxinA treatment in either the phase III or long-term extension study). Except for duration of effect, data were analyzed by onabotulinumtoxinA dose (200 or 300U) and treatment number (the number of sequential onabotulinumtoxinA treatments received by each patient). Mean changes from baseline with 95% confidence intervals were calculated for UI episodes/day, percent change in UI episodes/day, volume/void, and I-QOL total score. Missing I-QOL values were imputed from multi-item scales. If >50% of items on a scale were answered, then the missing items were imputed with the mean of the non-missing items at that visit. If ≤50% of items in a scale were answered, then the entire measure was considered as missing and no imputation was made. Overall median duration of effect was calculated from each patient’s individual median duration of effect, based on patients’ retreatment request date for all completed treatment cycles (i.e., had received their next injection).

AEs were summarized using the Medical Dictionary for Regulatory Activities version 16.0 by onabotulinumtoxinA treatment number and by relationship to treatment. AEs occurring within the first 12 weeks of each treatment are presented, as they represent the same exposure time per patient for each treatment. The proportion of patients initiating de novo CIC was summarized for each treatment cycle. The denominator was the number of patients who received onabotulinumtoxinA in the applicable cycle and had never...
initiated CIC before that cycle; the numerator represented the number of patients who initiated CIC for the first time during that cycle.

RESULTS

Patient Disposition and Baseline Characteristics

Of the 691 patients enrolled in the phase III studies, 559 completed the studies and could potentially enroll into the extension study.\(^5\,^6\) 396 patients entered the extension study per protocol. The majority of patients who did not enter the extension study were excluded for reasons including, but not limited to, the timeframe between completion of the phase III studies and entry into the extension study exceeded 6 months (due to delays in protocol availability and/or ethics committee approvals), study site closures, patient non-compliance, or patient no longer met inclusion criteria; others chose not to participate (e.g., due to study burden). Of the 396 patients who entered the extension study, 240 (60.6\%) were followed for at least 4 years (Fig. 1). The most common reasons for discontinuation were personal reason(s) (61/396; 15.4\%), study site closure (33/396; 8.3\%), and lost to follow-up (23/396; 5.8\%). Few patients discontinued due to lack of efficacy (8/396; 2.0\%) or AEs (12/396; 3.0\%), with only 2 of the 12 discontinuations due to AEs considered treatment-related by the investigator (1 due to UTI and 1 due to retention). Eight patients who received only placebo in the phase III studies never requested retreatment in the extension study; therefore, the onabotulinumtoxinA-treated population comprised 388 patients, which had a mean follow-up of 3.6 years.

Mean patient age (± SD) was 46.4 ± 12.6 years; 59.5\% of patients had MS and 40.5\% had SCI. At study baseline, patients reported a mean of 4.5 UI episodes/day, volume/void was 150.7 ml, and 53.9\% (209/388 patients) were using anticholinergics (Table 1); 15.7\% (33/209 patients) discontinued anticholinergic use during the study.

Efficacy Measures

The duration of effect of onabotulinumtoxinA, measured by time to request for retreatment, was different for each patient. Patients in whom onabotulinumtoxinA had a longer duration of effect received fewer treatments over the study period, whereas those with a shorter duration of effect received more treatments during the same study period. Data for patients who received up to six sequential onabotulinumtoxinA treatments are presented herein, as the number of patients who needed seven or more treatments during the study was not large enough to make meaningful comparisons (e.g., 48 patients received seven treatments [200U], whereas only one patient received 13 treatments). Data from all patients (up to 13 treatments) are shown in Supplementary Tables S1 and S2.

At week 6 following each treatment, onabotulinumtoxinA 200U consistently reduced the mean number of daily UI episodes (Fig. 2A). Mean reductions from baseline ranged from –3.2 to –4.1 UI episodes/day over six treatments, corresponding to mean percent changes from baseline of –75\% to –84\% (Fig. 2B). The proportion of patients achieving ≥50\% reduction in UI episodes/day was consistently over 83\%, whereas the percent of patients with a 100\% reduction in UI episodes/day ranged from 43\% to 56\% across six treatments (Fig. 2C).
Volume/void nearly doubled following each treatment (Fig. 2D). Overall, the median duration of effect of onabotulinumtoxinA was 9.0 months for patients who received 200U only. Median duration of effect was <6 months in 22% of patients, ≥6–12 months in 52%, and ≥12 months in 26%.

Increases in I-QOL total scores following onabotulinumtoxinA 200U were consistently ≥2 times the minimally important difference, ranging from 27.1 to 33.5 points across treatments in A 200U were consistently one in cycle 7, and one patient who was subsequently switched to 200U in cycle 5 seroconverted in that cycle). The overall seroconversion rate in patients who entered this extension study and received either 200U or 300U onabotulinumtoxinA was 2.1% (8/381 patients); the seroconversion rate for the approved 200U dose was 1.5% (3/200 patients). All eight patients had SCI, and four patients continued to experience clinical benefit after seroconversion defined as a 50% reduction from baseline in UI episodes in the treatment cycle immediately following seroconversion. Prior to seroconversion, these patients received treatment more frequently, as their overall median time between injections was 4.9 months, compared with 9.1 months in the overall population. One patient had a transient negative result after seroconverting and one was negative upon study exit.

**DISCUSSION**

Outcomes data following long-term treatment for UI due to NDO remain limited. The present study represents the longest follow-up of the safety and efficacy of any NDO treatment in a prospective clinical trial and demonstrates that onabotulinumtoxinA 200U treatment is effective and well tolerated through 4 years. Although these data are from an open-label study, the efficacy and safety results are consistent with findings from the placebo-controlled, phase III trials. In addition, these data further confirm that there are no clinically relevant differences in the treatment response between onabotulinumtoxinA 200 and 300U dose groups.

Patient retention in long-term trials over multiple years can be challenging; personal issues or “study fatigue” related to cumbersome study requirements can result in high discontinuation rates. However, as UI due to NDO is a chronic condition requiring continual treatment, it is critical to study the implications of long-term therapy. Despite the aforementioned challenges, over 60% of the patients who participated in our study continued through 4 years of treatment, which is quite high given the length and overall burden of the study. Although there are no comparable long-term trials of other treatments for NDO, the completion rate in a pooled analysis of two long-term studies of an anticholinergic in OAB patients (wet and dry OAB)
Fig. 2. (A) Mean change from baseline in UI episodes/day, (B) mean percent change from baseline in UI episodes/day, (C) proportion of patients with ≥50% and 100% reductions in UI episodes/day, and (D) mean change from baseline in volume/void at week 6 following onabotA 200U treatment (onabotA-treated population). OnabotA, onabotulinumtoxinA; UI, urinary incontinence.

*aBaseline is prior to first dose in initial phase III studies for all patients entering the extension study.

As recorded on bladder diary for all voids (voluntary and catheterization) over one 24 hr period. Data for each treatment cycle include patients who received onabotulinumtoxinA 200U in that treatment cycle (regardless if they received 300U in a prior treatment cycle). n-values are based on patients with data available at week 6. Error bars represent 95% confidence intervals.
and with/without prior anticholinergic exposure) was 49% after only 2 years. The most common reasons for discontinuation in our study were related to the length of the trial (personal reasons, site closures, and lost to follow-up), while discontinuations due to AEs or lack of efficacy were extremely low. This latter observation is in contrast to the high discontinuation rates due to AEs and insufficient efficacy seen with anticholinergics.

Consistent and clinically meaningful reductions in the number of daily UI episodes were observed following long-term, repeated treatment with onabotulinumtoxinA. High mean change from baseline in I-QOL total scores and proportion of I-QOL responders at week 6 following each onabotulinumtoxinA treatment (onabotulinumtoxinA-treated population). I-QOL, incontinence quality of life; MID, minimal important difference; onabotulinumtoxinA.

### TABLE II. AEs Occurring in >5% of Patients (and >1 Patient) Within the First 12 Weeks After OnabotulinumtoxinA Treatment (OnabotulinumtoxinA-Treated Population)

| AEs, n (%) | 200U (N = 203) | 300U (N = 185) | 200U (N = 177) | 300U (N = 153) | 200U (N = 110) | 300U (N = 34) | 200U (N = 70) | 300U (N = 16) |
|------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Overall AEs | 134 (66.6) | 123 (66.5) | 109 (58.3) | 89 (54.6) | 74 (48.4) | 36 (52.2) | 36 (51.4) | 7 (43.8) |
| Urinary tract infection | 56 (27.6) | 57 (30.8) | 49 (26.2) | 46 (28.2) | 45 (29.7) | 38 (21.7) | 20 (18.2) | 7 (43.8) |
| Urinary retention | 41 (20.2) | 42 (22.7) | 13 (7.0) | 13 (6.7) | 11 (6.3) | 8 (4.7) | 2 (1.8) | 0 (0.0) |

AE, adverse event.
proportions of patients with ≥50% reduction in UI episodes were observed over 4 years, similar to the phase III studies, and the proportion of patients who achieved complete continence with onabotulinumtoxinA (43–56%) is markedly higher than has been reported for other NDO treatments. OnabotulinumtoxinA also continued to improve the ability of the bladder to store urine, as evidenced by the consistent increases in volume/void with each treatment. Furthermore, the sustained improvements in urinary symptoms with onabotulinumtoxinA were complemented by clinically meaningful improvements in QOL, which were again consistent with the phase III studies. Taken together, the sustained improvements in QOL and urinary symptoms suggest that onabotulinumtoxinA could maximize the chance of treatment success, as it may lead to improved persistence with long-term therapy, which is important for chronic conditions such as UI due to NDO.

The design of the study allowed each patient to request retreatment with onabotulinumtoxinA at their discretion, as would be expected in clinical practice. Although duration of effect of onabotulinumtoxinA is individualized, the overall median duration of effect of onabotulinumtoxinA across all patients was 9 months, which is similar to the duration reported in the phase III studies, suggesting that the duration of effect remains consistent with repeated treatment.

This study also demonstrates that the long-term safety of onabotulinumtoxinA after multiple treatments is consistent with its established safety profile from the phase III trials. No new safety signals were observed with long-term treatment and there was no increase in AE rates over repeated treatments, suggesting that onabotulinumtoxinA does not have a cumulative dose or duration toxicity. AEs were primarily localized to the urinary tract and were easily managed, with no evidence of the adherence-limiting AEs associated with anticholinergic therapy. As there was no distinction between symptomatic and asymptomatic UTIs reported as AEs in this study, the rates of treated UTIs in the clinical setting are likely to be lower. The incidence of de novo CIC was highest after the first onabotulinumtoxinA treatment and was greatly reduced during subsequent treatments. As the majority of patients who were spontaneously voiding at baseline were MS patients, increased impairment in voiding function over time due to the natural history of MS progression may have contributed to some of the de novo CIC. Nonetheless, these results suggest that in clinical practice, patients are unlikely to need to initiate de novo CIC if they did not initiate it during their first onabotulinumtoxinA treatment. Overall rates of neutralizing antibody seroconversion observed in patients who entered this extension study were low, and half of the patients who seroconverted continued to experience clinical benefit. As the MPA assay is semiquantitative and does not distinguish between low- and high-neutralizing antibody titers, some patients who are antibody-positive according to the MPA may actually have low titers that may not fully block the clinical effect of onabotulinumtoxinA. Titers can also fluctuate over time, which may account for the negative MPA results observed in two patients who were previously positive.

Our study had several potential limitations. Only those patients who completed the double-blind studies were eligible to participate in the extension trial; these individuals may have been more motivated and more likely to respond to treatment. Furthermore, as patient participation in the extension study was voluntary, it is prone to selection bias in favor of those with a positive experience with onabotulinumtoxinA. The open-label design of the extension study may have introduced some observer bias in reporting of efficacy evaluations; however, the efficacy and safety results were consistent with the placebo-controlled phase III studies. Each botulinum toxin is a unique biological product. Dosing and results reported in this study are thus specific to onabotulinumtoxinA, and cannot be extrapolated to other formulations of botulinum toxins. Lastly, while many patients in the study likely had urodynamic follow-up as part of routine patient care, it was not a study requirement, so long-term urodynamic data are not available.

**CONCLUSIONS**

This long-term study demonstrated sustained, clinically meaningful improvement in urinary symptoms and QOL following onabotulinumtoxinA treatment in patients with UI due to NDO during the 4-year study, with no new safety signals. These results further support the use of onabotulinumtoxinA 200U in patients with NDO and UI who are inadequately managed by ≥1 anticholinergic medication.

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