

Ambulatory and Office Urology

Long-term Efficacy and Safety of OnabotulinumtoxinA in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity: An Interim Analysis

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OBJECTIVE

To evaluate the long-term efficacy and safety of repeat onabotulinumtoxinA injections in patients inadequately managed by anticholinergics for urinary incontinence (UI) due to neurogenic detrusor overactivity.

MATERIALS AND METHODS

Patients who completed either of 2 preceding phase III studies were offered entry into an extension study and received repeat onabotulinumtoxinA 200 U or 300 U. The data were integrated across the phase III and ongoing extension studies. The present interim analysis included all patients who received ≥ 1 onabotulinumtoxinA treatment. The data were analyzed by treatment cycle (cycles 1-5). The primary assessment was the change from baseline in UI episodes/wk at 6 weeks after each treatment. Additional assessments included $\geq 50\%$ and 100% reductions in UI episodes, volume/void, Incontinence Quality of Life responses, and adverse events.

RESULTS

A total of 387, 336, 241, 113, and 46 patients received 1, 2, 3, 4, and 5 onabotulinumtoxinA treatments, respectively. The UI episodes/wk were consistently reduced compared with baseline after repeated onabotulinumtoxinA treatment (-22.7 , -23.3 , -23.1 , -25.3 , and -31.9 for the 200-U onabotulinumtoxinA group in cycles 1-5). The proportion of patients reporting $\geq 50\%$ and 100% ("dry") reductions from baseline in UI episodes at week 6 ranged from 73%-94% and 36%-55%, respectively. Increases in the mean volume/void (mean increase >130 mL) and improvements in quality of life were also observed after repeat treatment. The most common adverse events were urinary tract infections and urinary retention, with no change in the adverse event profile over time.

CONCLUSION

The results of our study have shown that repeated onabotulinumtoxinA treatments provide sustained reductions in UI episodes and increases in the volume/void and quality of life in patients with neurogenic detrusor overactivity and UI who were inadequately managed by anticholinergics, with no new safety signals. UROLOGY 81: 491-497, 2013. © 2013 Elsevier Inc. Open access under [CC BY-NC-ND license](#).

The clinical benefits of onabotulinumtoxinA (BOTOX, Allergan, Irvine, CA) for the treatment of urinary incontinence (UI) due to

neurogenic detrusor overactivity (NDO) in patients who were not adequately managed by anticholinergics were first demonstrated in 2000 by Schurch et al.¹ These initial results were recently confirmed by 2 pivotal, phase III, randomized, placebo-controlled, double-blind trials.^{2,3} Both phase III studies demonstrated that onabotulinumtoxinA, administered at a dose of 200 U and 300 U, significantly reduced UI episodes and improved the urodynamic parameters and quality of life (QOL) in patients with NDO and UI due to spinal cord injury (SCI) or multiple sclerosis (MS) who were inadequately managed by anticholinergics (inadequate efficacy or intolerable side effects). No clinically relevant differences in efficacy or duration of effect were observed between the 200 U and 300 U onabotulinumtoxinA doses, with efficacy lasting approximately 9-10 mo/injection. Where approved, the

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200-U dose of onabotulinumtoxinA is the registered dose for the treatment of patients with UI due to NDO. OnabotulinumtoxinA is not interchangeable with other botulinum toxin preparations.

To evaluate the efficacy and safety of repeat injections of onabotulinumtoxinA in patients with UI due to NDO resulting from SCI and MS, a prospective, long-term, open-label, extension study of the phase III clinical trials was initiated, with patients able to participate for up to 3 years. This extension study is still ongoing. In the present study, we report an interim analysis of the results from the extension study, focusing on the results of repeated treatment for up to 5 treatment cycles.

MATERIAL AND METHODS

Patients and Study Design

Details regarding patient selection and the study designs of the pivotal phase III trials (the Double-blind InvestiGation of purified Neurotoxin complex in neurogenic detrusor overactivity [DIGNITY] studies) have been previously published (<http://www.clinicaltrials.gov> identifiers NCT00311376 and NCT00461292).^{2,3} In brief, the studies enrolled patients aged ≥ 18 years who had NDO due to SCI or MS with ≥ 14 UI episodes/wk and who were not adequately managed by anticholinergics (inadequate efficacy or intolerable side effects). Patients who were taking anticholinergics at study entry continued to take them during the remainder of the 52-week phase III trials. Patients who completed either of the phase III studies could enter the long-term, 3-year extension study, in which they would receive multiple intradetrusor treatments of onabotulinumtoxinA (<http://www.clinicaltrials.gov> identifier NCT00876447). All patients provided written informed consent, and each participating center obtained institutional review board or ethics committee approval.

The dose of onabotulinumtoxinA that patients received during the extension study was the same as the dose the patient had been randomized to receive in the preceding phase III studies (200 U or 300 U). The study protocol was amended in March 2011 such that all patients would receive onabotulinumtoxinA 200 U (the registered dose for NDO, where approved) regardless of whether they had received 200 U or 300 U in the preceding phase III studies. However, the interim data we report presents the results for both the 200-U and the 300-U dose groups (ie, the dose to which patients had been randomized in the phase III studies and also received in the extension study before the amendment).

Just as in the phase III trials, treatment was administered as 30 injections of 1 mL using cystoscopy (avoiding the trigone) with either no anesthesia, local anesthesia (with or without sedation according to local site practice), or general anesthesia. Patients could receive repeat treatment if the prespecified repeat treatment criteria had been fulfilled. These included patient initiation of a request for repeat treatment, a minimum of 12 weeks since the previous study treatment, and ≥ 1 UI episode within 3 days, as recorded in the 3-day patient diary before a study visit.

Safety and Efficacy Assessments

Patients recorded each voiding episode (UI, toilet void, clean intermittent catheterization [CIC] void) in a bladder diary in

the week preceding each study visit. For one 24-hour period, the volume of each void was also measured. The patients were evaluated at weeks 2, 6, and 12 after each treatment.

The primary efficacy measure was the change from study baseline in the number of weekly UI episodes. The prespecified primary point of assessment in each cycle was week 6 after each treatment, identical to the endpoint in the pivotal studies. Baseline was defined as the value before any study treatment in the preceding phase III studies. Additional efficacy variables at week 6 after each treatment included the proportion of patients with $\geq 50\%$ and 100% reductions from baseline in UI episodes, a change from baseline in the Incontinence Quality of Life (I-QOL) total summary scores,⁴ the I-QOL responder rates (proportion of patients achieving a ≥ 11 -point increase from baseline in I-QOL score), the duration of treatment effect (interval to patient request for repeat treatment), and the mean volume/void.

Adverse events (AEs) were also assessed. Urinary tract infections (UTIs, as reported by the investigators), were defined as positive urine culture results with a bacteriuria count of $>10^5$ colony-forming units/mL in conjunction with a leukocyturia of >5 /high powered field or positive urine culture findings that, in the investigator's opinion, required antibiotic therapy. Symptomatic and asymptomatic UTIs were not distinguished. No predefined definition was in place for urinary retention in the study protocol. Therefore, the interpretation of recording urinary retention as an AE and the need for the initiation of CIC after treatment were determined by the investigator's clinical judgment.

The presence of serum neutralizing antibodies was assessed using the mouse protection assay⁵ at baseline (in the preceding phase III studies), before each treatment, and at study exit.

Statistical Analysis

The long-term extension study had no formal statistical power or sample size calculation because only patients from the preceding phase III studies could be enrolled. The data from the patients in the interim analysis of the long-term extension study were integrated with the corresponding data from the preceding phase III studies. All patients who received ≥ 1 onabotulinumtoxinA treatment were included. The data were analyzed by onabotulinumtoxinA treatment cycle. The present report presents the efficacy and safety results from an interim analysis covering 5 treatment cycles.

Efficacy and safety analyses were conducted using the onabotulinumtoxinA-treated population. The mean changes from baseline with 95% confidence intervals were calculated for all efficacy variables. Because the long-term study used 3-day bladder diaries, weekly UI was calculated as the daily frequency of incontinence episodes multiplied by 7. Missing values for I-QOL measures were imputed from multi-item scales. The duration of treatment effect for each treatment cycle was calculated according to those patients who requested repeat treatment (and their repeat treatment request date) and was summarized using descriptive statistics. De novo (ie, first time) catheterization rates for patients not using CIC at baseline in the phase III studies were calculated for each treatment cycle. The denominator represented the number of patients who received onabotulinumtoxinA in the applicable cycle and had never initiated CIC before receiving treatment in that cycle, and the numerator represented the number of patients who initiated CIC for the first time during that cycle.

RESULTS

Baseline Demographics and Disease Characteristics

A total of 387 patients (200-U group, $n = 202$; 300-U group, $n = 185$) were included in the present interim analysis. Of these patients, 387, 336, 241, 113, 46, 25, and 9 patients received 1, 2, 3, 4, 5, 6, and 7 onabotulinumtoxinA treatments, respectively (Supplemental Fig. 1). At the point of the present interim analysis, with data for up to 7 cycles, only 3 of 387 patients had discontinued because of a lack of efficacy and 5 because of AEs. Because so few patients had received 6 or 7 treatments when the present interim analysis was performed, the efficacy and safety results are only presented for treatment cycles 1-5.

No significant differences were found in the baseline demographics or disease characteristics between the patients treated with onabotulinumtoxinA 200 U versus 300 U (Supplemental Table 1). The mean patient age was 46.4 years, 39.8% of patients were men, and 54% of patients were using anticholinergics. The mean duration of NDO in the 2 treatment groups was 8 years, and the mean number of UI episodes/wk at baseline was 31.2.

Efficacy Assessments

The number of UI episodes/wk at week 6 was significantly and consistently decreased after repeated onabotulinumtoxinA treatment. The reductions from baseline were -22.7 , -23.3 , -23.1 , -25.3 , and -31.9 in the 200-U dose group and -23.8 , -25.0 , -23.6 , -24.1 , and -29.5 in the 300-U dose group in treatment cycles 1-5, respectively (Fig. 1A). Most patients achieved at least a 50% reduction from baseline in UI with repeated onabotulinumtoxinA treatment cycles. The proportion of patients with at least a 50% reduction in UI episodes ranged from 73% (lowest, in cycle 4) to 94% (greatest, in cycle 5). A significant proportion of patients were also dry (100% reduction; Fig. 1B) after onabotulinumtoxinA treatment. The proportion of dry patients typically ranged from 36% to 55%, with the exception of the 300-U dose group in cycle 5, although the latter was considered an outlier because of the limited number of patients.

Consistent increases were seen from baseline in the mean volume/void at week 6 in each treatment cycle (Fig. 1C), with a mean increase of ≥ 130 mL (range 133-180) after each onabotulinumtoxinA treatment. Similarly, the mean I-QOL total summary scores consistently showed large increases from baseline with repeated onabotulinumtoxinA treatment. The mean increase in I-QOL total scores ranged from 27.5 to 44.6, much larger than the defined minimally important change of ≥ 11 points (Fig. 2A). Most patients (66%-93% across the 5 treatment cycles) achieved ≥ 11 -point increases in total I-QOL scores at 6 weeks after repeated treatment with onabotulinumtoxinA 200 U or 300 U (Fig. 2B).

The time to patient request for repeat treatment over cycles 1 and 2 (which most patients had completed;

Supplemental Fig. 1) remained consistent (~ 250 days or ~ 36 weeks; Table 1). Because the long-term study is ongoing, a considerable number of patients (44%-54%) in the latter treatment cycles (3-5) had not yet requested or had not yet received their next treatment and were therefore still continuing in these cycles (Supplemental Fig. 1). In these latter cycles, a trend toward a slight reduction in the time to patients' request for repeat treatment was observed; however, it is difficult to interpret these results because the cycles are not yet complete. A full analysis of this parameter can only be provided once the final analysis has been performed when most treatment cycles have been completed.

Safety Assessments

The AEs occurring in treatment cycles 1-5 are listed in Table 2. UTIs and urinary retention were the most common AEs. The incidence of each was similar within each treatment cycle in patients who received either dose of onabotulinumtoxinA (200 or 300 U). Specifically, the UTI rates for treatment cycles 1-5 were 58.4%, 46.0%, 39.4%, 28.8%, and 20.0% for patients in the 200-U dose group and 55.1%, 53.1%, 42.1%, 20.4%, and 23.8% in the 300-U dose group, respectively. The urinary retention rates for treatment cycles 1-5 were 20.3%, 9.1%, 6.3%, 0%, and 0% for patients in the 200-U dose group and 23.2%, 6.9%, 7.0%, 0%, and 0% for patients in the 300-U dose group. Again, it should be noted that a considerable number of patients in cycles 3-5 have not yet completed these cycles; therefore, the AE rates reported for these latter cycles are preliminary.

Of the 86 patients who were not using CIC at baseline in the phase III trials, the de novo catheterization rate in the 200-U dose group was 30.0% (26 of 86), 3.8% (2 of 52), 2.9% (1 of 35), 0% (0 of 22), and 0% (0 of 7) in treatment cycles 1, 2, 3, 4, and 5, respectively. Cumulatively, 29 of the 86 patients (33.7%) not using CIC at baseline before entry into the phase III studies initiated CIC at some point during the 5 cycles of onabotulinumtoxinA treatment. In the 300-U dose group, the corresponding proportion of patients initiating CIC was generally greater, with de novo CIC rates of 42.0% (36 of 85), 18.0% (7 of 39), 0%, 0%, and 0% in cycles 1-5. Overall, 50.6% of patients (43 of 85) initiate CIC at some point after repeat treatment.

Five patients (3 in the 200-U dose group and 2 in the 300-U dose group) discontinued the study because of AEs. One discontinuation was treatment-related (nonserious UTI). No deaths were reported in the present interim analysis. Of the 387 patients enrolled, only 1 patient developed toxin-neutralizing antibodies to onabotulinumtoxinA, which occurred after treatment 6. The patient (who had SCI) had received frequent repeat treatment with onabotulinumtoxinA 300 U nearly every 12 weeks. Although this patient's response was not long lasting, this patient did demonstrate a treatment response (ie, $\geq 50\%$ reduction in UI episodes from baseline) at week 6 for treatment cycles 1, 2, 4, and 5 (the week 6

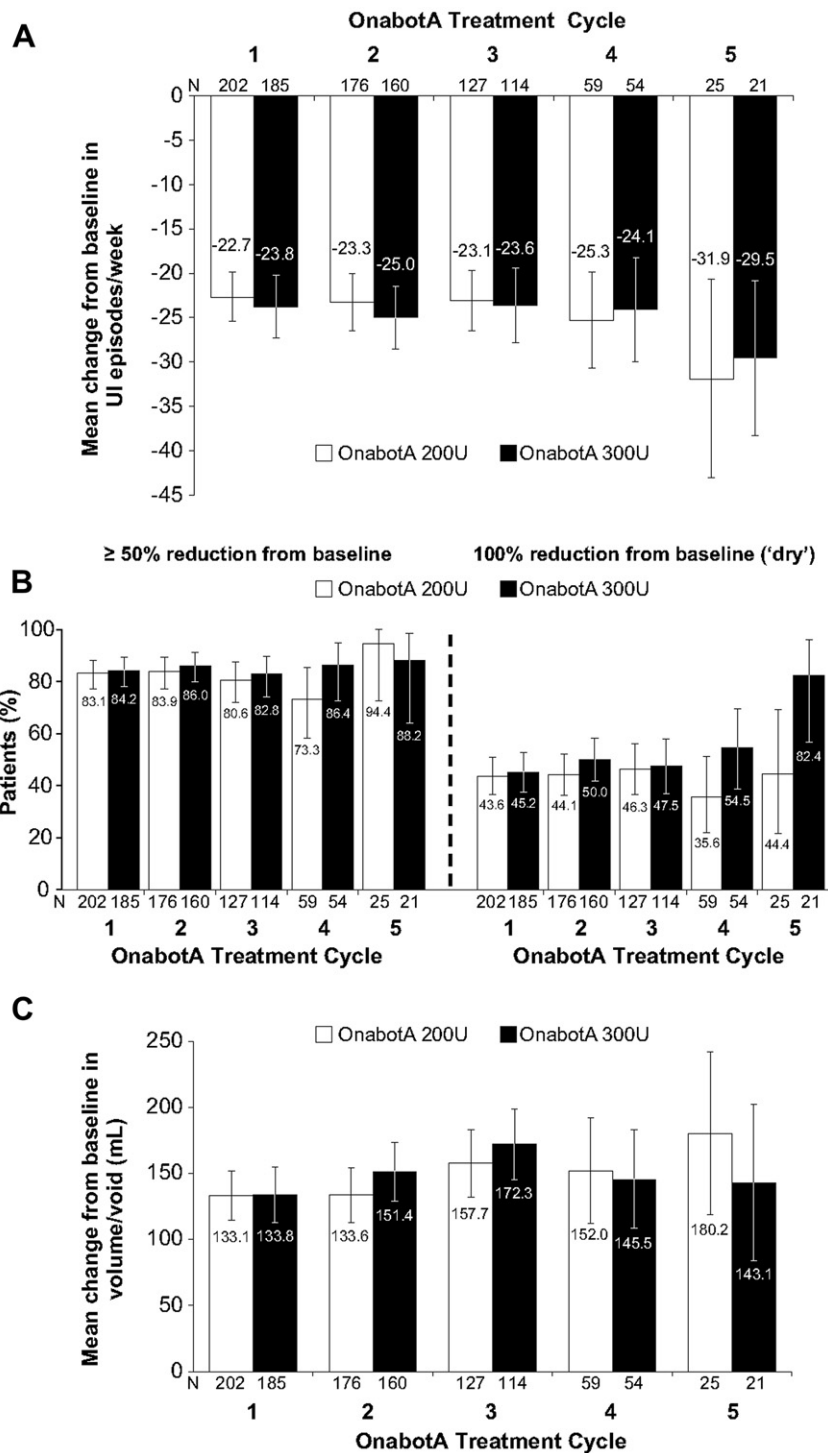


Figure 1. (A) Change from baseline in weekly urinary incontinence (UI) episodes, (B) proportion of patients who achieved a $\geq 50\%$ reduction or 100% reduction (total continence) of UI episodes, and (C) change from baseline in volume/void at week 6 after each treatment with onabotulinumtoxinA (onabotA). Data presented as mean \pm 95% confidence interval.

diary was missing for treatment cycle 3). During treatment cycle 6, when the patient tested positive for neutralizing antibodies, the patient was a nonresponder at the week 6 point but had responded again at week 12. This patient discontinued participation in the study owing to lack of efficacy.

COMMENT

Two recent, placebo-controlled, double-blind, phase III studies demonstrated that a single onabotulinumtoxinA treatment significantly reduced the UI episodes and improved urodynamic parameters and QOL in patients with UI due to SCI or MS. The efficacy last

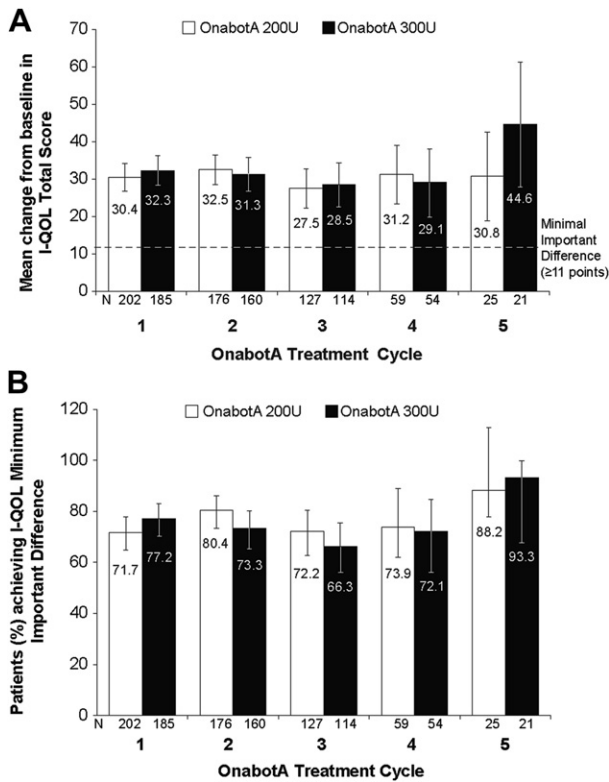


Figure 2. (A) Change from baseline in incontinence quality of life (I-QOL) total summary scores and (B) proportion of patients achieving minimal important difference (≥ 11 -point increase) in I-QOL at week 6 after each treatment with onabotulinumtoxinA (onabotA).

approximately 9-10 months.^{2,3} The present results have demonstrated that onabotulinumtoxinA is effective in the long term with repeated treatments in these patients who were inadequately managed by anticholinergics, without the emergence of new safety signals. The results are from a large cohort of patients with UI due to NDO who received multiple onabotulinumtoxinA treatments. More than 100 patients have received ≥ 4 onabotulinumtoxinA treatments and nearly 50 patients have received 5 onabotulinumtoxinA treatments.

A sustained, consistent, and clinically relevant reduction occurred in the number of weekly UI episodes across the 5 treatment cycles, with significant reductions from baseline (before any treatment) observed after each onabotulinumtoxinA treatment. In addition, approximately 40% of patients experienced a 100% reduction in UI episodes at week 6 in each treatment cycle. These results are consistent with those from the phase III studies,^{2,3} indicating that a proportion of patients are able to experience continence with repeated onabotulinumtoxinA treatment. OnabotulinumtoxinA treatment also continued to improve the ability of the bladder to store urine (the essential bladder function), as evidenced by the consistent increases in volume/void across the 5 treatment cycles.

Substantial and clinically meaningful improvements in QOL were observed after cycles 1-5 of onabotulinumtoxinA treatment. Approximately 70%-90% of

Table 1. Time to patient request for repeat treatment

	OnabotA Treatment Cycle				
	1	2	3	4	5
Treatment cycle not yet completed (%)	10.1%	22.0%	44.4%	54.0%	43.5%
Drug dosage (U)	200 (n = 202) 129	200 (n = 176) 93	200 (n = 127) 53	200 (n = 59) 25	200 (n = 25) 15
Patients requesting retreatment* (n)	300 (n = 185) 107	300 (n = 160) 72	300 (n = 114) 47	300 (n = 54) 20	300 (n = 21) 8
Mean time to retreatment request (wk)	36.3	36.1	26.3	23.0	20.9
	34.0	37.9	25.2	23.2	17.6

* Patients who requested repeat treatment after receiving onabotulinumtoxinA in treatment cycles referenced in Table 1, regardless of fulfillment of repeat treatment criteria. Patients with > 21 days between exit from phase III studies and entry into long-term study during treatment cycle 1 were excluded from present analysis. Although long-term protocol allowed for ≤ 6 months between exit from preceding studies and entry into long-term study, only patients with ≤ 21 days between studies (ie, those considered to have continuously participated and did not require re-entry into long-term study) were included in analysis to not overestimate duration of effect.

Table 2. Adverse events (AEs)* occurring in $\geq 5\%$ of patients in any onabotA treatment cycle (onabotA-treated population), n (%)[†]

AEs, n (%)	OnabotA Treatment Cycle 1		OnabotA Treatment Cycle 2		OnabotA Treatment Cycle 3		OnabotA Treatment Cycle 4		OnabotA Treatment Cycle 5	
	200U (n = 202)	300U (n = 185)	200U (n = 176)	300U (n = 160)	200U (n = 127)	300U (n = 114)	200U (n = 59)	300U (n = 54)	200U (n = 25)	300U (n = 21)
Overall AEs	175 (86.6)	156 (84.3)	135 (76.7)	120 (75.0)	80 (63.0)	78 (68.4)	32 (54.2)	33 (61.1)	17 (68.0)	11 (52.4)
Urinary tract infection	118 (58.4)	102 (55.1)	81 (46.0)	85 (53.1)	50 (39.4)	48 (42.1)	17 (28.8)	11 (20.4)	5 (20.0)	5 (23.8)
Urinary retention	41 (20.3)	43 (23.3)	16 (9.1)	11 (6.9)	8 (6.3)	8 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematuria	7 (3.5)	9 (4.9)	6 (3.4)	2 (1.3)	4 (3.1)	3 (2.6)	3 (5.1)	3 (5.6)	0 (0.0)	0 (0.0)
Fatigue	13 (6.4)	6 (3.2)	5 (2.8)	4 (2.5)	2 (1.6)	2 (1.8)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
CNS function test abnormal [‡]	10 (5.0)	6 (3.2)	8 (4.5)	13 (8.1)	3 (2.4)	4 (3.5)	1 (1.7)	2 (3.7)	0 (0.0)	0 (0.0)
Muscular weakness	8 (4.0)	5 (2.7)	7 (4.0)	9 (5.6)	3 (2.4)	2 (1.8)	0 (0.0)	2 (3.7)	0 (0.0)	0 (0.0)
Constipation	8 (4.0)	5 (2.7)	5 (2.8)	3 (1.9)	4 (3.1)	4 (3.5)	3 (5.1)	1 (1.9)	0 (0.0)	0 (0.0)
Fall	6 (3.0)	5 (2.7)	5 (2.8)	6 (3.8)	7 (5.5)	1 (0.9)	1 (1.7)	2 (3.7)	0 (0.0)	0 (0.0)
Pyrexia	16 (7.9)	4 (2.2)	4 (2.3)	3 (1.9)	2 (1.6)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious AE	32 (15.8)	24 (13.0)	16 (9.1)	24 (15.0)	10 (7.9)	14 (12.3)	3 (5.1)	7 (13.0)	2 (8.0)	0 (0.0)
AE leading to study discontinuation	2 (1.0)	1 (0.5)	0 (0.0)	1 (0.6)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE, adverse event; CNS, central nervous system; onabotA, onabotulinumtoxinA.

Cumulative duration of exposure for 200 U group (n = 202), 119.8 \pm 30.8 wk and for 300 U group (n = 185), 121.2 \pm 33.9 wk.

* AEs with start dates within each treatment cycle.

[†] Data are presented by onabotA treatment cycle; therefore, only data from onabotA treatment cycles were included. Placebo treatments received in the phase 3 studies were not represented (ie, the patient's second treatment with active drug was onabotA treatment 1).

[‡] As per the Expanded Disability Status Score, which is a general rating of MS neurological status.

patients achieved improvements greater than the reported minimally important difference of ≥ 11 points on the total I-QOL instrument.⁶ These results are consistent with those of the recent phase III studies, which showed significant QOL improvements after a single treatment with onabotulinumtoxinA.^{2,3}

The duration of effect was durable for the first 2 treatment cycles (for which most patients had completed the cycles); however, for the remaining cycles, in which 44%-55% of patients were still ongoing, a slight reduction in the time to patient request for repeat treatment was seen. This reduction was possibly because many patients in the later treatment cycles (after cycle 3) were still ongoing and had not yet requested or received their next treatment. It also is possible that once patients experienced reductions in their UI and improvements in QOL with onabotulinumtoxinA treatment, they might not accept the recurrence of UI episodes and might therefore request repeat treatment earlier. A thorough analysis of this parameter will only be possible once more treatment cycles have been completed and the 3-year extension study has finished.

Repeat treatments with onabotulinumtoxinA were well tolerated, and the AE profile remained comparable across the treatment cycles. Just as in the preceding phase III onabotulinumtoxinA trials, the most frequently reported AE was UTI. The rates we observed were comparable to those reported in the phase III trials.^{2,3} However, the rates in both the 200-U and 300-U dose groups appeared similar, unlike in the phase III trials in which the UTI rates were higher in the 300-U dose group, especially in the MS population. The UTI rates in the present analysis were also consistent with the rates reported in a large cohort of patients with NDO.⁷ In patients who were not using CIC at baseline, de novo CIC occurred most often after the first onabotulinumtoxinA treatment. However, some patients initiated CIC after the second or third injection. Many patients did not initiate CIC after repeated treatments, with some of these patients receiving 4 or 5 onabotulinumtoxinA injections. Overall, just over 40% of the patients not using CIC at baseline initiated CIC at some point after repeat treatment. However, because the analysis of the phase III trial results demonstrated that most patients not using CIC were predominantly patients with MS,^{2,3} it was difficult to differentiate de novo CIC purely due to onabotulinumtoxinA treatment vs de novo CIC resulting from additional impairment of voiding function from the underlying progressive disease. Because the long-term study is ongoing, the final analysis will provide a more complete analysis of these data.

The incidence of neutralizing antibody formation was low after repeat onabotulinumtoxinA injections. Only 1 patient developed neutralizing antibodies to onabotulinumtoxinA, in treatment cycle 6 after frequent treatment with 300 U, with injections nearly every 12 weeks. As previously reported, the relationship between the presence of neutralizing antibodies and treatment response

has not been established.⁸⁻¹⁰ However, some studies have suggested that the frequency of onabotulinumtoxinA injections and higher doses might lead to a greater incidence of antibody formation.^{9,11}

One limitation of these results is that they were from an interim analysis, which has only reported the safety and efficacy parameters up to the cutoff date. The evaluations are ongoing in the long-term study and will further characterize the safety and efficacy profile of onabotulinumtoxinA in this patient population.

CONCLUSION

Sustained reductions in UI episodes and improvements in QOL were observed with repeated treatments with onabotulinumtoxinA in patients with UI due to NDO who were inadequately managed by anticholinergics. The safety profile was consistent with that reported in the phase III trials with onabotulinumtoxinA, with no new safety signals observed with repeat treatment.

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APPENDIX

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.urology.2012.11.010>.