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Comparison of 100 U With 200 U of Intradetrusor OnabotulinumToxinA for Nonneurogenic Urgency Incontinence

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Abstract

Objectives: The objective of this study was to compare efficacy and adverse events between 100 U and 200 U of onabotulinumtoxinA for 6 months in women with nonneurogenic urgency incontinence.

Methods: This is a secondary analysis of 2 multicenter randomized controlled trials assessing efficacy of onabotulinumtoxinA in women with nonneurogenic urgency incontinence; one compared 100 U to anticholinergics and the other 200 U to sacral neuromodulation. Of 307 women who received onabotulinumtoxinA injections, 118 received 100 U, and 189 received 200 U. The primary outcome was mean adjusted change in daily urgency incontinence episodes from baseline over 6 months, measured on monthly bladder diaries. Secondary outcomes included

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perceived improvement, quality of life, and adverse events. The primary outcome was assessed via a multivariate linear mixed model.

Results: Women receiving 200 U had a lower mean reduction in urgency incontinence episodes by 6 months compared with 100 U (−3.65 vs −4.28 episodes per day; mean difference, 0.63 episodes per day [95% confidence interval (CI), 0.05–1.20]). Women receiving 200 U had lower perceptions of improvement (adjusted odds ratio, 0.32 [95% CI, 0.14–0.75]) and smaller improvement in severity score (adjusted mean difference, 12.0 [95% CI, 5.63–18.37]). Upon subanalysis of only women who were treated with prior anticholinergic medications, these differences between onabotulinumtoxinA doses were no longer statistically significant. There was no statistically significant difference in adverse events in women receiving 200 U (catheterization, 32% vs 23%; adjusted odds ratio, 1.4 [95% CI, 0.8–2.4]; urinary tract infection, 37% vs 27%; adjusted odds ratio, 1.5 [95% CI, 0.9–2.6]).

Conclusions: A higher dose of onabotulinumtoxinA may not directly result in improved outcomes, but rather baseline disease severity may be a more important prediction of outcomes.

Keywords

BoNT-A; Botox; urgency urinary incontinence; ABC; ROSETTA

Urgency urinary incontinence (UUI) is a common condition defined as the involuntary loss of urine associated with the sudden desire to pass urine, which is difficult to defer.[1] The prevalence of UUI increases with age, affecting 17% of women older than 40 years and 33% older than 60 years.[2,3] Those who are refractory to behavioral and medication therapy are offered third-line treatment with intradetrusor onabotulinumtoxinA (BoNT-A) injection, sacral neuromodulation (SNM), or percutaneous tibial nerve stimulation.[4,5]

OnabotulinumtoxinA is U.S. Food and Drug Administration approved at 100 U for idiopathic overactive bladder/UUI and 200 U for the treatment of neurogenic detrusor overactivity. There is conflicting evidence for increased efficacy with higher doses of BoNT-A.[6–13] Multiple systematic reviews and meta-analyses report the lack of sufficient evidence to determine an optimal starting dose of BoNT-A for idiopathic UUI.[12,14,15] A longer duration of effect may be attributed to higher BoNT-A doses; however, rates of urinary tract infection (UTI) and catheterization also increase with higher doses.[10,11,16] In a small randomized trial comparing 100 U with 200 U, there were no significant differences in efficacy at 6 months postinjection; however, by 9 months, the 200-U group maintained greater improvement in overactive bladder symptoms. Urinary tract infection rates were higher in those receiving 200 U.[10] It is possible that the increased risk of adverse events in those receiving 200 U might explain the equivocal short-term outcomes. However, this study was likely underpowered.[10]

Our aim was to compare objective and subjective outcomes between 100 U and 200 U doses of BoNT-A over 6 months in women with nonneurogenic UUI.

MATERIALS AND METHODS

This is a secondary analysis using a pooled approach of 2 previously conducted multicenter randomized controlled trials evaluating efficacy of BoNT-A in women with nonneurogenic UUI: Anticholinergic versus Botulinum Toxin Comparison (ABC) and Refractory Overactive Bladder: Sacral Neuromodulation vs Botulinum Toxin Assessment (ROSETTA).[17,18] Both studies were sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (Pelvic Floor Disorders Network), received institutional review board approval at all sites, and participants signed informed consent. This secondary analysis of deidentified data was considered exempt by the Duke University institutional review board.

The ABC trial compared an oral anticholinergic medication and one intradetrusor injection of saline to one 100 U intradetrusor injection of BoNT-A and an oral placebo in women with idiopathic UUI.[19] Enrolled participants were women with ≥5 episodes of UUI on a 3-day bladder diary and were anticholinergic naive or refractory to ≤2 anticholinergic medications. Women were followed monthly for 6 months. Off-protocol treatment was not allowed. The ROSETTA trial compared a 200 U intradetrusor injection of BoNT-A to SNM in women with refractory UUI.[20] Enrollment included women with ≥6 episodes of UUI on a 3-day bladder diary and were refractory to behavioral therapy and >2 anticholinergic medications. Women were followed monthly for 24 months. Women with <50% improvement in urgency urinary incontinence episodes (UUIE) at 1 month were allowed to receive off-protocol UUI treatment other than BoNT-A. At 6 months, all participants were allowed a repeat dose of BoNT-A if their Patient Global Symptom Control score was 1 to 2, indicating lack of adequate control of urinary leakage. Both trials excluded participants with neurogenic UUI, a preinjection postvoid residual (PVR) >150 mL, or prior surgery for stress urinary incontinence or prolapse.[19,20] The primary outcome in both trials was mean change in UUIE from baseline for 6 months. Assessment of baseline covariates, outcomes, and adverse events were comparable and conducted at similar intervals for each study. Details of study protocols have been published.[19,20] Women were included in this analysis if they received a BoNT-A injection as study treatment, completed a baseline bladder diary, and had at least 1 valid bladder diary after baseline.

Outcomes

The primary outcome of this study was mean adjusted change in daily UUIE from baseline reported on monthly 3-day bladder diaries for 6 months after BoNT-A. Secondary outcomes include the proportion of participants with complete resolution, ≥75% reduction, or ≥50% reduction in UUIE from baseline on at least 4 of 6 monthly bladder diaries for 6 months; time to recurrence (defined as <50% reduction in daily UUIE or off-protocol UUI therapy) over 6 months; participant perception of improvement assessed by a score of 1 to 3 on the Patient Global Impression of Improvement (PGI-I) (ranging from 1, “very much better,” to 7, “very much worse”) at 6 months; mean adjusted change in Overactive Bladder Questionnaire—Short Form (OABq-SF) (ranging from 0 to 100 with higher scores indicating better quality of life and greater bother); mean adjusted change in Urogenital Distress Inventory—Short Form (UDI-SF) (ranging from 0 to 100 with higher scores

indicating greater distress) and Incontinence Impact Questionnaire—Short Form (IIQ-SF) (ranging from 0 to 100 with higher scores indicating worse quality of life) scores between baseline and 6 months.

Adverse events were recorded monthly, including self-catheterization (initiated when PVR was >300 mL or PVR was >150 mL and there were symptoms of difficulty emptying) or UTI (defined as a urine culture with $\geq 10^3$ colony-forming units/mL or treatment for a UTI).[19,20] Rates of adverse events for 6 months were compared between BoNT-A doses. All outcomes after a patient received off-protocol UUI treatment were censored.

Statistical Analysis

Monthly change in daily UUIE from baseline between BoNT-A doses (100 U vs 200 U) over 6 months was assessed using a multivariate linear mixed model. To account for likely differences in baseline disease severity between cohorts, fixed effects were selected a priori, including BoNT-A dose, participant-month (1–6), age, baseline UUIE, baseline IIQ-SF, interaction of baseline UUIE with BoNT-A dose, and interaction of month with BoNT-A dose. Additional fixed effects were based on baseline differences between each BoNT-A dose at the 0.5 level to control for available measures of baseline severity. Participant ID was treated as a random effect to account for within-person correlations on outcome over time.

Cox proportional-hazard regression was used to assess time to recurrence controlling for age, ethnicity, maximum cystometric capacity, baseline UUIE, and baseline UDI-SF to account for baseline differences in severity of UUI. Given that the proportional-hazard assumption failed because of crossing hazards at 4 months, hazard ratios were calculated for 1–3 months and 4–6 months. The binary outcomes of recurrence and perception of improvement using PGI-I were assessed with logistic regression, adjusting for age, ethnicity, maximum cystometric capacity, baseline UUIE, and baseline UDI-SF. Otherwise, categorical outcomes were evaluated using logistic regression adjusted for age, baseline UUIE, baseline IIQ-SF, and ethnicity. Continuous outcomes were evaluated using linear regression adjusting for baseline values, baseline UUIE, age, and ethnicity. Comparison of baseline continuous variables between BoNT-A doses was evaluated using Mann-Whitney U test, and median differences were determined by the Hodges-Lehman test.

To limit bias and increase comparability of cohorts, each model was adjusted by available measures of baseline disease severity, such as baseline UUIE, age, baseline quality of life scores, and other differences between cohorts as noted previously. Final model selection for all models was based on optimizing Akaike Information Criterion and/or log-likelihood. Sample size calculations were not performed because of the fixed number of participants in the ABC and ROSETTA trials. All post hoc tests were corrected for multiple comparisons using the Sidak method, and α was defined as <0.05. Statistical analysis was performed using R version 3.6.0.

RESULTS

There were a total of 314 women who received a BoNT-A injection in the ABC and ROSETTA trials, with 307 meeting inclusion criteria for this analysis: 118 women received

100 U, and 189 women received 200 U. In the 100-U cohort, 60% (71/118) were refractory to medication, whereas all women who received 200 U were refractory. In the 200-U cohort, 19% (35/189) received off-protocol UUI treatment at or before 6 months, of which 3.7% (7/189) received other off-protocol therapy (eg, medication, behavioral interventions) between 2 months and 6 months, 3.2% (6/189) received SNM between 3 months and 6 months, and 11.6% (22/189) received a second BoNT-A injection at 6 months. At baseline, women who received 200 U were older, less likely Hispanic, had a higher rate of recurrent UTIs, lower maximum cystometric capacity, more daily UUIE, higher UDI-SF score, and worse symptom bother and quality of life on OABq-SF (Table 1).

The 200 U cohort had a lower adjusted mean reduction in daily UUIE (−3.65; 95% confidence interval [CI], −4.23 to −3.07) compared with 100 U (−4.28; 95% CI, −4.91 to −3.65) with a mean treatment difference of 0.63 (95% CI, 0.05–1.20) daily UUIE at 6 months (Table 2). There was a significant interaction between time and BoNT-A dose, where the 200 U cohort had a degradation in improvement, but after 100 U, there was no degradation over 6 months (Fig. 1A). Specifically, in the 200 U cohort, there was a decrease in improvement per month by 0.15 daily UUIE (95% CI, 0.07–0.23), whereas, in the 100 U cohort, the magnitude of change in daily UUIE per month was similar (−0.03 change in daily UUIE per month; 95% CI, −0.13 to 0.07) (Table 2).

Similarly, there was a significant interaction with baseline UUIE and BoNT-A dose in change in daily UUIE for 6 months (Fig. 1B). Those who received 200 U had on average a smaller improvement in UUIE over time per each increase in baseline UUIE (0.6; 95% CI, 0.5–0.8) compared with 100 U (0.9; 95% CI, 0.8–1.1) with a mean difference of 0.3 (95% CI, 0.1–0.4).

There was a nonstatistically significant difference in the proportion of clinical responders, defined as those who had ≥50% reduction in UUIE from baseline to 1 month (100 U, 78.3% vs 200 U, 84.1%; adjusted odds ratio [aOR], 1.8 [95% CI, 0.9–3.3]) (Table 3). Fewer women reported no leakage on bladder diaries in those receiving 200 U versus 100 U (100 U, 53% vs 200 U, 36%; aOR, 0.6 [95% C, 0.3–1.0]) (Table 3). When evaluating time to recurrence, the hazard ratio was not statistically different for the first 3 months between BoNT-A doses (adjusted hazard ratio, 0.8; 95% CI, 0.5–1.3); however, between 4 and 6 months, those receiving 200 U had a higher hazard of recurrence (adjusted hazard ratio, 3.4; 95% CI, 1.3–9.0) (Fig. 2).

At 6 months, those who received 200 U had a lower perception of improvement, measured by PGI-I (aOR, 0.3; 95% CI, 0.1–0.8). When evaluating change in quality of life at 6 months, in adjusted models, those who received 200 U compared with 100 U had smaller improvements in UDI-SF (mean difference, 12.0; 95% CI, 5.6–18.4). There is no well-defined minimal importance difference (MID) for the UDI-SF in women with UUI. Using the distributional method of one half the effect size, the MID was 9.4 (SD of baseline UDI-SF, 18.7), and thus, the difference in change in UDI-SF at 6 months met this MID.[21,22]

The rates of self-catheterization and UTI for 6 months were higher in the 200-U cohort, but this was not statistically significant (Table 3). When adjusting each model additionally for self-catheterization and/or UTI, there were no changes in primary or secondary outcomes.

A subanalysis of women with prior anticholinergic treatment in the 100 U cohort (n = 71) compared with the 200 U cohort (n = 189) was performed to explore differences in outcomes among those with refractory UUI. In this subanalysis, there were no longer statistically significant differences in change in UUIE from baseline for 6 months, global impression of improvement at 6 months, UDI-SF at 6 months, or time to recurrence for 6 months between BoNT-A doses (Appendix A, http://links.lww.com/FPMRS/A204; Appendix B, http://links.lww.com/FPMRS/A205).

DISCUSSION

Multiple systematic reviews and meta-analyses found no optimal starting dose of BoNT-A for nonneurogenic UUI.[12,14,15] The only randomized controlled trial comparing 100 U with 200 U reported no significant differences in efficacy at 6 months in the 80 participants with refractory idiopathic overactive bladder. However, by 9 months, the 200 U group maintained greater improvement in overactive bladder symptoms but had more UTIs.[10] Conversely, in the study herein, using 2 cohorts of women with nonneurogenic UUI, the 200 U cohort had a modestly lower perception of improvement, measured by PGI-I, and less of an improvement in symptom severity, measured by UDI-SF at 6 months. Similarly, improvement in UUIE was stable for 6 months in the 100 U cohort, whereas, in the 200 U cohort, there was a slow decline in improvement for 6 months. This led to more UUIE in the 200 U cohort by 6 months despite adjusting for baseline disease severity using baseline UUIE, age, and baseline quality-of-life measures. However, the difference of 0.63 daily UUIE between 100 U and 200 U may not be clinically significant.

These results highlight that a higher dose of BoNT-A may not directly result in improved outcomes. Instead, baseline disease severity is likely a more important contributor to treatment response because baseline UUIE was associated with most outcomes, including recurrence, change in UDI-SF, IIQ-SF, OABq-SF, and UUIE for 6 months by $P < 0.005$. Those with a higher baseline UUIE had greater improvement in each treatment dose, possibly representing a floor effect. However, the magnitude of impact of baseline UUIE on change in UUIE was different for each BoNT-A dose. At higher baseline UUIE, the 200 U cohort had less improvement for 6 months compared with 100 U for the same baseline UUIE. Furthermore, although baseline severity was controlled for in these analyses, using baseline UUIE, age, baseline quality-of-life markers, and other baseline differences as noted in the methods section, those enrolled in the ROSETTA study (200 U cohort) were all refractory to medical therapy, as dictated by inclusion criteria, compared with only 60%, who were refractory to medical therapy in the ABC study (100 U cohort). In a subanalysis of women refractory to medical management, the significance in outcomes disappeared. Thus, our findings may suggest that disease severity, not purely measured by UUIE, may explain the decline in efficacy and the lower improvement in UUIE in the 200 U cohort over 6 months.

This may also point to the heterogeneous nature of UUI. Those participants with a more severe phenotype may have a number of nonurologic and urologic factors contributing to the lack of treatment success with any dose of BoNT-A. Although results were adjusted for measured markers of baseline disease severity, such as baseline UUIE, age, and baseline quality-of-life measures, other unmeasured and, thus, uncontrolled for factors may significantly affect outcomes. This is highlighted in the subanalysis, where the less improvement after 200 U was no longer statistically significant when analyzing outcomes of only women refractory to medication. Moreover, recent studies identified characteristics associated with greater bother in urinary symptoms and greater UUI severity, such as prior treatments for urinary tract symptoms, depression, anxiety, stress, or worse baseline physical function, all of which may have differed between the 100 U and 200 U cohorts.[23,24] These factors may be important in predicting results after treatment for nonneurogenic UUI.

A strength of this study is the similarity and consistency in data collected for these 2 trials with respect to questionnaires, quality-of-life metrics, and diary keeping, which permitted these combined analyses. Additional strengths include the allowance for nonlinearity in the statistical models, use of a continuous variable as the primary outcome, and controlling for measures of disease severity in all models, including baseline daily UUIE, quality-of-life measures, and maximum cystometric capacity. The inherent limitation of combining and comparing data from 2 trials is that there are some intrinsic differences in the study groups. The women who received 200 U were slightly older, less likely Hispanic, had a greater frequency of recurrent UTI, and generally had greater symptom bother and worse overactive bladder–related quality of life at baseline. Even though analyses controlled for these differences, it is possible that unmeasured confounders biased the results toward the appearance of greater improvement in the 100 U cohort. Another limitation is that these analyses only extended to 6 months postinjection, and no reinjections were permitted earlier than 6 months. Evaluation to 12 months would have allowed determination of time to reinjection. In addition, there are likely clinically meaningful differences in observed rates of ever performing self-catheterization and postprocedural UTI. However, there were not statistically significant differences, likely because of the lack of power of these rare adverse events.

Given that UUI is multifaceted and complex, a single accurate measure of disease severity does not exist. Therefore, understanding other aspects that may contribute to disease severity may be crucial when counseling patients and choosing a treatment for nonneurogenic UUI. Further study is required to forecast the appropriate candidate patients who may benefit from an initial dose of 200 U versus 100 U of BoNT-A for nonneurogenic UUI and better clarify significant markers of disease severity and treatment response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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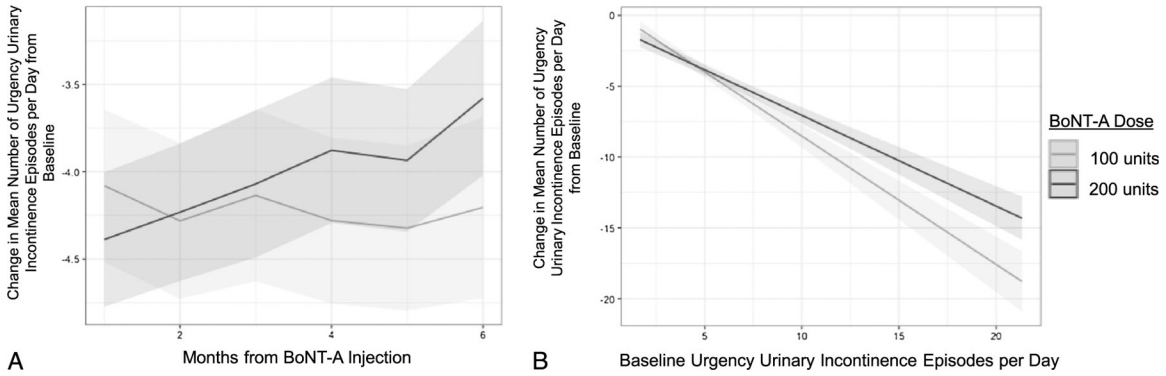

FIGURE 1.

Change from baseline in UUIEs per day for each BoNT-A dose by month and baseline urgency incontinence episodes per day. Values are estimated marginal means, and associated 95% CIs are calculated from the multivariate linear mixed model with fixed effects of time, BoNT-A dose, baseline UUIE, age, baseline IIQ-SF, ethnicity, baseline UUIE by BoNT-A dose interaction, time by BoNT-A dose interaction, and participant ID as random effect; models based on n = 118 for 100 U and n = 189 for 200 U. BoNT-A, onabotulinumtoxinA; IIQ-SF, Incontinence Impact Questionnaire—Short Form; UUIEs, urgency urinary incontinence episode.

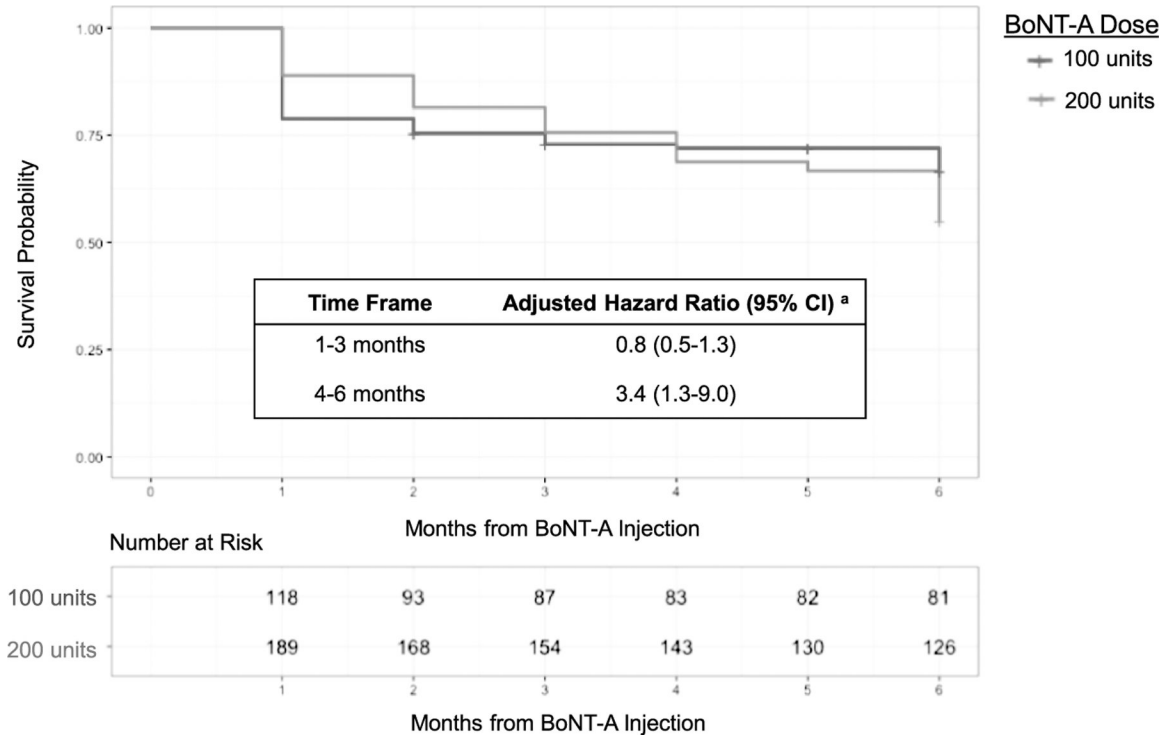

FIGURE 2.

Kaplan-Meier curve and risk table for time to recurrence over 6 months by BoNT-A dose. [a]Proportionality assumption was not met for BoNT-A dose because of crossing hazards; thus, hazard ratios were calculated for 1 to 3 months and 4 to 6 months. Model adjusted for age, baseline UUIE per day, baseline UDI-SF, ethnicity, maximum cystometric capacity; models based on n = 118 for 100 U and n = 189 for 200 U. BoNT-A, onabotulinumtoxinA; UDI-SF, Urogenital Distress Inventory—Short Form; UUIE, urgency urinary incontinence episode.

TABLE 1.

Baseline Demographics by BoNT-A Dose

Demographic	100 U (n = 118)	200 U (n = 189)	Error in Differences, Estimate (95% CI)*
Age, y, median (IQR)	59.9 (52.7–66.5)	63.7 (54.3–71.2)	−3.8 (−6.5 to −1.1)
Ethnicity, n (%)			
Hispanic	22 (18.6)	18(9.8)	0.5 (0.2–0.9)
Race, n (%)			
White	94 (79.7)	154 (82.4)	0.8 (0.5–1.5)
Black	17 (14.4)	22 (11.8)	
Other	7 (5.9)	11(5.9)	
BMI, median (IQR)	30.7 (26.7–35.7)	32.0 (26.8–38.0)	−0.3 (−2.1 to 1.5)
Current smoker, n (%)	14 (12.0)	22 (11.6)	1.0 (0.5–2.0)
Postmenopausal, n (%)	99 (86.8)	161 (89.0)	1.2 (0.6–2.5)
Recurrent UTI history, n (%)†	2(1.7)	24 (12.7)	8.4 (2.4–53.1)
Diabetes history, n (%)	18(15.4)	34 (18.0)	1.2 (0.7–2.3)
Detrusor overactivity, n (%)	84(71.2)	130 (68.8)	0.9 (0.5–1.5)
Maximum cytometric capacity, median (IQR)	345.0 (257.0–456.5) mL	295.0 (210.0–388.0) mL	52.0 (20.0–85.0)
Postvoid residual, median (IQR)	20.0 (6.5–50.0) mL	20.0 (5.0–40.0) mL	0.0 (−2.0 to 7.0)
Daily urgency incontinence episodes, median (IQR)	4.3 (3.0–6.3)	5.0 (3.7–6.3)	−0.7 (−1.0 to −0.0)
UDI-SF, median (IQR)‡	54.2 (45.8–66.7)	61.1 (50.0–72.2)	−5.6 (−11.1 to −0.0)
IIQ-SF, median (IQR)§	47.6(28.6–71.4)	52.4 (28.6–76.2)	−4.8 (−9.5 to 4.8)
OABq-SF, median (IQR)//			
Symptom bother	66.7 (53.3–83.3)	80.0 (63.3–90.0)	−6.7 (−13.3 to −3.3)
Quality of life	46.2 (32.3–58.5)	32.3 (21.5–56.4)	7.7(1.8–13.8)

*Hodges-Lehmann location shift (ie, median of differences) for continuous and ordinal variables; unadjusted odds ratios for categorical variables.

†Recurrent UTI defined as 3 or more UTIs (bladder or kidney) that required treatment during the past year.

‡Values range from 0 to 100, with higher scores indicating greater distress; responses based on n = 109 for 100 U and n = 189 for 200 U.

§Values range from 0 to 100, with higher scores indicating worse quality of life; responses are based on n = 109 for 100 U and n = 188 for 200 U.

[//]Values range from 0 to 100, with higher scores on the symptom bother scale indicating greater severity of symptoms and higher scores on the quality-of-life scale indicating better quality of life; responses based on n = 117 for 100 U and n = 189 for 200 U.

Abbreviations: BMI, body mass index; BoNT-A, onabotulinumtoxinA; IIQ-SF, Incontinence Impact Questionnaire—Short Form; IQR, interquartile range; OABq-SF, Overactive Bladder Questionnaire—Short Form; UDI-SF, Urogenital Distress Inventory—Short Form; UTI, urinary tract infection.

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TABLE 2.

Marginal Means of UUIEs over 6 Months by BoNT-A Dose

Time (Months Since BoNT-A)	100 U		200 U		Difference in Difference (95% CI)†
	Marginal Mean (95% CI)*	Difference From Baseline, Marginal Mean (95% CI)*	Marginal Mean (95% CI)*	Difference From Baseline, Marginal Mean (95% CI)*	
1	1.02 (0.48–1.55)	−4.15 (−4.69 to −3.61)	0.70 (0.19–1.22)	−4.46 (−4.98 to −3.93)	0.31 (−0.15 to 0.77)
2	0.81 (0.27–1.36)	−4.35 (−4.91 to −3.80)	0.86 (0.33–1.39)	−4.30 (−4.84 to −3.77)	−0.05 (−0.52 to 0.43)
3	0.96 (0.36–1.55)	−4.21 (−4.81 to −3.61)	1.02 (0.47–1.58)	−4.14 (−4.70 to −3.58)	−0.07 (−0.60 to 0.47)
4	0.82 (0.24–1.40)	−4.35 (−4.94 to −3.77)	1.22 (0.67–1.76)	−3.95 (−4.50 to −3.39)	−0.40 (−0.92 to 0.12)
5	0.77 (0.20–1.35)	−4.39 (−4.97 to −3.81)	1.16 (0.62–1.70)	−4.01 (−4.55 to −3.46)	−0.39 (−0.90 to 0.12)
6	0.89 (0.27–1.52)	−4.28 (−4.91 to −3.65)	1.51 (0.94–2.09)	−3.65 (−4.23 to −3.07)	−0.63 (−1.20 to −0.05)

*Marginal means of UUIEs calculated from multivariate linear mixed model with fixed effects of time, BoNT-A dose, baseline UUIE, age, baseline IIQ-SF, ethnicity, baseline UUIE by BoNT-A dose interaction, time by BoNT-A dose interaction and participant ID as random effect.

†Difference in difference is a post hoc pairwise calculation adjusted for multiple correlations using the Sidak method.

Abbreviations: BoNT-A, onabotulinumtoxinA; IIQ-SF, Incontinence Impact Questionnaire—Short Form; OABq-SF, Overactive Bladder Questionnaire—Short Form; UDI-SF, Urogenital Distress Inventory—Short Form; UUIEs, urgency urinary incontinence episodes.

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TABLE 3.

Adjusted Outcomes and Adverse Events by BoNT-A Dose

Outcomes	100 U (n = 118)	200 U (n = 189)	Treatment Difference (95% CI)*
Clinical responder at 1 mo, n (%)†‡	90 (78.3)	159 (84.1)	1.8 (0.9–3.3)
Resolution of urinary incontinence for 6 mo on ≥4 months of diaries, n (%)‡			
Complete resolution	63 (53.4)	68 (36.0)	0.6 (0.3–1.0)
≥75% reduction	80 (67.8)	116 (61.4)	0.9 (0.5–1.5)
≥50% reduction	92 (78.0)	142 (75.1)	1.2 (0.7–2.2)
Change from baseline in urinary incontinence at 6 mo, adjusted mean (95% CI)‡			
UUIEs	−3.8 (−4.3 to −3.4)	−3.5 (−3.8 to −3.1)	0.3 (−0.3 to 0.9)
Daytime voids	−0.8 (−1.2 to −0.41)	−0.8 (−1.1 to −0.5)	−0.1 (−0.6 to 0.5)
Nocturia episodes	−0.5 (−0.7 to −0.9)	−0.2 (−0.4 to −0.1)	0.3 (0.0–0.5)
No. pads used	−1.8 (−2.2 to −1.5)	−1.7 (−1.9 to −1.4)	0.1 (−0.4 to 0.5)
Change from baseline in quality of life at 6 mo, adjusted mean (95% CI)§			
UDI-SF‖	−36.3 (−42.2 to −30.5)	−24.3 (−29.8 to −18.9)	12.0 (5.6–18.4)
IIQ-SF¶	−32.8 (−38.4 to −27.2)	−28.3 (−33.5 to −23.2)	4.5 (−1.6 to 10.6)
OABq-SF#			
Symptom bother	−44.8 (−50.3 to −39.3)	−41.3 (−46.6 to −36.0)	3.5 (−2.8 to 9.8)
Quality of life	38.8 (34.0–43.6)	36.9 (32.3–41.6)	−1.9 (−7.4 to 3.7)
Outcomes, n (%)**			
Recurrence for 6 mo††	39 (33.1)	85 (45.0)	1.4 (0.8–2.4)
Perception of improvement at 6 mo‡‡	83 (89.2)	103 (71.0)	0.3 (0.1–0.8)
Adverse effects for 6 mo, n (%)‡			
Intermittent self-catheterization	27 (22.9)	60 (31.7)	1.4 (0.8–2.4)
UTI	32 (27.1)	70 (37.0)	1.5 (0.9–2.6)

*Adjusted marginal means and 95% CI are reported for continuous variables; adjusted odds ratios and 95% CI are reported for categorical variables.

†At 1 month ≥50% reduction in UUIE per day based on a 3-day bladder diary with UUIE averaged for 3 days (used to determine who would be allowed off-protocol non–BoNT-A treatment before 6 months in ROSETTA); responses are based on n = 115 for 100 U and n = 189 for 200 U.

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‡Values for clinical responder, percent resolution of urgency incontinence, UUIEs, daytime voids, nocturia episodes, number of pads, and adverse events used are based on mean number of episodes per day on a 3-day diary captured monthly and were calculated using model estimates adjusted for baseline values, age, baseline UUIE, baseline IIQ-SF, and ethnicity.

§Values for UDI-SF, IIQ-SF, and OABq-SF are calculated using models adjusted for baseline quality-of-life score, age, baseline UUIE, and ethnicity.

//Values range from 0 to 100, with higher scores indicating greater distress; responses are based on n = 85 for 100 U and n = 140 for 200 U.

¶Values range from 0 to 100, with higher scores indicating worse quality of life; responses are based on n = 85 for 100 U and n = 139 for 200 U.

#Values range from 0 to 100, with higher scores on the symptom bother scale indicating greater severity of symptoms and higher scores on the quality-of- life scale indicating better quality of life; responses are based on n = 109 for 100 U and n = 170 for 200 U.

**Adjusted for age, ethnicity, maximum cystometric capacity, baseline UUIE, and baseline UDI-SF.

††Defined as <50% reduction in mean UUIE for 6 months or off-protocol UUI treatment.

‡‡Defined by a PGI-I of 1 to 3 (“very much better” to “better”) in response to reported measure of perceived improvement after treatment on a 1 (“very much better”) to 7 (“very much worse”) scale; responses based on n = 93 for 100 U and n = 145 for 200 U.

Abbreviations: BoNT-A, onabotulinumtoxinA; IIQ-SF, Incontinence Impact Questionnaire—Short Form; OABq-SF, Overactive Bladder Questionnaire—Short Form; PGI-I, Patient Global Impression of Improvement; ROSETTA, Botulinum Toxin Assessment; UDI-SF, Urogenital Distress Inventory—Short Form; UTI, urinary tract infection; UUI, urgency urinary incontinence; UUIE, urgency urinary incontinence episode.