
Refractory Idiopathic Urge Urinary Incontinence and Botulinum A Injection

Linda Brubaker,* Holly E. Richter, Anthony Visco, Sangeeta Mahajan, Ingrid Nygaard, Thomas M. Braun, Matthew D. Barber, Shawn Menefee, Joseph Schaffer, Anne M. Weber and John Wei for the Pelvic Floor Disorders Network

From the Departments of Obstetrics and Gynecology and Urology, Loyola University Medical Center (LB), Maywood, Illinois, Departments of Obstetrics and Gynecology, University of Alabama at Birmingham (HER), Birmingham, Alabama, University of North Carolina at Chapel Hill (AV), Chapel Hill, North Carolina, University of Utah (IN), Salt Lake City, Utah, and University of Texas Southwest (JS), Dallas, Texas, Department of Obstetrics and Gynecology, Case Western University (SM) and Obstetrics/Gynecology and Women's Health Institute, Cleveland Clinic (MDB), Cleveland, Ohio, Departments of Biostatistics (TMB) and Urology (JW), University of Michigan, Ann Arbor, Michigan, Department of Obstetrics and Gynecology, Kaiser Permanente San Diego and Department of Reproductive Medicine, University of California-San Diego, San Diego (SM), California, and Contraception and Reproductive Health Branch, Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health (AMW), Bethesda, Maryland

Purpose: We compared 200 U intradetrusor botulinum toxin A vs placebo in women with refractory idiopathic urge incontinence.

Materials and Methods: This institutional review board approved, multicenter registered trial randomized women with refractory urge incontinence, detrusor overactivity incontinence and 6 or greater urge incontinence episodes in 3 days to botulinum toxin A or placebo at a 2:1 ratio. Refractory was defined as inadequate symptom control after 2 or more attempts at pharmacotherapy and 1 or more other first line therapies for detrusor overactivity incontinence. The primary outcome measure was time to failure, as evidenced by a Patient Global Impression of Improvement score of 4 or greater at least 2 months after injection, or changes in treatment (initiation or increase) at any time after injection. Safety data, including increased post-void residual volume, defined as more than 200 ml irrespective of symptoms, was obtained at specified time points.

Results: Approximately 60% of the women who received botulinum toxin A had a clinical response based on the Patient Global Impression of Improvement. The median duration of their responses was 373 days, significantly longer than the 62 days or less for placebo ($p < 0.0001$). In the botulinum toxin A group increased post-void residual urine (12 of 28 women or 43%) and urinary tract infection in those with increased post-void residual urine (9 of 12 or 75%) exceeded expected ranges. Further injections were stopped after 43 patients were randomized, including 28 to botulinum toxin A and 15 to placebo.

Conclusions: Local injection of 200 U botulinum toxin A was an effective and durable treatment for refractory overactive bladder. However, a transient post-void residual urine increase was experienced in 43% of patients. Botulinum toxin A for idiopathic overactive bladder is still under investigation.

Key Words: urinary bladder, overactive; questionnaires; botulinum toxin type A; urinary incontinence; female

In 2000 Schurch et al reported that BoNT-A was effective for refractory symptoms of neurogenic detrusor overactivity.¹ Of 19 patients with neurogenic DOI 17 were completely continent at 6 weeks after cystoscopic intradetrusor injection of 300 U BoNT-A. Since that landmark study many case series have demonstrated the efficacy of a range of toxin doses in patients with neurogenic and idiopathic DOI.²⁻⁴

Several randomized clinical trials have demonstrated excellent evidence of treatment outcomes, although limited to neurogenic only or mixed neurogenic and idiopathic patient populations.^{1,5} Although most DOI cases are idiopathic in etiology, only a handful of small randomized clinical trials have focused on IDO cases alone.⁵

The Refractory Urge Incontinence and Botulinum A Toxin Injection randomized clinical trial was designed to compare the effect of 200 U intradetrusor BoNT-A vs placebo on improvement in urge incontinence symptoms in neurologically normal women with DOI refractory to at least 2 first line treatments. This study also assessed changes in patient quality of life and the incidence of IEs based on standardized bladder diaries. The rates of posttreatment PVR increase and other associated complications were also assessed.

METHODS

This was a multi-institutional, randomized, double-blind, placebo controlled, institutional review board approved clin-

Submitted for publication October 5, 2007.

Supported by Grants 2U01 HD41249, 2U10 HD41250, 2U10 HD41261, 2U10 HD41267, 1U10 HD54136, 1U10 HD54214, 1U10 HD54215 and 1U10 HD54241 from the National Institute of Child Health and Human Development.

This trial is registered at www.clinicaltrials.gov under Registration No. NCT00373789.

* Correspondence: Loyola University Chicago, 2160 South First Ave., Maywood, Illinois 60153 (telephone: 708-216-2170; FAX: 708-216-2171; e-mail: Lbrubaker@lumc.edu).

For another article on a related topic see page 373.

ical trial done by participants in the National Institute of Child Health and Human Development sponsored Pelvic Floor Disorders Network. BoNT-A is not licensed for this indication and, therefore, an Investigational New Drug application was obtained from the Food and Drug Administration for research use in this trial. Participants were neurologically intact women at least 21 years old with refractory urge incontinence, defined as inadequate symptom control after at least 2 first line therapies, which had to include 2 anticholinergic medications and at least 1 of supervised behavioral therapy, physical therapy or biofeedback. Inclusion required at least 6 urge incontinence episodes in a standardized 3-day bladder diary and documented urodynamic DOI within the last year. The full methods of the trial have been previously published.⁶

Eligible participants underwent a standardized telephone interview approximately 14 days before their injection visit. The interview included the Pelvic Floor Distress Inventory,⁷ Pelvic Floor Impact Questionnaire,⁷ Sexual Function Questionnaire,⁸ Life Orientation test⁹ and SF-36TM.¹⁰

Participants were randomized at the time of first injection to BoNT-A or placebo in a 2:1 randomization. BoNT-A (200 U) was dissolved in 6 ml saline and provided in 2 syringes, each containing 3 ml. Two placebo syringes each contained 3 ml saline. For placebo and BoNT-A 0.1 ml indigo carmine was added to the total volume as a marker for detrusor injection sites. Syringes were prepared by study pharmacists and they appeared identical to the injecting physician. All physicians administering injections were experienced with cystoscopic injection techniques and they performed the procedure in standardized fashion, as instructed using an injection technique video.

Following the administration of local anesthesia 6 ml of masked substance were injected at approximately 15 to 20 detrusor muscle sites. Injections were spread out to cover the posterior bladder wall in 3 rows, sparing the bladder trigone and ureteral orifice. All subjects received an antibiotic before the injection and for 3 days thereafter. Subjects unable to void after injection were taught intermittent self-catheterization.

Subjects with inadequate symptom improvement (PGI-I 4 or greater) who requested a second injection were eligible to receive an open label injection of 200 U BoNT-A at least 8 weeks but no more than 52 weeks after the first injection. All subjects were to be followed for 12 months after the first injection but not less than 1 month following the second injection or to study withdrawal up to a maximum of 13 months.

Post-injection followup included telephone interviews by personnel at a single quality of life center as well as monthly research interviews by a coordinator from each clinical study site. Increased PVR was defined as a PVR volume of greater than 200 ml irrespective of symptoms. At the in person visit 4 weeks following the study procedure subjects with PVR more than 200 ml were instructed on catheterization techniques and a bladder drainage program was begun. Any subject with a clinically positive urine dipstick test was sent for urine culture and treated with antibiotics as necessary.

Subjects were followed up to 12 months unless they received any new treatment for overactive bladder symptoms. In that case they were withdrawn from study and end of study measures were performed. The primary outcome mea-

surement was time to failure (PGI-I 4 or greater) after the first injection.

To allow sufficient time for the onset of action of BoNT-A the earliest outcome measurement was 60 days after injection. Failure was defined as a PGI-I score of 4 or greater, the commencement of any new treatment at any time after the first injection or increased intensity of previously established treatment for DOI.

Secondary outcome measures were changes in the frequency of incontinence episodes, changes in symptom and quality of life measures, including the Patient Global Impression of Symptom Control, and the occurrence and duration of voiding dysfunction requiring catheterization. Safety and adverse events were reported and monitored at 3-month intervals by an independent data safety and monitoring board.

After interval analysis data revealed a higher than anticipated rate of increased PVR in subjects who received BoNT-A injection the study was placed on clinical hold and further injections were stopped. Increased surveillance of randomized participants included weekly telephone calls until PVR was less than 200 cc. In addition, subjects with increased PVR had an additional office visit 8 weeks after injection, at which time catheterized PVR was measured, and urinalysis and culture were done.

Statistical Analysis

This trial was designed to test efficacy rates of 30% for placebo and 50% for BoNT-A after approximately 6 months of followup. A dichotomous outcome (success/failure) was assumed with 2:1 randomization. A sample size of 210 subjects provided 80% power to test the hypothesis using a 2-tailed 5% level of significance. This sample size also permitted the testing of an effect size of 0.2 in the continuous measures of quality of life. No allowance was made for subjects lost to followup.

Analysis of the demographic variables was performed to evaluate the groups for similarity. The primary outcome (time to failure) was analyzed by fitting a Cox regression model. Comparisons between the continuous secondary outcomes (Pelvic Floor Distress Inventory, Pelvic Floor Impact Questionnaire, Sexual Function Questionnaire and SF-36) between groups were made with appropriate parametric and nonparametric testing.

RESULTS

Figure 1 shows the flow of participants through this clinical trial. A total of 43 subjects were randomized, including 28 to BoNT-A and 15 to placebo. The study was placed on clinical hold after these subjects were randomized due to higher than expected rates of increased PVR and associated UTI.

There were no significant differences in baseline demographic characteristics between the 2 cohorts (table 1). There were also no differences at baseline between the groups with respect to IEs on a 3-day urinary diary or lower urinary tract symptoms, condition specific and overall quality of life (table 1).

At 3 to 4 weeks 11 of 15 subjects in the placebo group and 6 of 28 in the BoNT-A group had met the failure criterion. However, the protocol stipulated that the first formal evaluation should be done at 2 months for 2 theoretical reasons, including the possibility of delayed drug action and the fact

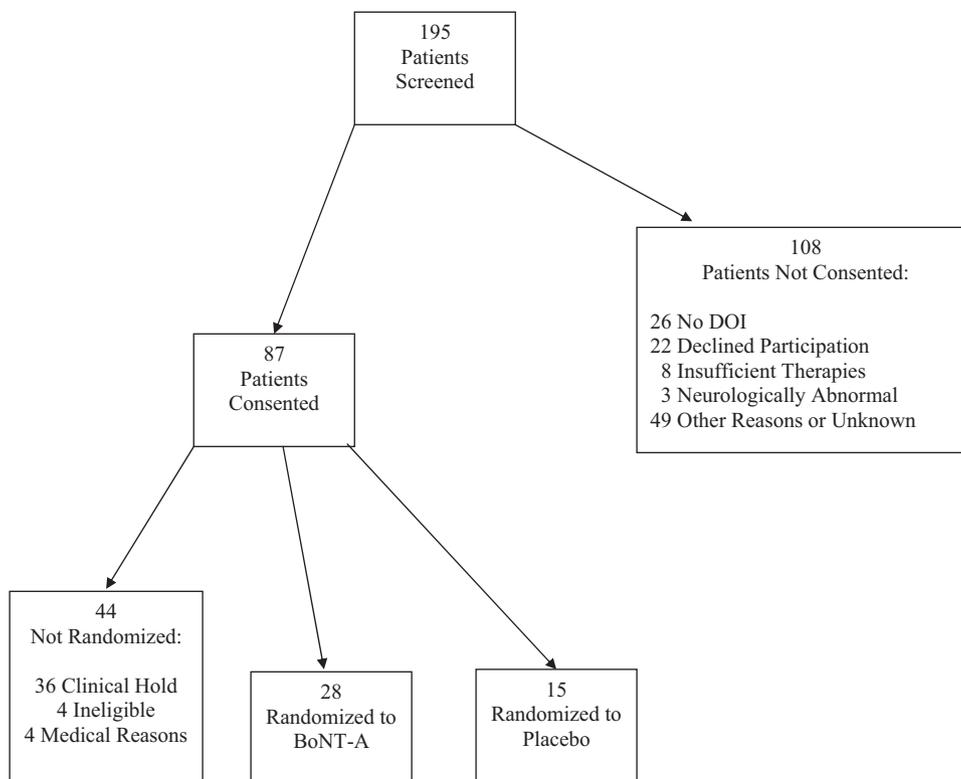


FIG. 1. Consolidated Standards of Reporting Trials diagram with participant flow through this clinical trial

that a placebo effect from the saline injection might be less prominent removed from the injection date. Survival curves demonstrated that median time to failure in the BoNT-A group was significantly longer than in the placebo group (307 days vs less than 62 days, the initial time point when failure was assessed, $p < 0.001$, [fig. 2](#)). Time to failure in those subjects with post-injection increased PVR was similar that in subjects without increased PVR in the BoNT-A group ($p = 0.72$).

Approximately 60% of the women who received BoNT-A had a clinical response based on PGI-I. The median duration of the response was 373 days. Mean PGI-I score 2 months after the initial injection was significantly better in the BoNT-A group (2.7 vs 4.0, $p = 0.003$). One month after injection there was a highly significant difference in the number of IEs and total IEs on a 3-day urinary diary (each $p < 0.0001$, [fig. 3](#)). Of the 25 women in the BoNT-A group who completed a second diary 18 (72%) experienced more than a 75% decreased number of IEs. No subject in the control group experienced that level of reduction.

Patient perception of the adequacy of symptom control was significantly better in the BoNT-A group ($p < 0.0001$, [fig. 4](#)). Symptom bother was significantly improved in the BoNT-A group with a significant decrease in the UDI urge subscale score ([table 2](#)).

Increases in PVR occurred exclusively in the BoNT-A group (12 of 28 women or 43%) ([table 3](#)). We did not detect a significant difference in age or median baseline PVR between subjects with vs without increased PVR. Median time to the initiation of intermittent self-catheterization was 30 days after injection, which was when we routinely assessed PVR, and self-catheterization lasted a median of 62 days. Before the clinical hold that stopped additional injections, 8

subjects received a second injection. One of these subjects had increased PVR starting 3 days after the second injection, which was ongoing at more than 157 days.

UTI also occurred at a rate higher than had originally been predicted. It was associated with increased PVR requiring intermittent self-catheterization in 9 of 12 women. UTI developed in twice as many subjects after BoNT-A treatment in our study than after placebo injection (44% vs 22%). We did not detect a difference in the proportion of women with UTI in the placebo group compared to the BoNT-A group without increased PVR (3 of 15 vs 3 of 16, respectively).

Other adverse events were uncommon. Three subjects in the BoNT-A arm and 2 in the placebo arm sustained serious adverse events, including nonurinary infection, cardiovascular, neurological and musculoskeletal system injury. There was 1 unrelated death in the placebo arm in an elderly subject with a history of congestive heart failure. Unexpected adverse events occurred in 6 subjects in the BoNT-A arm only, including gastrointestinal, gynecological, infection, musculoskeletal, neurological or miscellaneous symptoms.

DISCUSSION

In this double-blind, placebo controlled clinical trial we found significant improvement in lower urinary tract symptoms in approximately 60% of women after intradetrusor injection of 200 U Botox®. In women who responded favorably the median duration of effect was almost 12 months. However, there was a higher than expected rate of increased PVR and lower UTI. At the time that this protocol was developed the existing literature, which consisted exclusively of small, single institution case series, suggested that

TABLE 1. Select baseline characteristics in 2 cohorts

	BoNT-A	Placebo	p Value
No. pts	28	15	
Mean ± SD age	64.7 ± 14.5	69.2 ± 13.5	0.32
Mean ± SD no. prior treatments:	4.5 ± 1.4	4.4 ± 1.5	0.83
Medication	2.8 ± 0.9	2.9 ± 1.3	0.78
No medication	1.7 ± 0.8	1.5 ± 0.6	0.36
No. race (%):*			0.54
White	26 (93)	15 (100)	
Black	2 (7)	0	
No. married (%)	18 (64)	7 (47)	0.34
No. some college or greater (%)	19 (68)	14 (93)	0.13
No. health insurance (%):			0.93
Private only	9 (32)	5 (33)	
Medicare or Medicaid only	9 (32)	4 (27)	
Medicare + Medicaid	10 (36)	6 (40)	
Urge incontinence on 3-day bladder diary:			
Mean ± SD No. episodes	17.12 ± 13.4	16.15 ± 14.70	0.79
No. pts	25	13	
Incontinence on 3-day bladder diary:			
Mean ± SD total No. episodes	21.44 ± 22.7	19.0 ± 8.0	0.63
No. pts	25	13	
UDI:			
Mean ± SD total score	110.1 ± 60.9	97.2 ± 49.9	0.57
No. pts	28	15	
UDI obstructive subscale:			
Mean ± SD score	22.53 ± 25.5	14.10 ± 18.11	0.20
No. pts	28	15	
UDI irritative subscale:			
Mean ± SD score	54.5 ± 17.5	53.33 ± 15.2	1.0
No. pts	28	15	
UDI stress incontinence subscale:			
Mean ± SD score	33.13 ± 27.4	29.8 ± 30.2	0.49
No. pts	28	15	
Urinary Incontinence Impact Questionnaire:			
Mean ± SD total score	158.1 ± 78.3	143.4 ± 70.5	0.61
No. pts	28	15	
Mean ± SD SF-36 score:			
Physical component summary	39.5 ± 8.8	36.6 ± 11.6	0.52
Mental component summary	46.1 ± 12.6	52.6 ± 10.0	0.11

There were no Hispanic participants.

the rates of increased PVR and UTI after BoNT-A therapy in neurologically normal women were low (less than 5%).¹¹⁻¹⁵ Our findings are in agreement with another double-blind, placebo controlled trial in 34 men and women with idio-

pathic DO or DOI,⁵ which was published after we stopped our trial.

Recent evidence suggests that, in addition to its effect on efferent innervation, BoNT-A also has effects on the bladder

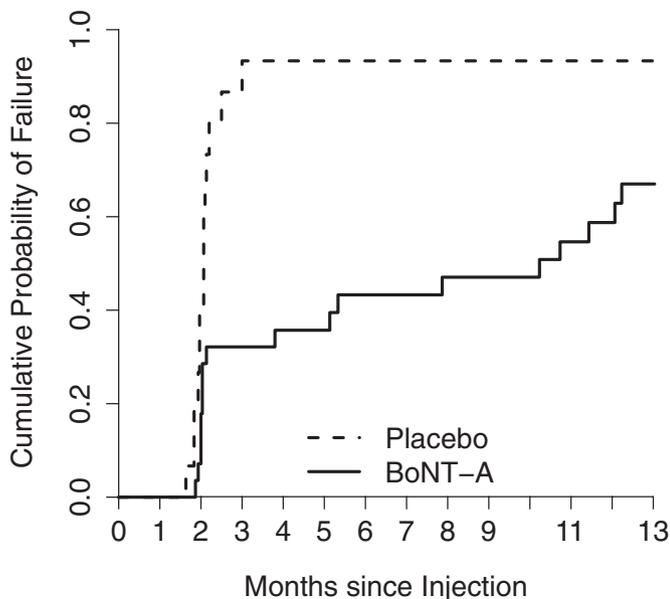


FIG. 2. Median time to failure in 2 groups

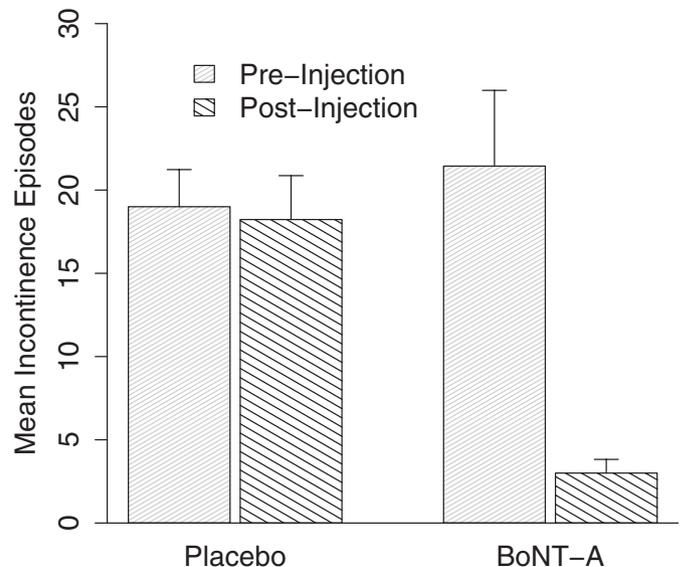


FIG. 3. Change in number of incontinence episodes on 3-day urinary diary.

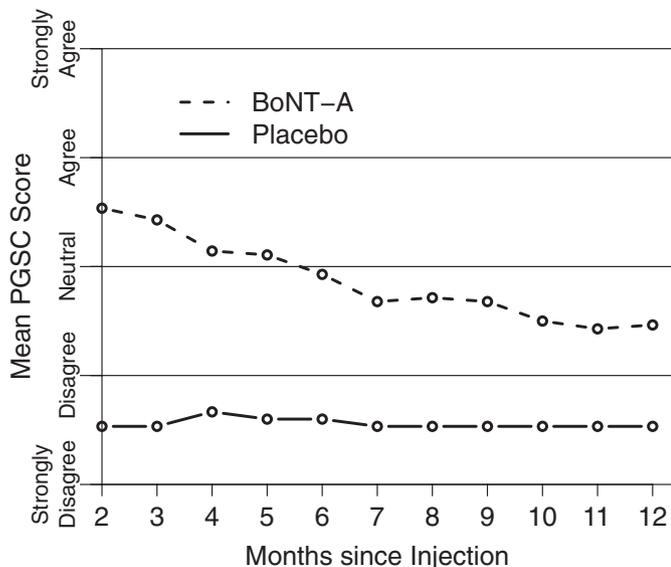


FIG. 4. Patient perception of symptom control adequacy

afferent innervation, inhibiting the release of adenosine triphosphate and substance P, and decreasing axonal expression of capsaicin and purinergic receptors.¹⁶ Consistent with the inhibition of bladder motor and sensory function, after intradetrusor injections of BoNT-A there were increases in maximum cystometric capacity, volume at strong desire to void, bladder compliance and PVR, and decreases in maximum detrusor pressure, detrusor pressure at maximum flow and urgency sensation.^{12,17-19}

Clinically we also found evidence that intradetrusor BoNT-A injection had motor and sensory effects, in that more than 40% of our participants who received BoNT-A showed impaired bladder emptying, which was diagnosed in 75% only because of routine PVR assessment at 4 weeks. The study design defined increased PVR as a PVR of more than 200 ml regardless of symptoms or the ability of patients to void alone. This definition may be different from that in clinical practice and it may explain the larger than expected number of patients with increased PVR in this study. The rate of CISC after BoNT-A treatment in the literature is 0% to 45%.^{4,5,11,12,18} This wide variation may be explained not only by a number of technical factors, including toxin dose and dilution, the number and location of injection sites, and injection depth (subepithelial vs intradetrusor),¹⁷ but also by the intensity of posttreatment surveillance, including the number and timing of PVR assessments, and the threshold

Pt No.	Initial PVR (cc)	No. Days After Injection		CISC Duration (days)
		To CISC Start	To CISC End	
1	130	5	206	201
2	30	37	41	4
3	20	43	125	82
4	3	27	32	5
5	50	30	60	30
6	110	30	72	42
7	30	7	61	54
8	25	3	75	72
9	5	22	91	69
10	110	35	160	125
11	120	42	124	82
12	30	30	56	26

for beginning CISC. Had we not routinely assessed PVR at 4 weeks in all participants, the rate of increased PVR in our study would have been approximately 14% since most participants with increased PVR were asymptomatic.

To our knowledge the clinical consequences of asymptomatic impaired bladder emptying after BoNT-A treatment are not known and it is unclear if or when CISC should be initiated in these patients. BoNT-A treatment results in decreased bladder contractility, causing decreased bladder pressure and increased bladder compliance.^{12,18,19} All subjects in our trial with a PVR of greater than 200 cc at 4 weeks were started on CISC whether or not they were symptomatic. Thus, we are unable to comment on the necessity of CISC or the relative safety of withholding CISC in this population. Notably subjects who were started on CISC in our study had similar improvements in bladder function, as assessed by PGI-I and the Patient Global Impression of Symptom Control, as those who received BoNT-A but did not have increased PVR despite the burden of CISC. This finding is similar to that of Kalsi et al, who noted in their series of 41 patients with neurogenic detrusor overactivity or IDO treated with BoNT-A that the need for de novo CISC had a less significant effect on patient quality of life than relief from urgency symptoms.²⁰

UTI occurred in twice as many subjects after BoNT-A treatment in our study than after placebo injection. This difference is largely attributable to the high rate of UTI in women performing CISC (75%). Consistent with our findings, Sahai et al noted that all subjects performing CISC in their trial had UTI and all except 1 with UTI was performing CISC.⁵ The rate of UTI in our trial is higher than in other series of BoNT-A treatment for IDO.¹⁷ This may be explained in part by a liberal definition of UTI, a low threshold for urine testing and frequent patient contact. There were no upper UTIs in this study.

The strengths of this trial include its robust design, well-defined study population, use of validated patient centered outcome measures and excellent followup. Despite the early clinical hold we noted differences in our primary outcome measure, providing evidence that BoNT-A is an effective treatment for women with refractory idiopathic DOI. However, the final sample size limited our ability to comment on some of our planned secondary outcomes and decreased the power to detect uncommon events, including infrequent adverse events. Additionally, the aim of this trial was to eval-

TABLE 2. Urinary symptoms on UDI⁷

Characteristic	Mean ± SD BoNT-A	Mean ± SD Placebo	p Value
No. pts	28	15	
UDI total:			
Baseline	110.1 ± 60.9	97.2 ± 49.9	0.57
1 Mo	67.7 ± 55.4	97.4 ± 58.3	0.09
UDI obstructive:			
Baseline	22.53 ± 25.5	14.10 ± 18.11	0.20
1 Mo	20.62 ± 20.5	13.08 ± 16.80	0.20
UDI irritative:			
Baseline	54.46 ± 17.54	53.33 ± 15.23	1.0
1 Mo	31.01 ± 21.45	52.33 ± 19.10	0.003
UDI stress:			
Baseline	33.13 ± 27.4	29.80 ± 30.21	0.49
1 Mo	16.20 ± 22.4	31.94 ± 33.80	0.06

uate the impact of BoNT-A treatment on subject symptoms and quality of life. We did not perform urodynamic evaluations after treatment and we are unable to comment on the physiological effects of BoNT-A treatment in our population.

CONCLUSIONS

This trial provides level 1 evidence that cystoscopically guided intradetrusor injection of 200 U BoNT-A decreases urge incontinence in women with idiopathic DOI and refractory urge incontinence. The median durability of the effect was almost 1 year, which may inform the design and performance of future clinical trials. Increased PVR and UTIs occur more frequently than previously reported. Based on our results we caution about the use of 200 U BoNT-A without appropriate PVR/UTI surveillance and adequate patient counseling. To our knowledge neither the optimal dose of BoNT-A nor the clinical significance of the posttreatment transient PVR increase is known. Further research is needed to define the optimal indications, dose and followup for women treated with intradetrusor BoNT-A.

ACKNOWLEDGMENTS

Botox was provided to the National Institutes of Health for this study by Allergan, Inc., Irvine, California under Investigational New Drug BB 12,780.

Abbreviations and Acronyms

BoNT-A	=	botulinum toxin A
CISC	=	clean intermittent self-catheterization
DOI	=	detrusor overactivity incontinence
IDO	=	idiopathic detrusor overactivity
IE	=	urinary incontinence episode
PGI-I	=	Patient Global Impression of Improvement
PVR	=	post-void residual urine
UDI	=	Urogenital Distress Inventory
UTI	=	urinary tract infection

REFERENCES

- Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G and Hauri D: Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol* 2000; **164**: 692.
- Giannantoni A, Di Stasi SM, Stephen RL, Bini V, Costantini E, Porena M: Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. *J Urol* 2004; **172**: 240.
- Karsenty G, Reitz A, Lindemann G, Boy S and Schurch B: Persistence of therapeutic effect after repeated injections of botulinum toxin type A to treat incontinence due to neurogenic detrusor overactivity. *Urology* 2006; **68**: 1193.
- Kuo HC: Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. *Urology* 2004; **63**: 868.
- Sahai A, Khan MS and Dasgupta P: Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. *J Urol* 2007; **177**: 2231.
- Brubaker L, Kreder K, Richter HE, Lavelle J, Wei JT, Mahaman S et al: Refractory urge urinary incontinence and botulinum A injection: the methods of the RUBI trial. *J Appl Res* 2006; **6**: 260.
- Barber MD, Kuchibhatla MN, Pieper CF and Bump RC: Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. *Am J Obstet Gynecol* 2001; **185**: 1388.
- Rogers RG, Kammerer-Doak D, Villarreal A, Coates K and Qualls C: A new instrument to measure sexual function in women with urinary incontinence or pelvic organ prolapse. *Am J Obstet Gynecol* 2001; **184**: 552.
- Scheier MF, Carver CS and Bridges MW: Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J Pers Soc Psychol* 1994; **67**: 1063.
- Ware JE Jr and Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473.
- Flynn MK, Webster GD and Amundsen CL: The effect of botulinum-A toxin on patients with severe urge urinary incontinence. *J Urol* 2004; **172**: 2316.
- Kessler TM, Danuser H, Schumacher M, Studer UE and Burkhard FC: Botulinum A toxin injections into the detrusor: an effective treatment in idiopathic and neurogenic detrusor overactivity? *Neurourol Urodyn* 2005; **24**: 231.
- Rapp DE, Lucioni A, Katz EE, O'Connor RC, Gerber GS and Bales GT: Use of botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. *Urology* 2004; **63**: 1071.
- Reitz A, Stohrer M, Kramer G, Del Popolo G, Chartier-Kastler E, Pannek J et al: European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. *Eur Urol* 2004; **45**: 510.
- Smith CP, Nishiguchi J, O'Leary M, Yoshimura N and Chancellor MB: Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. *Urology* 2005; **65**: 37.
- Apostolidis A, Dasgupta P and Fowler CJ: Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006; **49**: 644.
- Patel AK, Patterson JM and Chapple CR: Botulinum toxin injections for neurogenic and idiopathic detrusor overactivity: A critical analysis of results. *Eur Urol* 2006; **50**: 684.
- Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ and Dasgupta P: A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. *J Urol* 2005; **174**: 984.
- Schulte-Baukloh H, Weiss C, Stolze T, Herholz J, Stürzebecher B et al: Botulinum-A toxin detrusor and sphincter injection in treatment of overactive bladder syndrome: objective outcome and patient satisfaction. *Eur Urol* 2005; **48**: 984.
- Kalsi V, Apostolidis A, Popat R, Gonzales G, Fowler CJ and Dasgupta P: Quality of life changes in patients with neurogenic versus idiopathic detrusor overactivity after intradetrusor injections of botulinum neurotoxin type A and correlations with lower urinary tract symptoms and urodynamic changes. *Eur Urol* 2006; **49**: 528.