Refractory Urge Urinary Incontinence and Botulinum A Injection: The Methods of the RUBI Trial

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DISCLOSURES

This trial is registered at www.clinicaltrials.gov under Registration # PFDN1 12. The Botox was supplied to this study by Allergan, Inc. (Irvine, CA) under IND BB 12,780.

ABSTRACT

Objective: The purpose of this study was to describe the methods of a randomized clinical trial of intra-vesical botulinum toxin for refractory urge urinary incontinence.

Methods: Clinical sites of the Pelvic Floor Disorders Network (www.pfdn.org) recruited patients with refractory urge urinary incontinence and urodynamic evidence of detrusor overactivity incontinence (DOI) to a 2:1 placebo controlled cystoscopic injection of botulinum toxin A.

Results: The primary outcome is time to failure after first injection, with failure defined as a Patient Global Impression of Improvement (PGI-I) score 4 or greater at least 2 months after the first injection or the commencement of any new treatment at any time after the first injection, or an increased intensity of previously established treatment for DOI.

Conclusions: This trial was designed to test the efficacy of intra-detrusor botulinum toxin A for the treatment of refractory urge incontinence. Progress of the trial can be monitored on www.clinicaltrials.gov.

INTRODUCTION

Urge urinary incontinence (UUI) is the complaint of involuntary leakage of urine accompanied by or immediately preceded by urgency.[1] When this condition is associated with detrusor overactivity (DO), defined by the International Continence Society as the urodynamic observation of involuntary detrusor contractions during the cystometry phase which may be spontaneous or provoked, the condition is known as detrusor overactivity incontinence (DOI). Although DOI is more common among women with certain neurological conditions such as multiple sclerosis and stroke, the vast majority of DOI cases are idiopathic.

Traditionally, behavioral therapy including pelvic floor muscle training,[2] electrical stimulation,[3] and/or antimuscarinic medications have been the mainstays of therapy.[4] Treatment of refractory urge incontinence attributed to DO can be treated with invasive neuromodulation implants that require a 2-step surgery with general anesthesia.[5] Despite the efficacy of these therapies, many patients remain incontinent while others are unable to tolerate the anticholinergic side effects including dry mouth and constipation. Consequently, women with refractory DOI experience a significant decrement in their quality of life[6,7] due to the persistent symptoms.

The medical applications of botulinum toxin (Botox; Allergan, Inc. [Irvine, CA]), a potent neurotoxin, began in the late 1960s when Scott and colleagues used Botox in the treatment of hyperactive muscle disorders, such as the strabismus.[8] Current FDA approved uses of Botox therapy have been expanded to include treatment of glabellar lines, blepharospasm, strabismus, and cervical dystonia.

The possibility of treatment of refractory DOI by cystoscopic injection of Botox was suggested by Schurch et al in 2000 with their initial report of 24 patients who were incontinent yet dependent on intermittent self catheterization (ISC) for impaired voiding after spinal cord injury.[9] The majority of these patients (17/19) achieved continence and their maximum cystometric capacities increased. Although these patients had neurogenic etiologies for their DOI, more recent non-randomized studies have reported similar favorable results among women with idiopathic and refractory DOI.[10,11]

Information describing the determination of effective doses for use in the lower urinary tract is limited. Most studies use multiple intra-detrusor injection sites with diluted botulinum toxin A (total doses ranging from 100 to 300 units).[12,13] In the first randomized controlled trial looking at intra-detrusor botulinum toxin A dosing to treat DOI,[14] 300 units was superior to 200 units for patients with significant DOI who voided either spontaneously or voided by intermittent self-catheterization. In contrast, a recent randomized clinical trial[15] demonstrated no significant difference in improvement in symptom-specific quality of life measures (Urinary Distress Inventory[UDI-6]) and frequency of voiding among patients with idiopathic DOI treated with either 100 or 150 units of intra-detrusor botulinum A toxin. There are no published placebo-controlled trials of botulinum toxin in idiopathic DOI patients. It is well known that the placebo response in overactive bladder medication trials is approximately 30%. Prior to widespread clinical use of intra-detrusor botulinum, it is essential to evaluate the efficacy of this costly thera-

py in a well-designed clinical trial.

The primary purpose of the Refractory Urge Urinary Incontinence and Botulinum A toxin Injection (RUBI) randomized clinical trial is to compare the effect of 200 units of intra-detrusor botulinum toxin A (Botox) versus placebo on improvement in urinary symptoms in neurologically normal women with DOI refractory to at least two first-line urge incontinence treatments. In addition, we plan to assess quality of life, within-subject change, and between-group change in the number of urinary incontinence episodes by standardized bladder diary. Associated complications of therapy including urinary retention will also be determined.

METHODS

Clinical Trials Network Organization

The Pelvic Floor Disorders Network (PFDN) is a cooperative network of investigators from seven clinical centers and a Data Coordinating Center (DCC). The primary goal of the PFDN is to improve the level of knowledge about pelvic floor disorders (such as pelvic organ prolapse and urinary or fecal incontinence) in women. The PFDN is supported by cooperative agreements from the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH). This protocol was developed in collaboration at the following centers: Loyola University Medical Center, Maywood, IL; Johns Hopkins University, Baltimore, MD; University of Iowa, Iowa City, IA; University of Alabama at Birmingham, Birmingham, AL; University of North Carolina, Chapel Hill, NC; University of Pittsburgh, Pittsburgh, PA; University of Michigan, Ann Arbor, MI; and NICHD.

Study Approvals

This study received Investigational Review Board approval at all enrolling sites (listed in Appendix) and the Data Coordinating Center at the University of Michigan. Botox is not approved by the United Sates Food & Drug Administration (FDA) for intra-detrusor injection for treatment of DOI. This study is covered under the FDA IND BB 12,780.

Study Design

This is a randomized 2:1 Botox:placebo, double-blinded placebo-controlled clinical trial. Potential participants are neurologically intact women seeking treatment for urge incontinence symptoms that are refractory to non-surgical therapy and attributed to DOI. The primary outcome measurement is time to failure after first injection.

The study schema is illustrated in Figure 1. Following eligibility assessment, participants are randomized at the time of their first injection. Participants with inadequate symptom control can receive a second injection (open label 200 units of Botox) at least 8 weeks but no more than 52 weeks after the first injection. Participation ends when a subject completes follow-up, voluntarily withdraws, or is withdrawn by her physician for medical reasons. All subjects will be followed for 12 months after their first study injection but not less than 1 month following their second injection or study withdrawal up to a maximum of 13 months.

Eligibility Assessment

Study inclusion and exclusion criteria are outline in Table 1. Potential participants must be grossly neurologically intact women who are at least 21 years of age (no upper age limit). They will undergo initial determination for eligibility based on symptoms of urge incontinence with documentation of urodynamic evidence of DOI within the past year. Refractory DOI symptom control is defined as patients with inadequate symptom control after at least two first-line therapies

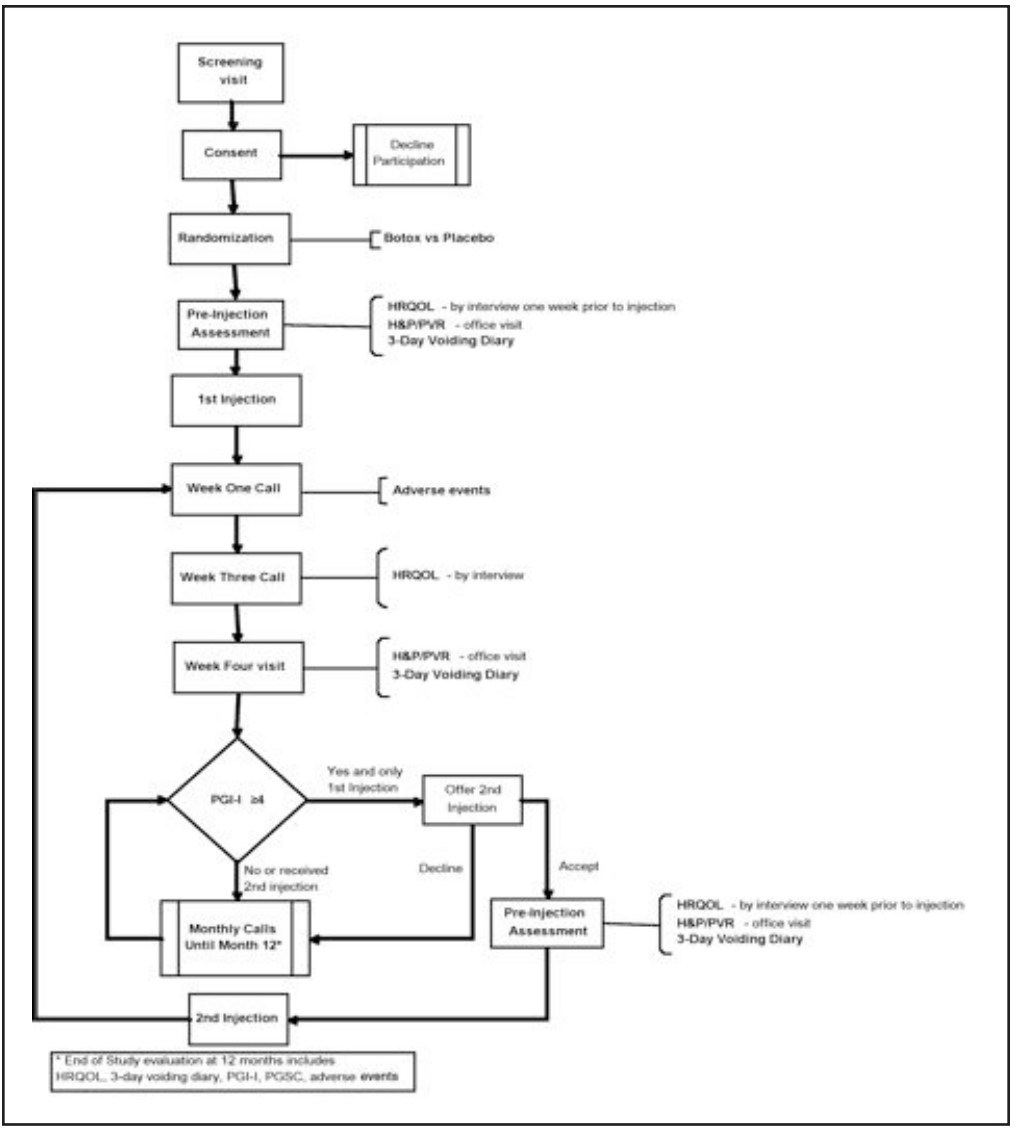

Figure 1. Study flow chart.

for DOI. First-line therapies include: pharmacotherapy, supervised behavioral therapy, supervised physical therapy, supervised biofeedback, and electrical stimulation (transvaginal or implanted neuromodulation). First-line pharmacotherapy must include at least two trials of DOI medication for a minimum of 1 month each unless the drug is not tolerated. Pharmacotherapy (anticholinergic medication) includes any form of oxybutynin, tolterodine, trospium chloride, solfenacin, or darifenacin. The pharmacotherapy requirement can be waived if drug therapy is contraindicated or if the patient is intolerant.

All potential participants complete a standardized written 3-day urinary diary and participants must report at least 6 urge incontinence episodes over the 3 days of the diary.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Females at least 21 years of age
2. Six or more urge incontinence episodes on a 3-day bladder diary. Urge incontinence episodes will be determined based on voiding diary and subject indication of coincident symptoms, allowing self-characterization of incontinence type.
3. Demonstrate DOI on urodynamic testing within the last year. If urodynamic testing was performed elsewhere, the study physician must review a copy of the urodynamic tracing or report to confirm the presence of DOI prior to subject study enrollment.
4. Refractory DOI symptom control, defined as patients with inadequate symptom control after at least two first-line therapies for DOI. First-line therapies include: pharmacotherapy, supervised behavioral therapy, supervised physical therapy, supervised biofeedback, and electrical stimulation (transvaginal or implanted neuromodulation). First-line pharmacotherapy must include at least two trials of DOI medication for a minimum of 1 month each unless the drug is not tolerated. Pharmacotherapy (anticholinergic medication) includes any form of oxybutynin, tolterodine, trospium chloride, solfenacin, or darifenacin. The pharmacotherapy requirement can be waived if drug therapy is contraindicated or if the patient is intolerant.
5. Neurologically normal on exam, defined as normal knee reflexes, perineal sensation, and no gross neurologic abnormalities believed to affect urinary function

Exclusion Criteria

1. Untreated urinary retention, defined as post-void residual greater than 150 mL after a measured void of greater than 150 mL within the last 3 months (including exclusion of patients using intermittent straight catheterization)
2. Surgically altered detrusor muscle, such as augmentation cystoplasty
3. Known allergy to Botox
4. Prior treatment with intra-detrusor Botox in the last year
5. Symptomatic urinary tract infection
6. Currently pregnant or lactating patients or patients planning pregnancy within the next year
7. Sexually active premenopausal women with a uterus not on a medically approved form of contraception for at least 3 months prior to study participation; eligible women must consent to continue to use the same medically approved method of contraception for the duration of the study.
8. Cystoscopic findings that preclude injection, in the opinion of the investigator
9. Current or prior bladder malignancy
10. Patients with known neurological diseases involving impaired neurotransmission, including myasthenia gravis and Charcot-Marie-Tooth disease
11. Patients who are on ambulatory anticoagulant therapy, including aspirin, who are unable to discontinue this treatment for 24 hours prior to the bladder injection
12. Suspected or previously diagnosed interstitial cystitis or chronic pelvic pain syndrome
13. Women with hematuria who have not undergone a clinically appropriate evaluation
14. Women taking aminoglycosides at the time of injection
15. Blood creatinine level greater than twice the upper limit of normal

Pre-Intervention Assessments

Coordinators contact subjects by phone to notify them of their eligibility status and to schedule the injection visit for eligible subjects who agree to participate in the trial. Eligible participants undergo a standardized telephone interview by the PFDN Quality of Life Interviewing

Center within 14 days prior to their injection visit. The phone assessment includes the Pelvic Floor Distress Inventory (PFDI),[16] Pelvic Floor Impact Questionnaire (PFIQ),[17] Sexual Function Questionnaire (PISQ),[18] Life Orientation test,[19] and Medical Outcomes study short form - 36.

First Injection Visit

All potentially fertile women undergo a urine pregnancy test at this visit and subjects with a positive urine pregnancy test are excluded from study participation. All subjects must have a documented negative urine culture or urinalysis before randomization to ensure that they are free of infection before injection. When the urinalysis is positive, the urine specimen is sent for culture and antibiotics prescribed, if appropriate. The Botox injection will be deferred until the urinary tract infection is documented as resolved.

Between screening and the first injection visit, subjects are asked about the initiation of therapy (pharmacological, behavioral, etc) for DOI or a change in any established therapy, such as increased dose of pharmacologic therapy. Any new therapy or increase in established therapy during this period makes the subject ineligible to receive an injection.

Randomization

The Botox is stored in the pharmacy at each clinical site. Prior to injection, the study coordinator selects the next available randomization number from a stratified list provided by the DCC that corresponds to an envelope that the pharmacist opens. A designated clinical site pharmacist opens the sealed randomization envelope and prepares the injection vial (active Botox or placebo) using standardized preparation techniques. Randomization (2:1 Botox:placebo) is performed using a random block size that is known only to the DCC. Randomization is stratified by site and by concurrent pharmacologic treatment.

Injection Preparation

Botox is prepared by the pharmacy to facilitate blinding of the patient and the clinical team, including the study coordinator and physician injector. Two hundred units of Botox are dissolved in 6 mL saline and provided to the clinical team in two syringes each containing 3 mL. Botox is stored as a vacuum dried medication at 2-8°C until reconstitution. If not used within 30 minutes from reconstitution, it can be stored for up to 4 hours in the vial in a refrigerator between 2-8°C. Placebo syringes contain saline. Both placebo and Botox have 0.1 mL of indigo carmine added to the total volume as a marker for detrusor injection sites.

Injection Procedure

All physicians administering injections have been certified through the use of a short instructional video demonstrating optimal techniques and detailing sites of drug injection in a standardized manner.

The participants are instructed about the injection procedure. The subject's bladder is emptied by catheterization; 30 mL of 1% lidocaine is instilled into the bladder and 10 mL of 1% lidocaine jelly is instilled into the urethra under sterile conditions and remain no less than 20 minutes before the injection.

Cystoscopy is performed using a 30-degree lens and an injection cystoscope (Richard Wolf Medical Instruments Corp, Vernon Hills, IL). Sufficient fluid volume is instilled during cystoscopy to allow adequate visualization of the entire bladder urothelium. In the absence of a finding that precludes injection, the injecting physician injects a total of 6 mL of the masked substance into approximately 15 to 20 different

Table 2. Selected Assessment Tools

The PGI-I consists of the following question:

Compared to how your urinary leakage was before treatment, do you feel that you are:

1. ☐ Very much better
2. ☐ Much better
3. ☐ Better
4. ☐ About the same
5. ☐ Worse
6. ☐ Much worse
7. ☐ Very much worse

The PGSC consists of the following item:

This treatment has given me adequate control of my urinary leakage.

Disagree Strongly	1	2	3	4	5	Agree Strongly

detrusor muscle sites under direct visualization. Injections are spread out to equally cover the entire dome of the bladder, but spare the bladder trigone and ureteral orifices. Peri-procedural adverse events are recorded.

The subject is observed in a post-procedure area until a spontaneous void occurs or it is determined that the subject needs to self-catheterize and has demonstrated the ability to do so independently or with the aid of family/friend as appropriate. If the subject is sent home on intermittent self catheterization, she is instructed to call the study coordinator when spontaneous voiding resumes. Through serial phone contacts, the subject is instructed when it is safe for her to discontinue intermittent self catheterization. All subjects are given an antibiotic prior to the injection and for 3 days afterwards.

Standardized post-injection instructions are given to the subject verbally and in written form. These instructions direct the subject to collect a consecutive 3-day diary in the week before the 4-week post-procedure visit.

Post-Intervention Assessments

Week one call—The study coordinator telephones the subject approximately 7 days post injection to ensure that the subject is voiding normally and to query for adverse events. If the subject is experiencing voiding difficulties, clean intermittent catheterization is started.

Week four assessment—The post-injection follow-up includes both telephone and in-person components. Approximately 7-10 days before the 4-week post-injection visit, the study coordinator phones the subject, administers the Patient Global Impression of Improvement (PGI-I) and the Patient Global Symptom Control (PGSC). These assessment tools are shown in Table 2. The study coordinator reminds the subject to complete the 3-day voiding diary to bring to the in-person visit. Subjects who respond with a PGI-I score of 4 or greater will be asked: "Would you like to talk with your doctor about your bladder symptoms?" When answered affirmatively or when the subject initiates a request to talk with the physician, the research coordinator will

schedule the contact. Within 7 days of the post-injection visit, the Quality of Life Interview Center will contact the subject by phone and administer the SF-36, PISQ, PFDI, and PFIQ questionnaires.

At the in-person visit 4 weeks following the study procedure, the 3-day diary is collected, as well as an updated, directed history and physical, and a urine dipstick and post-void residual are obtained. Any subjects with a post-void residual >200 mL will be instructed on catheterization techniques and a clinically appropriate program for bladder drainage will be instituted at the clinician's discretion.

The research coordinator verbally administers the PGI-I and the PGSC again. Subjects who respond with a PGI-I score of 4 or greater are asked "Would you like to talk with your doctor about your bladder symptoms?" Other ongoing therapies for DOI will again be recorded. Adverse events will also be recorded. Any subject with a positive urine dipstick will have a urine culture sent and will be treated with an appropriate urinary antibiotic as necessary. After completion of treatment for the UTI, they will repeat the 3-day diary and the coordinator will repeat the telephone interview (but the QOL interview will not be repeated).

Continued Follow-up

Subjects subsequently undergo follow-up phone calls from the research coordinator at monthly intervals, unless office evaluation is clinically indicated by a patient-initiated request for clinical care or contact resulting in clinical care. At each monthly telephone call, the research coordinator asks the subject the PGI-I, the PGSC, and pertinent adverse events. As before, a subject with a PGI-I score of 4 or greater will be asked "Would you like to talk with your doctor about your bladder symptoms?" If a subject would like to speak with her doctor, the research coordinator arranges the contact with the physician either in person or by phone.

Subjects will continue to be followed for the 12-month period unless the subject receives any new or increase in existing overactive bladder medication (other than one injection of 200 U open label Botox), electrical stimulation, supervised behavioral therapy, biofeedback or pelvic floor muscle training with exercises, or surgery for their condition, in which case they are withdrawn from the study.

Second Injection

A subject must have a PGI-I score of at least 4 to qualify for a second injection. If the subject wishes a second injection, she will be scheduled to receive a second injection which will be open-label Botox no sooner than 8 weeks but no later than 52 weeks following her first injection (without unmasking her prior injection).

If a second injection is requested, the second injection will always consist of Botox 200U. However, since the subjects and investigators are masked to the first injection assignment, neither will know whether it is the first or second Botox for that individual subject. The injection follow-up is identical to the follow-up after the first injection except that an additional Botox injection (ie, a third injection) may not be obtained as part of this study. The subject continues to be followed until 12 months from the initial injection or for a minimum of 1 month following the second injection, whichever is longer. After the second injection, the subjects have a 1-week phone call and a 4-week in-person visit. In addition, these subjects complete follow-up with bladder diary and questionnaires in the same fashion as subjects who have received only a single injection.

Outcomes

The primary outcome measurement is time to failure after first injection. Failure is defined as a PGI-I score 4 or greater at least 2 months after the first injection or the commencement of any new treatment at any time after the first injection, or an increased intensity of previously established treatment for DOI.

Secondary outcome measures include: changes in frequency of incontinence episodes (comparing voiding diary before injection and 4 weeks post injection); changes in symptom and quality of life measures before and 4 weeks post injection or prior to treatment failure; and the occurrence and duration of voiding dysfunction requiring catheterization. Safety and adverse events are reported and monitored at least every 6 months by an independent data monitoring safety board (DSMB) set up by the National Institutes of Health.

Statistical Analysis

This trial is designed to test efficacy rates of 30% placebo and 50% for Botox. The primary outcome is the time to failure after first injection as defined by the PGI-I score of 4 or greater. A dichotomous outcome (success/failure) is assumed with a 2:1 randomization. The sample size of 210 subjects provides 80% power to determine a successful outcome in 50% of Botox subjects and 30% placebo subjects with an effect size of 0.2 in the continuous measures of quality of life. No allowance in the model is made for subjects lost to follow up.

Analysis of the demographic variables is performed to evaluate the groups for similarity. The intention to treat analysis of the primary outcome (time to failure) will be managed using a Cox regression model. Comparisons between the continuous secondary outcomes (PFDI, PFIQ, PISQ, and SF-36) between groups will be made with appropriate parametric and non parametric testing.

DISCUSSION

The first urologic application of botulinum toxin therapy was in the management of neurogenic detrusor and urethral sphincter dysfunctions associated with spinal cord injury.[20] The mechanism of action has been well established in animal models and medical benefit is derived primarily from chemo-denervation at the neuromuscular endplate. Subsequent regeneration of new axons to the target organ results in re-innervation and explains why clinical benefit typically last only several months. The initial success of Botox injection for these complex patients has since sparked an interest for its use among women with idiopathic DO. Currently, there are two commercially available formulations of botulinum toxin: botulinum toxin A as Botox (Allergan, Inc., Irvine, CA) and a botulinum toxin B preparation, not currently available in the US, Dysport (Speywood Pharmaceuticals Limited, Berkshire, UK), however, these are distinct preparations and not interchangeable. Indeed, animal models suggest that botulinum toxin A has a better safety profile than botulinum toxin B.[21]

To date, most published studies have evaluated the use of botulinum toxin A for the treatment of DO and for the most part, reflect the experiences of small, single-institution, case series. In fact, few studies have included a placebo group, limiting their ability to draw any conclusions regarding efficacy. For example, Kessler et al reported on 11 patients with IDO and 11 patients with neurogenic detrusor overactivity (NDO) injected with 300 U of botulinum toxin A.[22] In both groups, the median daytime frequency decreased significantly as did median nocturia and median number of

pads used. Likewise, in another series of mixed NDO and IDO patients, 60% of the subjects were deemed responders at the 3-week evaluation and the benefit persisted through the 6-month evaluation.[12]

While these subjective endpoints were promising, objective evidence for a physiologic effect in humans were lacking until Flynn et al reported on 7 patients with IDO and refractory DOI treated with 150 U of botulinum toxin A.[23] Urodynamic studies were obtained at the 6-week and 3-month follow-up visits. Statistically significant changes in maximum cystometric capacity (>50%) were seen for all patients at all visits up to 3 months; however, most developed recurrent UUI by 6 months after injection. Similarly, Smith et al reported maximal efficacy occurs between 7 and 30 days and lasted approximately 6 months.[24]

Reitz et al reported on 231 patients with NDO treated with 300 U of botulinum toxin A injected into 30 different sites in the bladder.[25] This is the largest urodynamic study of Botox to date. With complete data on 200 patients, the mean cystometric bladder capacity increased significantly at the 12- and 36-week post-injection time points while the mean voiding pressure decreased significantly.

Although a standardized protocol for this off-label injection of botulinum toxin A into the detrusor does not exist, several trends are evident in the literature; the most obvious of which is the use of lower Botox doses and fewer injection sites among idiopathic compared to neuropathic patients. Several protocols have specifically injected Botox into the trigone while others specifically avoid trigonal injection for fear of causing reflux. In the RUBI trial, we intentionally avoid trigonal injections to minimize the likelihood of this adverse outcome. This is especially relevant, since we do not plan to screen for post-treatment ureteral reflux.

Despite its reputation as the most potent biological toxin known to man, botulinum toxin A has proven to be a safe and effective therapeutic option for a wide variety of neuromuscular disorders. Targeted injection leads to chemodenervation and targeted muscle relaxation. The growing body of clinical experience with botulinum toxin A for the treatment of DO offers great promise for management of refractory DOI. Based on these preliminary data, the PFDN has designed and will conduct the first randomized, placebo-controlled clinical trial of Botox injection therapy for refractory DOI.

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APPENDIX

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