Review Article

The use of botulinum toxin for the treatment of overactive bladder syndrome

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ABSTRACT

Over the last 50 years, botulinum toxin has been transformed from a cause of life-threatening disease to an effective medical therapy. It has been used in a variety of specialties for different indications, significantly improving patient quality of life. A recent growing body of evidence suggests that intra-detrusor injection of botulinum toxin may have beneficial effects in patients with medication refractory detrusor overactivity and may offer a new minimally invasive alternative to patients with severe overactive bladder symptoms. To review current data regarding the effects of botulinum toxin in patients with overactive bladder, a MEDLINE®/PubMed® literature search was carried out. The mechanism of action, clinical usage, adverse effects, and treatment efficacy were reviewed and the results are presented in this paper.

Key words: Botulinum toxin, idiopathic detrusor overactivity, lower urinary tract dysfunction, neurogenic detrusor overactivity, overactive bladder, urge incontinence

INTRODUCTION

Overactive bladder (OAB) is a syndrome consisting of any one of four key symptoms: urinary urgency, urge incontinence, urinary frequency, and nocturia. The physiologic basis of these symptoms is detrusor overactivity (DO), defined as spontaneous or provoked involuntary detrusor contractions. Neurogenic detrusor overactivity (NDO) is commonly associated with spinal cord injury, cerebrovascular accident, multiple sclerosis, dementia, Parkinson's disease, and other neurologic diseases. However, patients with even minor neurologic disorders may also be affected.[1] DO that is not clearly associated with neurologic cause is referred to as idiopathic detrusor overactivity (IDO). It is estimated that more than 90% of women with OAB symptoms have IDO and are noted to have no other recognizable neurological disorder.[2]

First line treatment for OAB is most commonly behavioural modifications or simply educating patients to be more strategic with regards to their fluid intake habits. Many patients and their caregivers are unaware of the significant impact of fluid intake habits on urinary incontinence frequency. In our practice, we recommend that patients try to moderate their fluids to no more than 4 to 6 ounces of fluid per hour and limit themselves to no more than one caffeinated beverage per day. In addition, we ask that patients to stop drinking fluids at least 2 to 3 hours prior to bedtime with the exception of a sip of fluid with medications as needed. With these minimal behavioural changes, many patients will demonstrate significant symptomatic improvements in their daily incontinence symptoms.[3]

For patients who do not respond to behavioural modifications, anti-muscarinic therapy has traditionally been utilized as the next line of treatment for OAB. However, significant side effects can limit the tolerability of this therapy for many patients even in cases of significant clinical success. Furthermore, not all patients respond to pharmacologic therapy and many still experience significant OAB symptoms refractory to anticholinergic medications or are unable to take these medications due to contraindications. In the past, surgical therapies were often recommended for patients as a last resort, including bladder augmentation or urinary diversion or more recently sacral neuromodulation

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(InterStim®, Medtronic, Inc., Minneapolis, MN). However, a recent growing body of evidence suggests that intra-detrusor injection of botulinum toxin may have beneficial effects in patients with medication refractory DO and may offer a new minimally invasive alternative to patients with severe OAB symptoms.

HISTORY

Botulinum toxin is a potent neurotoxin produced by the Gram-negative, rod shaped anaerobic bacteria *Clostridium botulinum*. The toxin was first described in 1895 by Emile van Ermengem[4] and, over the last 50 years, has been transformed from a cause of life-threatening disease to an effective medical therapy. In 1989, the Food and Drug Administration (FDA) approved Botox® (onabotulinumtoxinA, Allergan, Inc., Irvine, CA) for the treatment of strabismus, blepharospasm, and cervical dystonias in patients older than 12 years. In 2002, Botox® was approved for cosmetic uses (glabellar facial lines) and in 2004 for the treatment of axillary hyperhidrosis.[5] In 1988, Hallan *et al.*[6] used botulinum A toxin in patients with intractable constipation caused mainly by anismus. Their promising results opened new possibilities of using botulinum toxin in patients with detrusor sphincter dyssynergia and eventually with overactive bladder syndrome. Recently, in August 2011, FDA approved Botox® for the treatment of NDO, specifically "urinary incontinence due to detrusor overactivity associated with a neurological disease and refractory to oral medication".[7] Currently, many non-FDA–approved ('off-label') applications for botulinum toxin are being utilized in a variety of specialties, including laryngeal dystonias, occupational cramps, tension headaches, vaginismus, and urinary retention after suburethral sling, significantly improving patient quality of life.

MECHANISM OF ACTION

To date, seven antigenically distinct forms of botulinum toxin exist, including serotypes A, B, C, D, E, F, and G.[8] Only serotypes A and B are commercially available currently, with serotype A marketed as Botox® or Dysport® (abobotulinumtoxinA, Ipsen, Inc., Slough, UK), or Xeomin (incobotulinumtoxinA, Merz Pharmaceuticals, LLC, Greensboro, NC), and serotype B as Myobloc® (rimabotulinumtoxinB, US World, LLC, Louisville, KY). Individual formulations of the toxin differ in their structure, formulation, and potency due to manufacturing and assay methods of each company. However, all seven serotypes contain a core neurotoxin molecule consisting of a heavy and light chain linked by a disulfide bond.[9,10]

All serotypes of botulinum toxin act by inhibiting calcium- mediated release of acetylcholine vesicles at the pre-synaptic neuromuscular junction in peripheral nerve endings, resulting in temporary flaccid muscle paralysis.[11] Binding of toxin to both peripheral and central nerve ending is highly selective and saturable.[10] The toxin's specificity for cholinergic nerve endings is determined by the heavy chain component and the mechanism of action is a two-step process. First the molecule binds to the neuronal cell membrane with the heavy chain and the molecule is internalized.[12] A disulfide reaction then separates the heavy chain from the light chain. The light chain binds to the acetylcholine vesicles and acts as a zinc-dependent endopeptidase splitting several proteins needed for the fusion of neurotransmitter vesicles with the cell surface, thereby preventing acetylcholine exocytosis and blocking the neuromuscular end-plate.[5]

Botulinum toxin is not believed to enter the central nervous system, but no definitive evidence currently exists to support this belief.[13]

In 1990, Holds *et al.*[14] demonstrated the reversible nature of botulinum toxin effect on muscle after injection. Although the flaccid paralysis caused by toxin injection was initially thought to be permanent, muscle function was noted to eventually return in treated patients. Axonal rearborization over nerve endplates at the neuromuscular junction, replacing toxin-affected nerves with new ones, is responsible for the progressive return of muscle function after toxin treatment.[15] As a result, most patients require repeat dosing every 6 to 12 months within the bladder and even at more frequent intervals within other muscles in the body.[16] Unfortunately, a small percentage of patients undergoing repetitive treatment with botulinum toxin will eventually become resistant to toxin, probably via antibody- mediated resistance. Greene *et al.*[17,18] reported that 4% to 10% of patients have detectable antibodies to botulinum toxin after repeated treatment for cervical dystonias. Shorter dosing intervals, more booster doses, and higher overall treatment doses are significantly associated with increased antibody-mediated toxin resistance.[17]

Permanent changes in muscle fibers may occur with repetitive botulinum toxin treatment. Although there is no definitive evidence of change in muscle function with repetitive toxin treatment, it appears to cause some minor alteration in muscle fiber composition that could possible lead to long term reduction in muscle strength.[19] Given this concern and the mechanism of action of the toxin, the treatment with botulinum toxin should be avoided in patients with pre-existing neurologic disorders affecting transmission at the neuromuscular junction.

CLINICAL USAGE

Serotype A of botulinum toxin is the form most commonly used for treatment of lower urinary tract dysfunction. Within the United States, botulinum toxin is commonly available as Botox® (onabotulinumtoxinA); whereas, in Europe, it is available as Dysport® (abobotulinumtoxinA). The two formulations have very different potencies (1 U of

onabotulinumtoxinA is equivalent to approximately 3 to 5 U of abobotulinumtoxinA) and are supplied in very different dosages (Botox® is available in a 100 U or 200 U vial, whereas Dysport® comes in a 3000 U or 5000 U vial). Attempts to convert dosages between the two drug formulations are not reliable and should clearly be avoided.[20]

In our practice, patients are given the option of undergoing intra-detrusor botulinum toxin injection in the office or in the operating room under IV sedation, although the procedure is the same whether performed in the operating room or the office. If performed in the office, after checking a urine dip to ensure no active urinary tract infection, 30 cc of 1% lidocaine jelly is inserted transurethrally and allowed to site for at least 10 minutes. If they choose to go to the operating room, IV sedation is performed. In both cases informed consent is obtained prior to the procedure. Based on the specific patient, anywhere from 100 to 300 U of botulinum toxin is reconstituted in 20 cc of sterile saline and injected into the detrusor muscle just below the level of the bladder mucosa, creating a 'wheal' under the bladder mucosa demonstrating successful submucosal injection. In our practice, a rigid cystoscope with an injectable set up is utilized, although a flexible scope and non-injection set up may also be used. Early in the physician learning curve, adding a small amount of methylene blue or indigo carmine to the botulinum toxin mixture may be helpful to note the sites of previous injections to avoid retreating the same area. Injections are generally started in the midline just above the inter-ureteric ridge and then, moving to the right, injections are performed at 0.5 cm intervals to the level of the bladder sidewall and then back to the midline at the site of the initial injection, now moving to the left. Once the initial row is completed, the surgeon moves upward 0.5 to 1 cm and starts another row left and right. A total of anywhere from 15 to 20 injections may be performed. In general, most of our patients undergo treatment in the office with local anesthesia only and do well with minimal injection-associated discomfort. Some investigators have supported injection of the trigone and bladder base, but further studies are needed.[21]

No effect is seen immediately after injection and muscle paralysis occurs slowly over the next few days, with maximal effects occurring approximately 7 to 10 days after injection. Consistently, in our practice patients taking anticholinergic medications are asked to stay on their current regimen for 5 days post-treatment before discontinuing these drugs. Toxin effects in the detrusor muscle generally last 6 to 12 months, but may vary based on the amount of toxin injected, with larger doses tending to have longer lasting effects, but also to be associated with higher rates of urinary retention.[5]

ADVERSE EFFECTS AND COMPLICATIONS

Systemic effects are rarely observed with lower urinary tract injection of botulinum toxin. However, due to its paralytic mechanism, theoretical concerns for systemic effects do exist. Possible side effects may include generalized weakness, dysphagia, diplopia, and blurred vision.[20] Weakness has been reported in 2 to 6 percent of patients treated with 1000 U Dysport®, but were also reported with 750 U Dysport® and with 300 U Botox®.[22] The reported duration of such symptoms varies from two weeks to two months.[22] Wyndaele and Van Dromme[23] reported two cases of severe generalized muscle weakness after injection of botulinum toxin in the detrusor muscle for neurogenic bladder overactivity. However, to date there have been no reports of respiratory paralysis after lower urinary tract injection of botulinum toxin.[24] Most documented severe cases of respiratory paralysis from Botox® treatment have occurred after cosmetic uses due to incorrect dilution of high-potency research formulations.

In a systematic review of the literature regarding intra-detrusor Botox® injections in adults with NDO, Karsenty *et al.*[25] found that the most common reported complaints after treatment appeared to be pain at the injection site, procedure-related urinary tract infections (2-32%), mild hematuria (2-21%), and an increase in post-void residual (PVR) volume potentially resulting in urinary retention (0-33%) or de novo intermittent self-catheterization (6-88%).

Kuo *et al.*[26] investigated the risk factors of increasing adverse effects after Botox® injection in 217 patients with refractory IDO. During the follow-up period, specific side effects occurred in 113 patients (52.1%). Acute urinary retention occurred in 8% of patients, large PVR (>150 ml) in 47%, and straining to void in 46%. Gross hematuria was found in 8% of patients, urinary tract infections in 14%, and general weakness in 3%. Patients with acute urinary retention were treated with an indwelling Foley catheter for 3-7 days and most of the patients could void without performing intermittent self-catheterization. In this study, male gender and baseline PVR >100 ml were independent predictors of acute urinary retention. A baseline PVR >100 ml and having received >100 U Botox® were predictors of straining to void.

In 2009, FDA issued a warning based upon reports of life-threatening systemic toxicity from local Botox® injections.[27] These cases were similar to botulism, and were thought to occur due to spread of Botox® beyond the injection site. Symptoms in adult patients included asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. The most severe cases were observed in children with cerebral palsy who received local Botox® injections for limb spasticity and developed difficulty swallowing or breathing. Because of these cases, the FDA recommends that practitioners who use Botox® be alert for potential systemic effects, which may occur as early as hours and as late as several weeks after treatment.

Cases of fatal cardiovascular compromise (including myocardial infarction or arrhythmia) or spontaneous death caused by major debility are cited in the drug package insert.[5] Special precautions should be taken in patients with known neurologic disease if being considered for treatment with botulinum toxin. Patients with impaired neurotransmission (i.e. Myasthenia Gravis, Charcot-Marie-Tooth disease) are at high risk to experience detrimental effects from botulinum toxin's distal effects and should be treated with caution.[5]

Although the lethal dose of Botox® in humans is unknown, it is estimated that 2800 U would be lethal for a 70 kg person.[28] Most therapeutic doses of Botox® range from 25 to 300 U and for Dysport® range from 250 to 1000 U. Peak neuromuscular blockade is achieved within 24 to 72 hours after treatment and persists for several weeks to months, depending upon the dose administered and muscle treated.[13] An antidote to the toxin is available in cases of overdose, but is only useful in an acute setting and should be reserved for patients who demonstrate significant cardiopulmonary compromise thought to be secondary to toxin overdose. Furthermore, the antidote is ineffective on the long-lasting symptoms of botulism.[5] With the small amounts of botulinum toxin used clinically, a significant overdose is unlikely to occur and it is not generally recommended that physicians administering botulinum toxin A have the antitoxin on hand. However, adequate supportive care facilities (i.e. intensive care unit) and a local health department that has a supply of antitoxin should be readily accessible on the rare chance that a medical emergency should occur. Administration of antitoxin should only be performed in an acute/supportive care setting.

In our practice, we advise patients with a PVR of >150 mL post-treatment to perform intermittent self-catheterization (ISC). All patients who do not routinely catheterized pre-treatment are instructed on ISC (either at the time of their injection or at a follow-up visit 2 weeks later). Patients are given informational handouts with clear diagrams and instruction and all necessary supplies. All catheterizing patients are asked to keep a voiding diary in which they record their PVR after at least 3 voids during the day (catheterizing first thing in am, once in afternoon and prior to bed). Based on their diary, once the PVR is consistently less than 100 ml they can stop catheterizing. Patients are also instructed to take a prophylactic antibiotic (nitrofurantoin 100 mg, trimethoprim 100 mg, or cephalexin 500 mg) every day that they catheterize to prevent urinary tract infection. Patients may be required to self-catheterize for 2-4 weeks after injection. We do not routinely check a post-void residual on patients at their 4 week post-treatment visit unless they are symptomatic. Hopefully, prior to the 4-week post-treatment visit, symptomatic patients have already contacted the office and instituted ISC.

DOSING

Current FDA guidelines approving Botox® for the treatment of NDO specify that a dose of 200 U of Botox® should be used. Although many clinicians have until now routinely used a 300 U Botox® dose in catheter-dependent NDO patients, recent data suggests no significant benefit to the higher dosing, supporting the FDA guidelines.[29] In our practice we currently administer an intra-detrusor dose of 200 to 300 U in NDO patients and 100 U to 150 U in IDO patients. Patients are counselled carefully about the risks and benefits of different doses (longer effect duration but higher retention rates with larger dose) before a final dose amount is decided specific to that patient.

Although OAB has been treated with 100 to 300 U of Botox® in most studies, the optimal dose is still under investigation. In their review, Karsenty *et al.*[25] found that most investigators used 300 U Botox® (range 100-400 U) injected under cystoscopic guidance in 30 injection sites (range: 15-40) of 10 U/ml (range: 6.7-25 U/ml) in the bladder, usually sparing the trigone. The investigators performed flexible or rigid cystoscopy with no or under local spinal or general anesthesia.

TREATMENT EFFICACY

The use of intra-detrusor botulinum toxin for the treatment of DO has revolutionized the care of patients with OAB. In 2000, Schurch *et al.*[30] published their landmark case series on the efficacy of botulinum toxin injections into the detrusor muscle in spinal cord injury patients with NDO resistant to anticholinergic drugs. A total of 200 to 300 U of Botox® were injected into the detrusor muscle at 20 to 30 sites, sparing the trigone. After treatment, maximum cystometric capacity and PVR increased; whereas, mean maximum detrusor voiding pressure decreased significantly, 17 of 19 patients were continent at 6 weeks follow-up and anticholinergic medication use was markedly decreased or withdrawn.

Since 2000, multiple trials have supported the efficacy and safety of intra-detrusor botulinum A toxin for the treatment of NDO [Table 1]. Accordingly, in fall 2011, the United States FDA approved Botox® for the treatment of NDO, opening up a new treatment option (and potential insurance coverage) for patients with severely refractory symptoms. Although definitely not considered a first-line treatment for DO, intra-detrusor botulinum A toxin is an important new option for the treatment of patients with inadequate response to more conservative therapies. In their literature review, Karsenty *et al.*[25] compiled outcomes from eighteen articles evaluating the efficacy or safety of Botox® in patients with NDO resistant to antimuscarinic therapy, consisting mostly of open-label studies containing fewer than 50, but totalling 698 patients. Data from all patients was pooled.

Table 1: Studies examining the efficacy of intra-detrusor botulinum toxin for the treatment of neurogenic detrusor overactivity (NDO) (mixed gender, adult patients unless otherwise specified)

Author	Year	N	Toxin dose	Outcome	Patient population	Study design
Deffontaines-Rufin *et al.*[31]	2011	71	300 U Botox®	46% of patients were continent and 31% improved at 3months after injection; improved urodynamic parameters	Multiple sclerosis patients with refractory DO	Prospective cohort study
Giannantoni *et al.*[32]	2011	8	100 U Botox®	100% of patients with decreased urinary frequency, and UI episodes, increased QoL scores and improved urodynamic findings	Patients with Parkinson's disease and refractory DO	Prospective cohort study
Herschorn *et al.*[33]	2011	57	300 U Botox® or placebo	57%-25% reduction in incontinence episodes frequency with Botox® vs. placebo at 6 and 36 weeks respectively; improved urodynamic and QoL parameters for treatment vs. placebo at week 6 and persisted to weeks 24 to 36	Spinal cord injury or multiple sclerosis patients and refractory DO	Multicenter prospective, randomized, double-blind, placebo-controlled trial
Khan *et al.*[34]	2011	137	300 U Botox®	76% of patients continent and 24% improved with increased QoL	Multiple sclerosis patients and refractory DO	Prospective cohort study
Chen *et al.*[35]	2011	38	200 U Botox®	60% of patients reported satisfactory response; significant improvements in QoL and increases of cystometric bladder capacity and post-void residual volume	Chronic suprasacral spinal cord injury patients and DO	Prospective cohort study
Chen *et al.*[36]	2011	108	300 U BTXA™ (Lanzhou Institute, Lanzhou, China)	64% continent and 29% improved; improved QoL and urodynamic parameters	Spinal cord injury patients and DO	Prospective cohort study
Wefer *et al.*[37]	2010	214	300 U Botox®	62% reduction in incontinence episodes; reduction of urinary tract infections episodes (>50%) per patient; urodynamic parameters improved	Spinal cord injury, myelomeningocele or multiple sclerosis patients and DO	Multicenter, cross-sectional, retrospective cohort study
Stoehrer *et al.*[38]	2009	216	Botox® 300 MU (mouse units) or Dysport® 750 MU	Incontinence and urodynamic parameters improved; no differences were noted between the two preparations; the effect was noted after 2 weeks and lasted for 9 months	Refractory NDO	Retrospective cohort study
Pannek *et al.*[39]	2009	27	300 U Botox®	74% long-term success rate for urinary incontinence by urodynamic and clinical criteria	Spinal cord injury patients and refractory DO	Retrospective cohort study
Ghalayini *et al.*[40]	2009	22	500 or 1000 U Dysport®	58%(60% for 1000 U) of patients were continent and the rest with atleast 50% reduction in leak episodes; improved urodynamic parameters and no statistically significant differences for the two treatment groups	NDO	Prospective cohort study
Giannantoni *et al.*[41]	2009	17	300 U Botox®	82% complete clinical and urodynamic urinary continence at one and three-year follow-up and 88% at six-year follow-up; improved urodynamic and QoL parameters	Spinal cord-injured patients with refractory DO	Prospective cohort study
Ehren *et al.*[42]	2007	31	500 U Dysport® or placebo	Cystometric capacity, maximum detrusor pressure, frequency of UI and QoL improved in the treatment group compared to placebo; decrease in anticholinergic medication in the treatment group	NDO	Prospective, randomized, double-blind, placebo-controlled trial
Schurch *et al.*[43]	2007	59	200 or 300 U Botox® or placebo	QoL improved in the treatment group compared to placebo	Spinal cord injury or multiple sclerosis patients and DO	Multicenter prospective, randomized, double-blind, placebo-controlled trial
Tow *et al.*[44]	2007	15	300 U Botox®	75% continent at 6 weeks; 50% dry at 39 weeks post treatment; 60% of patients were completely off medications at 6 and 26 weeks	Spinal cord-injured patients with refractory DO	Prospective cohort study

Table 1: Contd...

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Author	Year	N	Toxin dose	Outcome	Patient population	Study design
Karsenty *et al.*[45]	2006	17	300 U Botox®	The mean number of incontinence episodes per day decreased from 3 at baseline to 0 after the first injection, and remained at 0 after the last injection (mean number of injections per patient was 5); urodynamic parameters improved	NDO	Retrospective cohort study
Grosse *et al.*[46]	2005	66	300 U Botox® or 750 U Dysport®	Repeat injections are as effective as initial injections; the satisfaction was high and anticholinergics use decreased substantially	NDO	Prospective cohort study
Smith *et al.*[47]	2005	110	100 to 200 U Botox® into the external sphincter of urethra (42 patients) or 100-300 U into the bladder (68 patients)	67% of patients reported decreased or no incontinence; maximal efficacy occurred between 7 and 30 days and lasted for at least 6 months; decrease in both daytime and nighttime voiding symptoms; improved QoL	NDO	Prospective cohort study
Schurch *et al.*[48]	2005	59	200 or 300 U Botox® or placebo	Significant decrease in UI episodes in both treatment groups vs. placebo; improved QoL and urodynamic parameters; benefits were observed from the first evaluation at week 2 to the end of the 24-week study	Spinal cord injury or multiple sclerosis patients and DO	Prospective, randomized, placebo-controlled trial

DO = Detrusor Overactivity; NDO = Neurogenic Detrusor Overactivity; QoL = Quality of Life; UI = Urinary Incontinence

All patients underwent intra-detrusor injections (excluding the trigone) under cystoscopic guidance usually with 300 U Botox®. Between 42% and 87% of patients reported complete continence after treatment. Treatment with Botox® resulted in a 60-80% decrease in urinary incontinence (UI) episodes and a 40-60% decrease in urinary frequency complaints, as well as a 35-65% increase in quality of life measures. Urodynamic parameters demonstrated significant improvement on post-treatment testing: the mean maximum detrusor pressure decreased approximately 40-60% from baseline and the maximum cystometric capacity increased by 40% to 60% from baseline.

The largest study to date continues to be that by Reitz *et al.*[49] demonstrating complete resolution of NDO symptoms in 73% of patients after intra-detrusor Botox® and significant improvement in the remaining 27% of patients (total $N = 231$). All patients underwent cystoscopic intra-detrusor muscle injections with 300 U of Botox® at 30 different locations, while sparing the trigone. Urodynamic testing pre- and post-treatment demonstrated improved mean cystometric bladder capacity and mean reflex volume, while the mean voiding pressure decreased significantly. No injection related complications or toxin-related side effects were reported. Patients reported considerably reduced anticholinergic drug dose requirements and were satisfied with the treatment.

More recently, Wefer *et al.*[37] published a multi-center, cross-sectional, retrospective cohort study on 214 patients with NDO due to spinal cord injury, myelomeningocele, or multiple sclerosis. The mean dosage of Botox® was 291 ± 57 U with a mean number of 29 injections into the detrusor muscle per treatment. The mean maximum detrusor pressure, maximum cystometric capacity and detrusor compliance improved significantly after the treatment. Also, prior to therapy, 68% reported urinary tract infections, 63% had incontinence episodes, and 58% used incontinence aids. These numbers decreased with more than 50% after treatment.

In a recent prospective, double-blinded, randomized multicenter study, Hertschorn *et al.*[33] compared Botox® 300 U and placebo in 57 patients with NDO (secondary to spinal cord injury or multiple sclerosis) and UI despite anti-muscarinic treatment. They found that the mean daily frequency of UI episodes was significantly lower for treatment than for placebo at week 6, 24 and 36. Urodynamic and quality of life parameters for treatment vs. placebo were higher at week 6 and persisted to weeks 24 to 36. The most common adverse event in each group was urinary tract infection.

Allergan Pharmaceuticals (the manufacturer of Botox®) recently conducted two phase III clinical trials evaluating the safety and efficacy of Botox® as a treatment for DO associated with a neurologic condition such as multiple sclerosis or spinal cord injury.[7,50]

The two phase III multi-centered randomized controlled trials enrolled 691 participants with NDO due to spinal cord injury or multiple sclerosis refractory or intolerant to at least one anticholinergic medication. Patients were randomized

to receive either 200 U of Botox® (n = 227), 300 U of Botox® (n = 223), or placebo (n = 241). Both studies showed significant reductions in the frequency of UI episodes in patients treated with 200 U of Botox® compared to placebo. After two weeks the mean weekly frequency of UI episodes decreased with 15 in study 1 and 18 in study 2 in patients treated with Botox® injections vs. 10 and 8, respectively, in placebo patients. At six weeks after treatment, there were approximately 20 fewer UI episodes in treated patients vs. placebo (20 and 20 episodes/week vs. 11 and 11, respectively). Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. The decision to retreat the patients was based on loss of effect on incontinence episode frequency (50% of effect in study 1; 70% of effect in study 2). The median duration of response was 295-337 days (42-48 weeks) for the 200 U dose group compared to 96-127 days (13- 18 weeks) for placebo. The most frequently reported adverse reactions within 12 weeks of treatment included urinary tract infection (24%), urinary retention (17%), hematuria (4%), fatigue (4%), and insomnia (2%). Of note, an additional benefit of 300 U over 200 U was not demonstrated.[7]

Based on above findings, in August 2011 the FDA approved Botox® (on a botulinum toxin A) for the treatment of UI due to NDO in adults with symptoms refractory to or intolerant of an anticholinergic medications.[7] Stipulations on treatment include that patients be screened for acute urinary tract infection prior to treatment and receive prophylactic antibiotics (except aminoglycosides) 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment. No more than 200 U of Botox® per treatment should be injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The treatment could be repeated when the clinical effect of the previous injection diminishes, but no sooner than 12 weeks. Intra-detrusor injection of Botox® is contraindicated in patients with acute urinary tract infection, and in patients with chronic urinary retention who are not catheterized. FDA cautions regarding the increased incidence of autonomic dysreflexia after intradetrusor injections of Botox®, a condition that require prompt medical therapy. Also, the proportion of subjects who were not using intermittent catheterization prior to injection and who subsequently required catheterization for urinary retention following treatment with Botox® was higher compared with placebo (31% vs. 7% respectively). FDA recommends that in patients who are not catheterizing, PVR to be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks. Catheterization should be instituted if PVR urine volume exceeds 200 ml and continued until PVR falls below 200 ml. The most common side effects cited in the FDA document after Botox® 200 U (median duration of 44 weeks of exposure) were: urinary tract infections (49%), urinary retention (17%), fatigue (6%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), insomnia (3%), and muscle spasm (2%).

Although the initial studies were focused on patients with refractory NDO, an increasing number of recent studies have examined outcomes in IDO patients, the most common cause of DOI [Table 2]. The efficacy of botulinum A toxin for the treatment of IDO is the newest area of research in the lower urinary tract. In their prospective, randomized, double-blind, placebo-controlled trial, Denys *et al.*[51] demonstrated complete continence in 55% and 50% patients after 100 U and 150 U Botox® treatment, respectively, at 3 months. Also >50% improvement vs. baseline in urgency and urge urinary incontinence was observed in 65% and 56% of patients who respectively received 100 U and 150 U toxin injections and more than75% improvement in 40% of patients of both groups. The frequency symptoms and quality of life were significantly improved up to 6 months after treatment.

In their multicenter, randomized, placebo-controlled study Brubaker *et al.* compared 200 U intra-detrusor Botox® vs. placebo in 43 women with refractory idiopathic urge incontinence (RUBI trial).[56] They found that 60% of women in the therapeutic group had a clinical response based on the Patient Global Impression of Improvement with a duration of their responses of 373 days, significantly longer than the 62 days or less in the placebo group.

Recently, Rovner *et al.*[52] randomized 313 patients with OAB to double-blind intra-detrusor injection with placebo (n = 44) or 1 of 5 Botox® doses (50-300 U; n = 269). They found that at 12 weeks after treatment, 16% of placebo and 30-57% of 50-300 U toxin recipients, respectively, were continent. Changes from baseline in maximum cystometric capacity and volume at first involuntary detrusor contraction with Botox® ≥100 U were superior to placebo at week 12, generally decreasing by week 36. Their data suggested a dose-response relationship, however doses >150 U were more commonly associated with PVR >200 ml.

All these studies suggest that intra-detrusor injection of botulinum A toxin for the treatment of IDO is associated with significant subjective and objective improvements in refractory IDO. Therefore, it remains a highly effective and minimally invasive new option for patients unresponsive to other therapies. However, larger randomized controlled trials are needed to demonstrate the efficacy of botulinum A toxin for the treatment of IDO, resulting in this currently non-FDA–approved therapy being made safely available to all patients with IDO.

CONCLUSIONS

Botulinum toxin is a new therapy with multiple applications in a variety of medical specialties. In patients with OB refractory to anticholinergics it appears to be effective, long-lasting and repeatable. Injected into the detrusor muscle, botulinum A toxin is well tolerated with minimal risk of systemic side effects. However, future research must focus on the completion

Table 2: Studies examining the efficacy of intra-detrusor botulinum A toxin for the treatment of idiopathic detrusor overactivity (IDO) with or without incontinence refractory to conservative therapies (mixed gender, adult patients unless otherwise specified)

Author	Year	N	Toxin dose	Outcome	Patient population	Study design
Denys *et al.*[51]	2011	99	50 U, 100 U, 150 U Botox® or placebo	55% and 50% of patients continent and 65% and 56% of patients improved in urgency and UUI (>50% over baseline) after 100 U and 150 U respectively; frequency symptoms and QoL improved	Refractory IDO	Prospective, randomized, double-blind, placebo-controlled trial
Rovner *et al.*[52]	2011	313	50-300 U Botox® or placebo	30-57% of 50-300 U recipients were continent at 12 weeks vs. 16% of placebo; improved urodynamic parameters	Idiopathic OAB and UUI with or without DO	Prospective, randomized, double-blind, placebo-controlled trial
Lie *et al.*[53]	2010	19	200 U Botox®	81% of patients showed improvement in QoL scores; improvement in incontinence episodes and urodynamic parameters at 3 months	Refractory IDO	Prospective cohort study
Marte *et al.*[54]	2010	21	12.5 U/kg body weight (maximum 200 U) Botox®	38% of patients cured and 57% improved at 6 months; after the partial and non-responders received a second treatment, 76% were cured and 19% improved at 12 months; similarly, after the third injection, 85% were cured and 9.5% improved at 18 months	Children with IDO unresponsive to antimuscarinic agents	Prospective cohort study
Sahai *et al.*[55]	2009	34	200 U Botox® or placebo	Overall QoL was significantly improved in the treated patients compared with placebo for at least 24 weeks	Refractory IDO	Single center, prospective, randomized, double-blind, placebo-controlled trial
Brubaker *et al.*[56]	2008	43	200 U Botox® or placebo	60% of patients significantly improved; median duration of effect almost 12 months (62 days or less for placebo); 43% in the treated group with increased post-void residual volume; urinary tract infection in 75% of patients with increased post-void residual volume	Refractory IDO	Prospective, randomized, double-blind, placebo-controlled trial
Mohanty *et al.*[57]	2008	35	200 U Botox®	85.7% of patients showed improvement of frequency, urgency, nocturia, and incontinence within 1 week of injection (lasted for a mean period of 7 months); improved urodynamic parameters	Refractory IDO	Prospective cohort study
Jeffery *et al.*[58]	2007	25	500 U Dysport®	63% of patients were continent from 1 week after treatment and 32% were dry at 3 and 6 months; incontinence improved at 6 weeks and was sustained at 9 months	Refractory IDO	Prospective cohort study
Schmid *et al.*[59]	2006	100	100 U Botox®	86% of patients were continent and 82% with no urgency within 1 to 2 weeks post treatment; mean frequency and nocturia decreased; improved urodynamic parameters	Refractory IDO	Prospective cohort study
Werner *et al.*[60]	2005	26	100 U Botox®	69% subjective cure at 4 weeks and 80% at 12 weeks after treatment; improved QoL and urodynamic parameters	Refractory IDO	Prospective cohort study

IDO = Idiopathic Detrusor Overactivity; OAB = Overactive Bladder; QoL = Quality of Life; UUI = Urge Urinary Incontinence.

of well-planned randomized controlled trials to help establish standardized injection protocols and discern the optimal dose to achieve a durable response length. With further research, the use and role of botulinum toxin therapy will be clarified and established in patients with lower urinary tract symptoms not controlled with more traditional therapies.

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