Review Article

The role of botulinum toxin A in treating neurogenic bladder

Filip Weckx[1], Manuela Tutolo[1], Dirk De Ridder[1,2], Frank Van der Aa[1,2]

[1]Department of Urology, University Hospitals Leuven, Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium; [2]Department of Development and Regeneration, KU Leuven, Leuven, Belgium

Contributions: (I) Conception and design: F Weckx, F Van der Aa; (II) Administrative support: None; (III) Provision of study materials or patients: F Weckx, F Van der Aa; (IV) Collection and assembly of data: F Weckx; (V) Data analysis and interpretation: F Weckx, F Van der Aa; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Frank Van der Aa, MD, PhD. Department of Urology, University Hospitals Leuven, Campus Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. Email: frank.vanderaa@uzleuven.be.

Abstract: Neurogenic detrusor overactivity (NDO) can result in lower and upper urinary tract complications and eventually even in end-stage kidney failure. Since the driving force of this clinical cascade is high bladder pressure, controlling intravesical pressure in NDO patients improves both quality of life and life-expectancy in these patients. Botulinum toxin A (BTX-A) has proven its efficacy in reducing intravesical pressure and in reducing incontinence episodes. BTX-A also improves quality of life in patients with NDO. Both onabotulinumtoxinA (Botox®, Allergan, Irvine, USA) and abobotulinumtoxinA (Dysport®, Ipsen, Paris, France) have a level A recommendation for NDO-treatment. The recommended dose for intradetrusor injections in NDO patients is 200 U of onabotulinumtoxinA or 500 U of abobotulinumtoxinA. The drug is generally administered extratrigonal in the detrusor muscle, via cystoscopic guided injection at 20 sites in 1 mL injections. Intradetrusor BTX-A injections are safe, with mostly local complications such as urinary tract infection and high post-void residual or retention. The effect of the toxin lasts for approximately 9 months. Repeat injections can be performed without loss of efficacy. Different injection techniques, novel ways of BTX-A administration, eliminating the need for injection or new BTX-A types with better/longer response rates could change the field in the future.

Keywords: Botulinum toxin; neurogenic detrusor overactivity; onabotulinumtoxinA; abobotulinumtoxinA; neurogenic bladder

Submitted Oct 02, 2015. Accepted for publication Dec 29, 2015.
doi: 10.3978/j.issn.2223-4683.2016.01.10
View this article at: http://dx.doi.org/10.3978/j.issn.2223-4683.2016.01.10

What is botulinum toxin?

Working mechanism

Botulinum toxin A (BTX-A) as it is used today is a derivate of 1 (out of 7) subtype of the original neurotoxin produced by the bacteria Clostridium botulinum, the causative agent of botulism. Clostridium produces seven botulinum neurotoxin subtypes (A, B, C, D, E, F and G), from which types A, B, E and rarely F can cause human botulism. They are all large (150 KDa) proteins that consist of a light chain and a heavy chain. The differences between different types are located in the light chains. Injection of BTX-A in the detrusor muscle has an important direct effect on the motoric function of the urinary bladder, and an indirect effect on the sensory regulation of bladder function.

BTX-A inhibits acetylcholine exocytosis, the most important excitatory neurotransmitter in the bladder. To initiate normal voiding, parasympathetic postganglionic nerves release acetylcholine in the neuromuscular synapse. Acetylcholine then binds with the M2 and M3 muscarinic receptor in the detrusor muscle, leading to contraction (1).

BTX-A exerts its inhibition of exocytosis at the neural side of the neuromuscular junction by cleaving the soluble N-ethylmaleimide-sensitive factor attachment (SNARE) proteins at its light chain. These SNARE proteins play a key role in the fusion of the synaptic vesicles to the neuronal

cell membrane (2). When the vesicles cannot anchor to the cell membrane, no acetylcholine is shed into the synaptic cleft.

The other part of the BTX-A toxin, the heavy chain, facilitates entering of the toxin in the nerve cells via endocytosis (2).

The second effect of intradetrusor injections of BTX-A is via the afferent, sensory pathway. Afferent output from the bladder is normally conducted by myelinated Aδ-fibers that carry the signals to the higher brain regions. When these pathways are damaged by neurological disease, a spinal reflex arc consisting of small, unmyelinated C-fibers arises. This involuntary reflex arc leads to uncontrolled bladder contractions and neurogenic detrusor overactivity (NDO) (1,3). BTX-A injections reduces sensory receptor levels in the bladder suburothelium. In its turn, this may reduce the sensitivity of aberrant C-fibers to mechanical stimulation (4).

Different types

Currently, four different formulations of botulinum toxin, three BTX-A and one botulinum toxin B (BTX-B) are commercially available in Europe and the USA: onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, USA), abobotulinumtoxinA (Dysport®, Ipsen Limited, Paris, France), incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Raleigh, USA) and rimabotulinumtoxinB (Neurobloc/Myobloc®, Solstice Neurosciences Inc., San Francisco, USA). Adequate clinical data are available on both onabotulinumtoxinA and abobotulinumtoxinA as a treatment option for NDO. Therefore, only recommendations for these two formulations to treat NDO can be made (5). Both formulations have proven to be safe and effective. Depending on local health care authorities, both formulations can be used to treat NDO, but in many countries only onabotulinum toxin A is approved for use in NDO.

Studies comparing onabotulinumtoxinA and abobotulinumtoxinA in NDO patients are rare. Grosse *et al.* presented a small case control study in 56 patients with variable dosing that could only point out a significant difference in continence volume at three months (volume reported by the patient in the bladder diary at which he felt securely continent) with an advantage for 500–1,000 U of Dysport® compared to 300 U of Botox® (459 *vs.* 396 mL). At 9 months, no difference between the two formulations was noticed (6). The two toxins are not interchangeable and have different dosing (7). One small non-randomized cohort study in 26 patients suggested that in case of treatment failure at first injection, replacement of abobotulinumtoxinA by onabotulinum toxin can be effective (8).

No studies are available comparing different BTX types in the field of urology. Compared to BTX-A preparations, BTX-B formulations have a shorter effect, are more immunogenic and cause more pain when injected in hand muscles. BTX-F has the shortest duration of activity, which makes it a less desirable drug in the field of urology (9).

Both commercially available formulations of abobotulinum toxin and onabotulinum toxin contain human albumin to prevent the neurotoxin from adhering to the wall of the vial or syringe (10). Because of this, there is a theoretical risk of transmission of viruses. No such cases of transmission have been reported so far.

In the BTX-A formulation by Lanzhou Institute for Biological Products in Lanzhou, China, and distributed by Hugh Source in Hong Kong under several different brand names in different countries (Prosigne®, Lanzox®, Lantox®, Liftox®, and Redux®), no human albumin, but gelatin made from bovine skin is used, which increases the risk for allergy and anti-BTX-A antibody formation. In a small prospective non randomized single center cohort study (n=45) this toxin has been shown to be less effective compared to Botox® (Allergan) with an increase in maximum cystometric capacity of 42% compared to 103% (11).

Dosing

Different formulations of BTX-A have different dosing and are not easily interchangeable. It's generally accepted that a dosage of 200–300 U of onabotulinum toxin is comparable with 500–750 U of abobotulinum toxin (12). These are considered the optimal doses for intradetrusor injections in NDO (12-15). Both 750 U of abobotulinum toxin and 300 U of onabotulinum toxin have not shown better results compared to 500 U abobotulinum toxin or 200 U onabotulinum toxin respectively (12,16).

A conversion factor between onabotulinumtoxin and abobotulinumtoxin of 1:2.5 was suggested by Grosse *et al.* (17), however, this assumption was not scientifically proven. It's believed a variable conversion rate of the two toxins between 1:2 and 1:3 is applicable.

History of botulinum toxin treatment in neurogenic bladder disease

Botulinum neurotoxin was discovered and identified as

the cause of botulism in 1895 by van Ermengem (18). The first published urological application was detrusor-sphincter dyssynergia by Dykstra *et al.* (19). BTX-A was injected in the sphincter of 11 male patients with detrusor-sphincter dyssynergia (19). In 2000, Schurch *et al.* published the results of the first intradetrusor injections of onabotulinumtoxin A in 21 spinal cord injured patients. She reported decreased bladder pressure on urodynamic study, improved continence rates and decreased intake of anticholinergics (20). In August 2011 after the two Dignity studies, prospective RCTs including more than 1,000 patients, FDA approved Botox® for the treatment of NDO, more specifically "urinary incontinence due to detrusor overactivity associated with a neurological disease and refractory to oral medication".

Current position of botulinum toxin treatment

In the treatment algorithm

When it comes to management of incomplete bladder emptying, guidelines do not promote Crédé or Valsalva maneuvers because these may provoke high bladder pressure and weaken the pelvic floor. Triggered reflex voiding, for example by tapping of the abdomen, may also provoke high bladder pressure, so patients performing these techniques should be closely surveyed. Ideally, yearly monitoring of the urinary tract in these patients should be performed using serum creatinine, sonography and urodynamics. The standard of care for incomplete bladder emptying is intermittent (self) catheterization.

Anticholinergic therapy is generally considered first line treatment for NDO and storage symptoms. In meta-analysis, anticholinergics reduce intravesical pressure and incontinence episodes and increase bladder volume. Main side effects of anticholinergic therapy are dry mouth and constipation (21).

In case of insufficient control of detrusor overactivity despite a high dosage of anticholinergic therapy, $beta_3$-receptor agonists or phosphodiesterase inhibitors could be attractive adjuvant therapies, although they are currently off label for this indication (22). Alternative routes for administration of anticholinergic therapy (transdermal or intravesical) are proven to be equally effective and to have less systemic side effects (23,24).

When anticholinergic therapy is insufficient or comes with too many side effects, intradetrusor injections with BTX-A are recommended. BTX injection is recommended grade A in the EAU guidelines to be the most effective minimally invasive treatment to reduce NDO (22). These injections might increase post-void residual urine and might introduce the need for intermittent catheterization. In a recent large prospective RCT, including SCI and MS patients, roughly 90% of the SCI patients and 20% of the MS patients already performed CIC prior to the first BTX injection (15).

BTX-A treatment has proven its efficiency in reducing lower and upper urinary tract complications in both NDO (15) and detrusor sphincter dyssynergia patients (20). BTX-A administration significantly increases detrusor compliance both in SCI and MS patients (15).

If BTX-A injections are insufficient, a surgical approach should be considered. Both bladder augmentation and urinary diversion are successful treatment options for selected patients with absolute refractory NDO.

Efficacy

The main goals of NDO treatment are related to patient safety (protection of the upper urinary tract) and patients' quality of life (achievement of urinary continence). Intradetrusor BTX-A injections have proven to positively affect all of the above effectively for a mean period of 9 months (9-11,25-27).

Consequently, preservation of renal function by maintaining safe intradetrusor pressures is the main therapeutic goal in NDO patients. Systematic review of 18 articles showed a significant reduction in maximal intravesical pressure after BTX-A injections (25). The mean reduction in maximal detrusor pressure after BTX-A injections is approximately 40–60%, compared to baseline (25). Even existing vesico-ureteral reflux can disappear after BTX-A injections (28).

The RCT by Cruz *et al.* compared 275 patients in three groups: placebo, 200 and 300 U of onabotulinum toxin A (15). Compared to placebo (–13.2 episodes), both 200 U (–21.8 episodes) and 300 U (–19.4 episodes) had a significant effect on reduction of urge incontinence episodes per week. After injection of 200 and 300 U, respectively 38% and 39.6% of patients became fully continent. This study showed that maximal detrusor pressure during involuntary contractions decreased after onabotulinum toxin A compared to placebo (50 cmH_2O in placebo treated patients, 37.1 cmH_2O in the 200 U group and 30.4 cmH_2O in the 300 U group). Maximal cystometric capacity and detrusor compliance increased. An increased volume per void was measured.

Quality of life has been studied by Schurch *et al.* in a randomized, placebo-controlled, multicenter study using onabotulinumtoxinA 200 and 300 U in 59 patients with NDO with a significant improvement in I-QOL scores after 2, 6, 12 and 24 weeks (29).

Dose

The injections of both 200 and 300 U onabotulinum toxin are safe and effective. Cruz *et al.* (15) described a dose-ceiling effect for doses higher than 200 U: injection of more than 200 U does not increase the effect of the injection or the interval between injections. Side effects however are dose-related. Because injection of 300 U is more expensive, does not increase effect on storage complaints and causes more side effects (15,30), it is preferable to inject 200 U.

The only FDA approved dose and formulation for NDO is 200 U of Botox®. However injection of 200-300 U of Botox® and 500-750 U of Dysport® are common (12).

Each 100 U of Botox® should be dissolved in 10 mL saline. The toxin should be well solved; the best method is to inject 10 mL of saline in one flacon of 100 U of Botox® and shake this gently but thoroughly before aspirating the solution. When injecting 200 U, it's easiest to use two 10 mL syringes with both 100 U of Botox®. Varying volumes can be used.

The highest cumulative dose of Botox® studied by the FDA for limb spasticity disorders is 360 U in a 90-day interval (31). It is recommended not to exceed this dose, even when using Botox® for multiple indications since there seems to be a relationship between the dose of botulinum toxin and the risk to develop adverse effects (32).

When adverse effects such as retention in spontaneously voiding patients follow the first injection, one might consider to diminish the follow up dose of onabotulinum toxin to 100 U. In case of insufficient effect of a first 200 U of onabotulinum toxin, some clinicians will increase the dose to 300 U for following injections. The RCT by Cruz *et al.* does not support this upward dose titration (15). Both doses are off label and the patient should be adequately counseled prior to deviate from the standard, labeled dose.

Although the maximal cumulative dose of 360 U of onabotulinum toxin in 90 days is recommended, a study describing 13 patients treated with higher doses (400–1,900 U), did not report any life-threatening events in a follow-up period of 6 to 108 months (31). However, local and generalized adverse effects were reported in four patients.

On the other hand, some case reports (33-35) escribe life-threatening events after normal doses of BTX-A injections in a non-urological setting; caution is recommended and, again, deviation from the standard dose should not be done routinely or without serious consideration of possible consequences and other treatment modalities.

Injection technique

It is standard practice to perform 20 injections of 200 U onabotulinumtoxinA in the detrusor muscle sparing the trigone.

Currently there are limited data comparing different techniques. To our knowledge, no data are available comparing intradetrusor, suburothelial and bladder base injections in neurogenic patients. In 45 non neurogenic patients with idiopathic OAB, a success-rate of 93% for intradetrusor, 80% for suburothelial and 67% for bladder base injections after three months was achieved (36). Subjectively, all groups had less urgency complaints after injection, although bladder capacity and post-void residual volume did not rise in the bladder base injection group.

In a pilot study in neurogenic patients (n=23) no differences in efficacy were found between the intradetrusor and suburothelial groups after injection of 300 U onabotulinumtoxinA (37). Given the small amount of patients involved in the study, more research is required.

It is common practice to inject only the extratrigonal part of the bladder because intratrigonal injections can theoretically cause vesico-ureteral reflux. The trigone of the bladder has a prominent submucosal nerve plexus. Since this plexus serves mainly sensory purposes, intratrigonal injections could cause more damage to the sensory nerve endings in theory (36).

Two small studies compared intra- and extra-trigonal BTX-A injections respectively in 21 neurogenic and in 22 non neurogenic patients. They showed that the intratrigonal injection was not associated with vesico-urethral reflux, or with increased post-void residual or increased need for self-catheterization in comparison to extratrigonal injections (38,39). For IDO patients it was even concluded that the intratrigonal injections were more efficient in controlling OAB complaints (40). Abdel-Meguid reported an increased efficacy of including the trigone when injecting spinal cord injured patients suffering from refractory NDO. He prospectively compared onabotulinumtoxinA 300 U intradetrusor with 200 U intradetrusor plus 100 intratrigonal in 36 patients (41).

The popularity of the toxin has raised the interest to

find the optimal injection technique. A ultrafine needle (22–27 gauge, 4 mm in length) is recommended in literature (38,39,42). A stopper helps in preventing bladder perforation. It has also a function in reducing leakage to the bladder lumen or extravesical tissues (39).

A PubMed literature search and a survey of thirteen experts out of ten countries agreed about the following features to be important for a needle (42): for the expert survey, questionnaires were used.

- A stopper to avoid leakage and bladder wall perforation;
- Easy to inject;
- Low cost;
- Easy penetration of the bladder wall; sharpness;
- Avoiding bleeding;
- Low risk of injection pain;
- No damage to cystoscope;
- Flexible shaft to allow better tactile feel;
- Good connection with syringe.

Most papers agree that BTX-A should be distributed over 20–30 injection sites in patients with NDO. In 2009 a consensus panel agreed that every 100 U of onabotulinum toxin A should be diluted in 10 mL of saline. This solution should be infiltrated at 1 mL/site. Following this recommendation 200 U of onabotulinum toxin A should be infiltrated in 20 sites and 300 U in 30 sites. Recently Liao *et al.* proved that injection of 100 U of onabotulinum toxin A in 10, 20 or 40 sites did not influence efficacy of complication rate in 67 patients with both neurogenic and non-neurogenic storage symptoms (43). No significant differences in urodynamics, symptoms or quality of life parameters have been found in open-label and placebo-controlled studies comparing flexible and rigid cystoscope injection (14). Some experimental evidence is available, advocating that infiltration of onabotulinumtoxinA in fewer injection sites can result in adequate spread throughout the bladder (44). Also, higher volumes of solution (so more diluted) would result in a better spread throughout the bladder (44).

Setting

To our knowledge, no studies are available comparing local versus general or regional anesthetics when it comes to BTX-A infiltrations. Both methods are common practice and considered safe (45). There is no reason to believe that there is a difference in efficacy or safety. When it comes to local anesthetics, mostly lidocaine 2% instillations are used [50 mL for 10–30 min (42)]. When using local anesthetics, a flexible cystoscope is preferred for injection in male patients. In its approval, the FDA did not implement any restrictions as to the type of scope or anesthesia. Major factors in this choice are the patient's preferences the surgeon's experience and the organization of the healthcare system.

It has been shown that BTX-A injections can be safely performed in an outpatient setting (45). A study in 64 patients of which 21 were treated in an inpatient setting, and 43 in an outpatient setting did not show any disadvantages for the outpatient treated patients (45). To our knowledge, no data are available comparing efficacy between in- and outpatient treated patients.

Safety

Intradetrusor BTX-A injections are considered a safe therapy for NDO. Serious adverse effects are extremely rare. Patients should be informed about the risk of high post-void residuals or retention with potential need of self-catheterisation, (mild) hematuria and urinary tract infection. Although extremely rare, patients should be informed to consult a doctor quickly when difficulties speaking, breathing or swallowing occur. This could be a sign of central effects of the neurotoxin. Because of insufficient data in pregnant or breastfeeding patients, usage of BTX-A injections in these populations is not recommended.

In a study with 42 patients (17 spinal cord injury, 14 multiple sclerosis, all performing CIC), up to 7.1% of patients developed a symptomatic urinary tract infection 1 week after injections when no antibiotics were administered post-operatively (46). Two patients developed fever (4.7%). Asymptomatic bacteriuria combined with pyuria (>10 WBC/high power field) is even more frequent (31%) (47). Based on a recent meta-analysis of 1,049 patients, the relative risk for UTI is 1.48 (95% CI, 1.2–1.81) (48).

Antibiotic prophylaxis is recommended (46). As an example, nitrofurantoin 100 mg, twice daily could be used for ten days after the injections.

High post-void residuals (50%) and retention (23.7%) are relatively frequent (47). Because of the high risk for infection, CIC might be necessary. It's important to realize a lot of NDO-patients already perform CIC prior to BTX-A therapy. In the RCT of Ginsberg *et al.*, 84.8% of spinal cord injured patients performed CIC, compared to 29.4% of multiple sclerosis patients (30). In these patients counseling for catheterization before treatment is therefore even more important. Assessment of the general condition, hand function and mobility of the patients should be performed

prior to the first injection and before repeat injections in case of progression of the neurological disease.

Hematuria is mostly mild and placement of a (rinsing) catheter is rarely necessary if the patient is not taking anti-coagulant or anti-aggregate medication. These medications can be stopped temporarily when performing an injection, although acetylsalicylic acid 80 mg in monotherapy can be continued. Whenever a rinsing catheter has to be placed because of macroscopic hematuria, it can generally be removed the very same day. After BTX injections the relative risk for hematuria is 1.81 (95% CI, 1.00–3.24) (48).

Other rare (<5%) side effects are nausea, vomitus and flu-like symptoms, depression, muscle spasm, constipation, muscle weakness, insomnia, dizziness, diarrhea and *de novo* autonomic dysreflexia.

BTX-A injections should not be performed in patients with an active urinary tract infection. In this case, antibiotic treatment should be prescribed. Patients performing CIC are prone to develop urinary tract infections. In these patients, it's recommended to perform a urinary culture a couple of days before the BTX injections and choose an antibiotic prophylaxis based on the anti-biogram. Also patients diagnosed with a general muscle disorder such as myasthenia gravis, Eaton Lambert or amyloid lateral sclerosis should not receive BTX-A injections. Patients with an allergy to BTX-A or one of the formulations components should obviously avoid these products. As stated before, the possibility of CIC should be discussed with the patient upfront. A priori refusal of possible catheterization is a relative contra-indication for intradetrusor BTX-A injections.

No life threatening adverse effects have been reported after BTX-A injections for urological use. Some case reports (nine patients) have reported dysphagia (potentially leading to aspiration) and paralysis of respiratory musculature (potentially leading to intubation and ventilation) after administrations for non-urological purposes (33-35).

Follow-up and repeat injections

Since the effect of BTX-A injections is noticeable after one week, a first check-up with measurement of the post-voiding residual is recommended after 7–10 days in spontaneously voiding patients. In case of high PVR, CIC might be necessary (depending on the amount of residual urine and the presence of symptoms). A second check-up to evaluate the efficacy of the injections is recommended after 2–3 months. Patients who received multiple injections will be able to diagnose themselves when the effect of the toxin is decreasing, so they can be asked to make an appointment for new injections themselves. The interval between repeat injections appears to be relatively constant in a single patient, after initial reduction in the time to patient request for repeat treatment (49). For less experienced patients, closer follow-up is recommended. BTX-A-injections cause a muscle relaxation for approximately 9 months (10,16,25,26).

An open label study by Kennelly *et al.* studied the effect, adverse events and continuation rates of NDO patients (49). A relatively high discontinuation rate after the first few injections was noticed, with only 49 of the initial 387 patients undergoing a fifth injection. This might seem remarkable since the reduction in incontinence episodes rises (from −22.7 to −31.9 episodes/week) and the infection rate diminishes (58% to 20%) with repeat injections. An explanation is selection bias, since patients with insufficient effect or too many adverse events tend to end therapy earlier.

Some studies describe a phenomenon called "secondary failure". This term is used for patients who responded well to the first injection(s), but eventually had very limited benefit after subsequent injections. Secondary failure has been reported by a small (n=31) study by Gaillet *et al.*, in which 7% of patients stopped therapy because of secondary failure (50). This phenomenon, however, is inconsistently reported in literature; some studies show a stable or even improved efficacy with increasing numbers of injections. The EAU-guidelines state, based on two RCTs (n=275, n=66), that subsequent onabotulinum A injections retain their efficacy (17,18,28,37). Several hypotheses about secondary failure have been postulated. Underlying immunological mechanism (anti BTX-A antibodies) or a technical issue with subsequent injections (less adequate delivery) could cause secondary failure. Therefore, one repeat injection at least 3 months after the failed injection should be performed in patients with secondary failure. Neurogenic patients with progressive disease (such as MS) may also experience a rise in their NDO symptoms due to progression of their underlying neurological disorder.

Studies have confirmed the presence of BTX-A antibodies and their relationship with therapy failure. A small study (n=31) showed that positive antibody titers are associated with therapy failure (5/5 patients) (51). A borderline titer might be associated with therapy failure (33%). Patients without antibodies did not experience therapy failure. Further data are required to confirm this hypothesis.

Future developments

Alternative administration routes

Preliminary results have been published on liposome enucleated BTX-A instillations. Liposomes are artificially created particles consisting of a double phospholipid outer layer, and a liquid center. Since phospholipid layers are the main structures in the human cellular membrane, liposomes have the ability to fuse with the cellular membrane and deliver the central liquid intracellular. Liposomes have the ability to carry BTX-A across the urothelial bladder, with successful SNARE-cleavage as a result in rats (52).

In a pilot study of 24 patients, liposome enucleated BTX-A has proven to effectively reduce urgency and frequency in patients with idiopathic overactive bladder (53). A two center double blind RCT with 62 patients with idiopathic overactive bladder, the liposome enucleated BTX-A did not cause urinary tract infection or high (>150 cc) post-void residual.

No data are available for NDO patients. Hence, further research on the subject is required.

New types of botulinum toxin

As discussed above antibody formation in BTX-A naïve patients may contribute to secondary therapy failure. As a consequence, research was performed to develop a less immunogenic type of BTX.

Xeomin® (incobotulinumtoxinA) is produced to be a less immunogenic type of BTX. During its production complexing proteins are removed by chromatography. Therefore the human immune system should be triggered less after injection, resulting in fewer patients producing anti-BTX antibodies. In phase III and IV trials for blepharospasm (n=300) and cervical dystonia (n=463), no cases of *de novo* antibody formation were registered (54).

Currently Xeomin is only registered for treatment of blepharospasm, spasmodic torticollis and upper limb spasms after ischemic brain injury. No studies in the field of urology are available.

Also, longer-term data from a large number of patients are required to further explore the immunogenic potential of incobotulinumtoxinA (54).

Acknowledgements

None.

Footnote

Conflicts of Interest: F Van der Aa has received institutional research grants from Allergan, Astellas and Ipsen. The other authors have no conflicts of interest to declare.

References

1. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci 2008;9:453-66.
2. Aoki KR, Guyer B. Botulinum toxin type A and other botulinum toxin serotypes: a comparative review of biochemical and pharmacological actions. Eur J Neurol 2001;8 Suppl 5:21-9.
3. Tanagho EA, McAninch JW, editors. Smith's General Urology. 17th ed. New York: The McGraw-Hill Companies, Inc., 2008,438–53.
4. Sellers DJ, McKay N. Developments in the pharmacotherapy of the overactive bladder. Curr Opin Urol 2007;17:223-30.
5. Chancellor MB, Elovic E, Esquenazi A, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of urologic conditions. Toxicon 2013;67:129-40.
6. Grosse J, Kramer G, Jakse G. Comparing two types of botulinum-A toxin detrusor injections in patients with severe neurogenic detrusor overactivity: a case-control study. BJU Int 2009;104:651-6.
7. Mangera A, Andersson KE, Apostolidis A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol 2011;60:784-95.
8. Peyronnet B, Roumiguié M, Castel-Lacanal E, et al. Preliminary results of botulinum toxin A switch after first detrusor injection failure as a treatment of neurogenic detrusor overactivity. Neurourol Urodyn 2014. [Epub ahead of print].
9. Eleopra R, Tugnoli V, Quatrale R, et al. Different types of botulinum toxin in humans. Mov Disord 2004;19 Suppl 8:S53-9.
10. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. J Clin Aesthet Dermatol 2014;7:31-9.
11. Gomes CM, Castro Filho JE, Rejowski RF, et al. Experience with different botulinum toxins for the treatment of refractory neurogenic detrusor overactivity. Int Braz J Urol 2010;36:66-74.

12. Grise P, Ruffion A, Denys P, et al. Efficacy and tolerability of botulinum toxin type A in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: comparison of two doses. Eur Urol 2010;58:759-66.
13. Ehren I, Volz D, Farrelly E, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: a randomised, placebo-controlled, double-blind study. Scand J Urol Nephrol 2007;41:335-40.
14. Schurch B, de Sèze M, Denys P, et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol 2005;174:196-200.
15. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol 2011;60:742-50.
16. Mohee A, Khan A, Harris N, et al. Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). BJU Int 2013;111:106-13.
17. Grosse J, Kramer G, Stöhrer M. Success of repeat detrusor injections of botulinum a toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol 2005;47:653-9.
18. Erbguth FJ. Historical notes on botulism, Clostridium botulinum, botulinum toxin, and the idea of the therapeutic use of the toxin. Mov Disord 2004;19 Suppl 8:S2-6.
19. Dykstra DD, Sidi AA, Scott AB, et al. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol 1988;139:919-22.
20. Schurch B, Stöhrer M, Kramer G, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol 2000;164:692-7.
21. Madhuvrata P, Singh M, Hasafa Z, et al. Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. Eur Urol 2012;62:816-30.
22. Blok B, Panek J, Castro Diaz D, et al. Guidelines on neuro-urology. Available online: http://uroweb.org/wp-content/uploads/21-Neuro-Urology_LR2.pdf
23. Schröder A, Albrecht U, Schnitker J, et al. Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial. Neurourol Urodyn 2015. [Epub ahead of print].
24. Rovner E, Kennelly M, Schulte-Baukloh H, et al. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. Neurourol Urodyn 2011;30:556-62.
25. Karsenty G, Denys P, Amarenco G, et al. Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. Eur Urol 2008;53:275-87.
26. Reitz A, Stöhrer M, Kramer G, 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;45:510-5.
27. Dorsher PT, McIntosh PM. Neurogenic bladder. Adv Urol 2012;2012:816274.
28. Del Popolo G, Filocamo MT, Li Marzi V, et al. Neurogenic detrusor overactivity treated with english botulinum toxin a: 8-year experience of one single centre. Eur Urol 2008;53:1013-19.
29. Schurch B, Denys P, Kozma CM, et al. Botulinum toxin A improves the quality of life of patients with neurogenic urinary incontinence. Eur Urol 2007;52:850-8.
30. Ginsberg D, Cruz F, Herschorn S, et al. OnabotulinumtoxinA is effective in patients with urinary incontinence due to neurogenic detrusor overactivity [corrected] regardless of concomitant anticholinergic use or neurologic etiology. Adv Ther 2013;30:819-33.
31. Nuanthaisong U, Abraham N, Goldman HB. Incidence of adverse events after high doses of onabotulinumtoxinA for multiple indications. Urology 2014;84:1044-8.
32. Coté TR, Mohan A, Polder J, et al. Botulinum toxin type A injections: Adverse events reported tot he US Food and Drug Administration in therapeutic and cosmetic sases. J Am Acad Dermatol 2005;53:407-15.
33. Coban A, Matur Z, Hanagasi HA, et al. Iatrogenic botulism after botulinum toxin type A injections. Clin Neuropharmacol 2010;33:158-60.
34. Ghasemi M, Norouzi R, Salari M, et al. Iatrogenic botulism after the therapeutic use of botulinum toxin-A: a case report and review of the literature. Clin Neuropharmacol 2012;35:254-7.
35. Chertow DS, Tan ET, Maslanka SE, et al. Botulism in 4 adults following cosmetic injections with an unlicensed, highly concentrated botulinum preparation. JAMA

2006;296:2476-9.
36. Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. J Urol 2007;178:1359-63.
37. Šámal V, Mečl J, Šrám J. Submucosal administration of onabotulinumtoxinA in the treatment of neurogenic detrusor overactivity: pilot single-centre experience and comparison with standard injection into the detrusor. Urol Int 2013;91:423-8.
38. Apostolidis A, Dasgupta P, Denys P, et al. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. Eur Urol 2009;55:100-19.
39. Dasgupta P. Volume matters: bladder injections of botulinum toxin type A. Eur Urol 2012;61:1185-6; discussion 1886-7.
40. Manecksha RP, Cullen IM, Ahmad S, et al. Prospective randomised controlled trial comparing trigone-sparing versus trigone-including intradetrusor injection of abobotulinumtoxinA for refractory idiopathic detrusor overactivity. Eur Urol 2012;61:928-35.
41. Abdel-Meguid TA. Botulinum toxin-A injections into neurogenic overactive bladder--to include or exclude the trigone? A prospective, randomized, controlled trial. J Urol 2010;184:2423-8.
42. Karsenty G, Baverstock R, Carlson K, et al. Technical aspects of botulinum toxin type A injection in the bladder to treat urinary incontinence: reviewing the procedure. Int J Clin Pract 2014;68:731-42.
43. Liao CH, Chen SF, Kuo HC. Different number of intravesical onabotulinumtoxinA injections for patients with refractory detrusor overactivity do not affect treatment outcome: A prospective randomized comparative study. Neurourol Urodyn 2015;10:1002.
44. Coelho A, Cruz F, Cruz CD, et al. Spread of onabotulinumtoxinA after bladder injection. Experimental study using the distribution of cleaved SNAP-25 as the marker of the toxin action. Eur Urol 2012;61:1178-84.
45. Giannantoni A, Proietti S, Costantini E, et al. OnabotulinumtoxinA intravesical treatment in patients affected by overactive bladder syndrome: best practice in real-life management. Urologia 2015;82:179-83.
46. Mouttalib S, Khan S, Castel-Lacanal E, et al. Risk of urinary tract infection after detrusor botulinum toxin A injections for refractory neurogenic detrusor overactivity in patients with no antibiotic treatment. BJU Int 2010;106:1677-80.
47. Soljanik I. Efficacy and safety of botulinum toxin A intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic review. Drugs 2013;73:1055-66.
48. Zhou X, Yan HL, Cui YS, et al. Efficacy and safety of onabotulinumtoxinA in treating neurogenic detrusor overactivity: a systematic review and meta-analysis. Chin Med J (Engl) 2015;128:963-8.
49. Kennelly M, Dmochowski R, Ethans K, et al. Long-term efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: an interim analysis. Urology 2013;81:491-7.
50. Gaillet S, Bardot P, Bernuz B, et al. Five years follow-up study and failures analysis of Botulinum toxin repeated injections in treatment of detrusor overactivity. Prog Urol 2012; 22:1064-70.
51. Hegele A, Frohme C, Varga Z, et al. Antibodies after botulinum toxin A injection into musculus detrusor vesicae: incidence and clinical relevance. Urol Int 2011;87:439-44.
52. Chuang YC, Tyagi P, Huang CC, et al. Urodynamic and immunohistochemical evaluation of intravesical botulinum toxin A delivery using liposomes. J Urol 2009;182:786-92.
53. Kuo HC, Liu HT, Chuang YC, et al. Pilot study of liposome-encapsulated onabotulinumtoxina for patients with overactive bladder: a single-center study. Eur Urol 2014;65:1117-24.
54. Jost WH, Benecke R, Hauschke D, et al. Clinical and pharmacological properties of incobotulinumtoxinA and its use in neurological disorders. Drug Des Devel Ther 2015;9:1913-26.

Cite this article as: Weckx F, Tutolo M, De Ridder D, Van der Aa F. The role of botulinum toxin A in treating neurogenic bladder. Transl Androl Urol 2016;5(1):63-71. doi: 10.3978/j.issn.2223-4683.2016.01.10

