REVIEW

Botulinum neurotoxin A for overactive bladder treatment: advantages and pitfalls

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Introduction: *Overactive bladder (OAB) syndrome is a special condition characterized by urgency, with or without urinary urge incontinence (UUI), associated to frequency and nocturia, with important consequences on patients' quality of life (QoL). Administered as intradetrusor injections, botulinum neurotoxin type A (BoNT/A) is a new, promising, minimally invasive treatment option for OAB patients, non-compliant to conventional antimuscarinics. The aim of our study was to perform a systematic review of the literature concerning the efficiency and safety of different BoNT/A products in the treatment of OAB.*

Materials and methods: *A thorough PubMed search was performed. After having applied strict inclusion criteria, relevant articles were selected for review. Priority was given to large, multicenter, placebo-controlled trials and systematic reviews.*

Results: *Most of the eligible studies were centered around onabotulinumtoxin A (Botox), with treatment doses ranging from 50 U to 300 U. An increased efficiency of onabotulinumtoxin A was found for both OAB types, clinically resulting in a significant decrease in UUI episodes, improved urodynamic parameters and patient QoL. The most common adverse events were urinary tract infections and an increased post-void residue, with the necessity for clean intermittent self catheterization. Abobotulinumtoxin A (Dysport) obtained similar results, but with a much smaller number of trials available to date.*

Conclusion: *Onabotulinumtoxin A is a promising, efficient, minimally invasive approach to OAB patients with official recommendations for both OAB types, offering large perspectives in daily urological practice. Abobotulinumtoxin A revealed similar results to onabotulinumtoxin A, making it a valid therapeutic alternative.*

Key Words: abobotulinumtoxin A, botulinum neurotoxin A, overactive, bladder, neurogenic, idiopathic, onabotulinumtoxin A

Introduction

Overactive bladder (OAB) syndrome is a condition defined by the International Continence Society as urgency, with or without urgency incontinence, associated to frequency and nocturia in the absence of infection or other obvious disease.[1,2]

OAB symptoms are generally perceived as embarrassing and exert influence over the patient's quality of life (QoL), work productivity, mental health and sleep quality.[3] The prevalence of OAB was reported at values of 11.8% by dedicated observational studies such as the EPIC study, a large multi-center survey performed in four European Countries and Canada.[3]

Based on its etiology, OAB can be classified as neurogenic, when associated with an underlying neurologic disorder (like multiple sclerosis and spinal trauma), or idiopathic, in the absence of a clear etiologic factor. OAB diagnosis is set using clinical data (specific signs and symptoms, medical history, physical exam), voiding patterns (obtained from voiding diaries and questionnaires) and urodynamic studies. In some patients, it is associated to detrusor overactivity (DO), a series of uninhibited detrusor contractions that appear in the filling phase of an urodynamic study. According to its etiology, DO can also be classified as neurogenic or idiopathic. However, these two notions (OAB and DO) are not interchangeable as there are patients with OAB symptoms that show no DO.[1]

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First intention treatment for OAB consists in lifestyle changes (weight loss, decrease in alcohol and coffee intake) and pharmacotherapy using antimuscarinic drugs.[2] Although antimuscarinics' efficiency has been demonstrated for the treatment of OAB, patients' tolerance to these drugs largely varies according to the different product that is administered. There is a large array of potential side effects (dry mouth, constipation, impaired vision, severe cardiac effects - QT prolongation) that can be associated to antimuscarinic therapy leading to poor tolerance and the majority of dropout cases.[2,4]

An alternative for antimuscarinics are intradetrusor injections using botulinum neurotoxins, particularly the type A botulinum neurotoxin (BoNT/A) that have been recently considered as second line treatment options for OAB, with positive results.[5,6]

The aim of our study was to perform a systematic review of the literature concerning the history, structure, mechanism of action, efficiency and safety of BoNT/A products for both neurogenic and idiopathic OAB treatment.

Material and methods

We performed a thorough PubMed search using the following keywords: overactive bladder, botulinum toxin A, abobotulinumtoxin A, onabotulinumtoxin A, Botox, Dysport. Using the "AND" connector, these keywords were combined in sequence with the following: overactive bladder, overactive bladder syndrome, OAB, idiopathic overactive bladder, neurogenic overactive bladder.

Our search returned a series of 4336 articles for "overactive bladder" and 6186 articles for "botulinum toxin A". In association, the search found 329 common articles for these search terms. Restricting to clinical trials, a series of 69 articles was found. The other terms returned similar results.

A series of filters were applied. Articles were limited to clinical trials and reviews, written in English or French and published in the last 5 years. The lot was subjected to a series of strict inclusion and exclusion criteria. Reviews had to be systematic, well documented, with recent studies included and a proper methodology. For clinical trials, priority was given to large, multi-center, randomized controlled trials. Regulatory studies, with their uniform methodology and specific treatment protocol in terms of volumes and injections (essential for approval from government agencies), represented most of our reference studies. Series of cases and case reports were considered only if they would have a contributive role to our review.

The resulting list was analyzed in terms of titles and abstracts (83 articles). Articles with inconclusive abstracts or studies performed on less than 30 patients were discarded. Where available, full-text versions were analyzed and processed for the remaining lot.

A comparison was performed between different trials concerning their outcomes, selection protocols, injection protocol, follow up period and adverse events.

Results and discussion

History: discovery and emerging clinical applications

A disease known from the ancient times, botulism is caused by botulinum toxin ingestion in humans, a product of the bacillus clostridium botulinum. It is characterized clinically by specific signs and symptoms: muscle weakness, mydriasis, intestinal and bladder paralysis and progressive skeletal muscle paralysis that can evolve towards respiratory muscle paralysis and death.[7]

Records of botulism are scarce until the late 18th century when the German physician and romantic poet Justinus Kerner described the disease clinically. At that time, a possible theory on its physiopathology and epidemiology was launched, the author suspecting a food-borne disease ("sausage poisoning").[7]

Structure and function

There are seven types of botulinum toxins (A-G) sharing the same mechanism of action: blocking acetylcholine exocytosis from the presinaptic neuron in the neuromuscular junction. For the moment being, only the A and B types are available for clinical use.[8]

BoNT/A is synthesized as a biologically inactive single-strand polypeptide (150kDa), that is activated by proteolytic cleavage into a 100kDa heavy chain and a 50kDa light chain, linked by a disulfide bond. The heavy chain facilitates BoNT binding to neurons in the peripheral nervous system and protrusion in the neuronal cytoplasm. The light chain contributes to the cleavage of proteins responsible for transporting acethycholine vesicles to the sinaptic cleft (SNARE protein complex).[6,9] This effect on the terminal nerve is fully reversible and does not lead to neurodegeneration. After the BoNT-imposed blockade, sprouts emerge from the motor neuron, aiming to replace the impaired connections. Using specific staining methods, de Paiva et al found motor impulse transmission only in these sprouts at 30 days after the blockade. They suggested that the sprouts were the only structures assuring motor activity following intoxication.[10] Sprouting is considered to be stimulated by a series of factors like

calcium influx in the nerve, growth factors and even perisynaptic Schwann cells.[11]

BoNT is also considered to have off-site effects. An ability for transcytosis and retrograde axonal transport was suggested, resulting in a possible pathway for central nervous system access. Several animal studies demonstrated that this mechanism could have explained the antinociceptive ability of BoNT. Good results were obtained on neuropathic pain in diabetic animals that was relieved after BoNT/A administration. In such studies, Bach-Rojecky et al obtained faster analgesia in intratechal (24 h) than in subcutaneous administration (5 days), therefore supporting the retrograde transport theory.[9,12]

Commercially, BoNT/A is available as several pre-toxin products, according to the different purification processes and vendors. The first issued product was onabotulinumtoxin A (Botox- Allergan, Irvine, CA, USA), followed by abobotulinumtoxin A (Dysport- Ipsen, Slough, Berkshire, UK) and incobotulinumtoxin A (Xeomin-Merz Pharmaceuticals, Germany). The only commercially available B-type toxin is rimabotulinumtoxin B (Myobloc- Solstice Neurosciences, LLC, USA).[5,6]

Each product has an unique dosing profile and molecular structure. This is reflected in terms of clinical potency, both in intensity and duration of the therapeutic effect. Dosage is performed using units specific for each product. Thus, these units of biological activity are not equivalent between products, they cannot be inter-converted and the products are not interchangeable.[6,8]

BoNT/A in medicine

The first medical use of botulinum neurotoxin Type A (BoNT/A) was recorded in 1973 when Alan Scott, an ophthalmologist, looked for a non-surgical remedy for strabismus. He performed animal experiments (BoNT/A injections in the striated ocular muscles of laboratory animals) and obtained favorable results which were later applied to human subjects. This was the turning point that introduced BoNT/A for the treatment of diseases characterized by excessive muscular tone. In 1989, the FDA approved the drug for the treatment of benign blepharospasm, strabismus and troubles of the VIIth nerve. It was later extended to gastrointestinal, orthopedic, dermatological, secretory and cosmetic disorders.[8]

In urology, Dykstra et al published in 1988 the first clinical trial on BoNT/A use in detrusor-sphincter dissinergia. The study assessed the efficiency of onabotulinumtoxin A injections in neurologic patients with detrusor-sphincter dissinergia and obtained a decrease in post-void residue (PVR) for eight patients with a lasting effect of 50 days.[13]

In OAB, the first published study using BoNT/A was performed by Schurch et al on onabotulinumtoxin A use at different doses (200 U and 300 U) in neurogenic OAB patients. They reported that 300 U would be the necessary dose of onabotulinumtoxinA for adequate OAB management.[14]

BoNT/A in neurogenic OAB (including neurogenic DO)

Cruz et al performed a randomized, double-blind, placebo-controlled, dose-ranging, regulatory trial and assessed the outcomes of placebo, 200 U and 300 U of onabotulinumtoxin A in neurogenic DO treatment. At baseline, all patients reported a mean of 33.5 UUI episodes/week. At week 6, a decrease in UUI episodes was found in BoNT/A patients belonging to both dose groups (-21.8 for 200 U and -19.4 for 300 U compared to -13.4 placebo, $p < 0.01$). At the same time point, complete continence was present in 7.6%, 38% and 39.6% of patients using placebo, 200 U and 300 U, respectively. Significant improvements in urodynamic parameters (maximum cystometric capacity - MCC, maximum detrussor pressure - pDetMax) was also found but with no statistically significant difference between the two doses. Patient QoL improved significantly at week 6, with a 24-point increase in both BoNT/A groups when compared to placebo (11.7). The median duration of the effect was 42.1 weeks for both BoNT/A groups, significantly longer than placebo (13.1 weeks, $p < 0.01$). Re-treatment was possible for BoNT/A patients responsive in cycle 1, with positive results.[15]

Herschorn et al performed a similar regulatory study on multiple sclerosis and spinal cord injury patients suffering from neurogenic DO, with more than 1 UUI episode/day on current antimuscarinic treatment. Onabotulinumtoxin A was initiated at 300 U in a trigone-sparing injection pattern with gradual re-initiation of antimuscarinic therapy after the 3rd week. At week 6, a significant decrease in daily UUI episodes was reported, (baseline: 3.06 ± 1.69/4.03 ± 2.36 versus 1.31 ± 1.25/4.76 ± 2.91 for (BoNT/A)/placebo groups). Improvements in urodynamic parameters were also reported, such as a higher MCC (297.5 mL at week 6 compared to 297.5 mL at baseline and 241 mL on placebo) and a lower PDetMax (32.5 cm H_2O at week 6 compared to 60 at baseline). Questionnaires like the International Consultation on Incontinence Modular Questionnaire (ICIQ) and Incontinence-Quality of Life (I-QoL) revealed a decrease in the intensity of OAB symptoms together with a significant increase in patient QoL. The therapeutic effect persisted to

week 36 and was further prolonged with open-label BoNT/A re-treatment to weeks 48 and 60. Urinary tract infections (UTIs) were the most frequent adverse events (16 patients for each BoNT/A and placebo groups), followed by headaches in 6 (21%), nausea ± vomiting in 6 (21%) and voiding difficulty/retention in 6 (21%) patients.[16]

Kennelly et al performed an interim analysis on patients having completed two large, multicenter, placebo-controlled, dose ranging, regulatory trials on onabotulinumtoxin A 200 U and 300 U, previously published by Cruz et al (see above) and Ginsberg et al in neurogenic OAB patients (multiple sclerosis and spine lesions) showing DO on urodynamics. The long term efficiency and safety of repeated BoNT/A injections (up to 5 cycles) was analyzed. A total of 387, 336, 241, 113, and 46 patients received 1, 2, 3, 4, and 5 cycles of BoNT/A. At the 6 weeks timepoint, the number of weekly UI episodes significantly decreased from baseline as follows: -22.7, -23.3, -23.1, -25.3 and -31.9 in the 200 U group and -23.8, -25.0, -23.6, -24.1 and 29.5 in the 300 U group, respectively. Complete continence rates ranged from 35.6% (cycle 4) to 46.3% (cycle 3) in the 200 U group while for the 300 U the corresponding figures were: 45.2% (cycle 1) and 82.4% (cycle 5). The mean QoL showed a significant increase in both BoNT/A groups, and ranged from 27.5 (cycle 3) to 32.5 (cycle 2) in the 200 U group, and 28.5 (cycle 3) to 44.6 (cycle 5) in the 300 U, respectively. The mean time to re-treatment in cycles 1 and 2 was a constant 36 weeks. The most common adverse events (AEs) were UTIs and urinary retention in all cycles. UTIs ranged from 20% (cycle 5) to 58.4% (cycle 1) for the 200 U and 20.4% (cycle 4) to 55.1 (cycle 1), respectively. Urinary retention was mostly present during cycle 1 (20.3% - 200 U and 23.3% - 300 U), decreasing to 0 in the 4th and 5th cycles. Clean intermittent self catheterization (CISC) rates respected a similar trend, with the highest in cycle 1 for both doses (30% - 200 U and 42% - 300 U).[15,17,18]

A comparative, multicenter, dose-ranging trial was performed by Grise et al using 500 U and 750 U of abobotulinumtoxin A in a series of 78 neurogenic DO patients (39 for 500 U and 38 for 750 U). They obtained complete continence in 22/39 (56.4%) patients using 500 U and 28/38 (73.7%) ones using 750 U. Reappearance of leakages was assessed in the 50 patients who were fully continent at day 30. In the first 80 days after treatment, UUI reoccurrence rates were slower in the high-dose 750 U abobotulinumtoxin A group when compared to the 500 U one, the authors finding no further significant differences between the two groups later on. Median time-to-recurrence was 168 days, with 164.5 days for 500 U and 173.5 in the 750 U, respectively. Pad usage was smaller in the 750 U group although not statistically significant. Both doses improved urodynamic parameters and patient QoL, although with non-statistically significant differences. The authors reported an overall good tolerability, with the exception of a patient that developed general fatigue and dizziness that were considered study drug-related. The therapeutic effect was present for a minimum of 168 days. In summary, results were not statistically different between the two doses.[19]

These clinical trials demonstrated that BoNT/A is more efficient than placebo in improving the various signs and symptoms of neurogenic DO. This is reflected by: improvements in daily/weekly UUI episodes, significant gains in full continence rates and improvements in urodynamic parameters. The duration of the effect varies according to author, but spans between 6 to 9 months per injection. BoNT/A reinjection was available as open label therapy for prolonging the therapeutic effect in initial responders without the reporting of significant AEs and decreases in clinical response.[15,16,18]

Although the reported results present a high variability, if we summarize the ones issued by the largest studies (mainly regulatory ones), the following generalized results can be found:

1. The frequency of incontinence episodes decreased by 43%-57%.
2. Continence is achieved in 38%-73% of patients.
3. Mean cystometric capacity is increased by 157 mL-243 mL.
4. Maximal detrusor pressure is reduced by 26.9 cm-28.5 cm H_2O.
5. The duration of the effect ranges between 6 and 9 months.
6. Patient QoL was improved in all studies according to various questionnaires.
7. BoNT/A reinjections are an option for responsive patients and can prolong the therapeutic effect without the risk of serious AEs.

Adverse events (AE's)

The most common local AEs were UTIs and urinary retention. UTIs were present in proportions up to 64%. Complicated UTIs were also reported (1 pyelonephritis and 1 pyelonephritis + urosepsis) but were not related to the study drug.[15,16]

An increase in PVR was present in most BoNT/A groups. For onabotulinumtoxin A a dose-dependent increase in PVR was reported, with rates up to 53% in the 300 U users.[15,16] CISC was initiated at PVR values higher than 200 mL and was necessary in up to 42% of 300 U and 30%-35% of 200 U onabotulinumtoxin A users.[15,17]

Authors	No. of patients	Change from baseline in UUI: (criteria +value)	Continence	Quality of life improvement	MCC (mL)	pDetMax (cm H_2O)	UTIs	CISC	Other adverse events (treatment related)	Duration of benefit
Cruz et al 2011#	*275*	*Episodes/week at Week 6*	*Week 6*	*Week 6*	*Week 6*			*Week 12*		
Placebo	92	-13.2	7.6%	+11.7 I-Qol	+6.5	+6.4	36(39.1%)	12.2%		13.1 weeks
Botox 200U	92	-21.8	38%	+24.4 I-Qol	+157	-28.5	51(55.4%)	29.5%	1 Muscular	42.1 weeks
Botox 300U	91	-19.4	39.6%	+24.3 I-Qol	+157.2	-26.9	57(62.6%)	42.2%	weakness case; 2 Autonomic dysreflexia cases	42.1 weeks
Herschorn et al 2011#	*58*	*Episodes/day at Week 6*	*Week 24*		*Week 6*		*Week 36*			
Placebo	29	-12.5%	0	NA	-29	+13	16 (55%)	6(21%)	NA	NA
Botox 300U	29	-57.14%	10.7%	NA	+224.5	-27.5	16 (57%)	2(7%)	3 muscular weakness cases	< 36 weeks
Grise et al 2010	*78*	*Pad usage Day 30*	*Day 30*	*Day 30*	*Day 30*		*Day 30*			
Dysport 500U	39	-43%	56.4%	+19.8% SIUP	+ 192.1 ± 226.9	NA	0	NA	0	164.5 days
Dysport 750U	38	-52%	73.7%	+35.5% SIUP	243.0 ± 174.8	NA	2 (5.26%)	NA	General fatigue with vertigo	173.5 days
Kennelly et al 2013#	*387*	*Episodes/week at Week 6*	*Week 6/cycle*	*Week 6 - IQol/cycle*	*W*	*Week 6/cycle*		*Week 6/cycle*		
Botox 200U	202									weeks
Cycle 1	202	-22.7	43.6%	+30.4	NA	NA	58.4%	30%	Fatigue, muscular	36.3
Cycle 2	176	-23.3	44.1%	+32.5	NA	NA	46.0%	3.8%	weakness,	36.1
Cycle 3*	127	-23.1	46.3%	+27.5	NA	NA	39.4%	2.9%	constipation, fall,	26.3
Cycle 4*	59	-25.3	35.6%	+31.2	NA	NA	28.8%	0	pyrexia	23
Cycle 5*	25	-31.9	44.4%	+30.8	NA	NA	20%%	0		20.9
Botox 300U	185									
Cycle 1	185	-23.8	45.2%	+32.3	NA	NA	55.1%	42.0%	Fatigue, muscular	34.0
Cycle 2	160	-25.0	50%	+31.3	NA	NA	53.1%	18%	weakness,	37.9
Cycle 3*	114	-23.6	47.5%	+28.5	NA	NA	42.1%	0	constipation, fall,	25.2
Cycle 4*	54	-24.1	54.5%	+29.1	NA	NA	20.4%	0	pyrexia	23.2
Cycle 5*	21	-29.5	82.4%	+44.6	NA	NA	23.8%	0		17.6

#regulatory study; *cycles not completed at publishing; I-Qol = incontinence-quality of life; SIUP = specific impact of urinaryproblems quest; NA = not available

Figure 1. Studies on BoNT/A use in neurogenic detrusor overactivity.

Systemic side effects like autonomic dysreflexia, treatment-related general fatigue and generalized muscle weakness were also present. Muscle weakness was evidenced by patient transfer difficulty.[15,19,16] Other AEs such as hematuria and injection site pain were considered transient.[15,19,16] Detailed data can be found in Figure 1.

BoNT/A in idiopathic OAB

Chapple et al in their recent regulatory study on idiopathic OAB and urinary incontinence assessed the efficiency, safety and health-related QoL in patients treated with onabotulinumtoxin A at a dose of 100 U. They reported a significant decrease (53.2% versus 13.9% in BoNT/A and placebo, respectively) in incontinence episodes/day at week 12 (-2.80 versus -0.82). Significant decreases were also reported for urgency (-3.67 versus -1.24) and nocturia (-0.54 versus -0.25). At 12 weeks, OAB symptoms registered a statistically significant decrease as follows: UUI episodes decreased with -53.1% and -16.8% in the BoNT/A and placebo groups while nocturia decreased with -25.1% and -8.8% in the same groups. The authors reported a significant difference in terms of patient's perception of change in their condition: 62.8% in the BoNT/A group and 26.8% for placebo, $p < 0.01$. This reflected in patients' QoL (at 12 weeks the I-QoL scores were 23.1/6.3 for BoNT/A/placebo). This pattern was also seen in the seven items of the King's Health Questionnaire (KHQ) ($p < 0.001$). The most common AEs at 12 weeks were UTIs: 56 (20.4%) in the BoNT/A group and 14 (5.2%) in the placebo one. CISC was initiated for all patients showing a PVR greater than 350 mL (10/11), while for PVR values ranging between 200 mL and 350 mL, CISC was performed only in symptomatic patients (7/17).[20]

A similar double-blind, randomized, placebo-controlled, dose-ranging, regulatory trial was performed by Fowler et al using onabotulinumtoxin A in doses of 50 U, 100 U, 150 U, 200 U and 300 U in idiopathic OAB patients (with and without DO). At week 12, the authors reported a significant decrease in weekly UUI episodes: -17.4/-20.7/-18.4/-23.0/-19.6 and -19.4 for the placebo/50/100/150/200 and 300 U BoNT/A groups. Complete continence was achieved in 15.9%/ 29.8% /37.0% /40.8%/50.9% and 57.1% for the same previously described groups. A statistically significant decrease in UUI episodes was obtained using BoNT/A doses of 100 U and higher. In terms of patient quality of life, the I-QoL questionnaire revealed a statistically significant improvement for all patients having received doses of 100 U and above. The same was available for the KHQ. In the Medical Outcomes Study Short Form (36) Health Survey (SF 36), statistically significant improvements were seen in 1 subscale for 200 U and 4 out of 8 subscales for 300 U.[21]

In the United Kingdom, Tincello et al treated idiopathic OAB patients (with DO) with 200 U onabotulinumtoxin A in a double-blind, placebo-controlled, randomized trial. At 6 month follow up, they reported a statistically significant decrease in frequency (8.3 versus 9.67, $p = 0.0001$), urgency (3.83 versus 6.33, $p < 0.0001$) and leakage episodes (1.67 versus 6, $p < 0.0001$) together with an increase in continence: 31% versus 11% in the BoNT/A group compared to placebo. Patients' QoL was assessed using a series of questionnaires (Indevus Urgency Severity Scale-IUSS, ICIQ, IQOL). Significant improvements were reported in the BoNT/A group, with the reserve that no score returned to normal. Relapse of OAB symptoms occurred in an ascendant trend towards the 6 months range, with a higher rate in the placebo group. Urinary infections were the most frequent AEs (31% versus 11%), together with voiding difficulty requiring CISC (16% versus 4%). Severe drug-related AEs also occurred: 2 generalized muscle weakness cases (1 for each allocation arm) and 1 bronchopneumonia case.[22]

Denys et al in their multicenter, double-blind, randomized, placebo-controlled trial, treated refractory idiopathic DO patients with onabotulinumtoxin A at different dose ranges (50 U, 100 U and 150 U) and found and a 50% improvement in urgency and UUI for 65% and 56% of patients receiving 100 U and 150 U of BoNT/A, respectively. A 75% improvement was found in 40% of both BoNT/A groups compared to placebo (22%). Frequency was significantly improved in the 150 U group, the difference from placebo persisting for the entire study period. At month 5, complete continence was achieved in 15.8%, 45%, 45.8% and 7.1% for the 50 U, 100 U, 150 U and placebo groups. For the 50 U group, symptom improvement was never significantly different from placebo. At urodynamics, significant improvements were found at 3 month follow up for the 150 U group and showed a tendency to decrease towards the 6 month study period. QoL improved at month 1 for the 100 U and 150 U patients but not all parameters were statistically significant. PVR increased in all treatment groups, and was statistically different at day 8, month 3 and month 6. CISC was required in 8 patients, with 4 in the BoNT/A 150 U group.[23]

Alloussi et al performed an observational study on two separate groups of neurogenic and idiopathic DO patients treated with abobotulinumtoxin A in doses of 500 U (neurogenic OAB) and 250 U (idiopathic OAB) using a specific trigone-involving injection pattern. They reported full continence in 52 (80%) neurogenic and 158 (93%) idiopathic OAB patients. The duration of treatment effect lasted as long as 5.7 ± 2.2 months in neurogenic and 4.9 ± 1.2 months in idiopathic OAB patients. At 12 months, a relapse rate of 94% was reported for neurogenic OAB patients and a corresponding 83% one for idiopathic OAB ones. An increase in PVR (> 50 mL) was reported for 24 (14%) idiopathic OAB patients, with CISC being initiated in 7 patients (4%) that had a PVR larger than 100 mL. No serious AEs or systemic effects were reported.[24]

In idiopathic OAB, we found that onabotulinumtoxin A in doses of 100 U and higher is an efficient treatment method, with reporting of significant improvements in UUI events, frequency, nocturia and other OAB symptoms. Patient QoL was assessed using various types of questionnaires like I-QoL and King's Health. These complex instruments quantified various aspects relevant to patients' everyday life and found improvements in BoNT/A treated patients for both BoNT/A products.[20-24]

A summary of the reported results from the placebo-controlled trials on idiopathic OAB patients treated with BoNT/A included in this review would show the following:

1. BoNT/A treatment decreased the total number of UUI episodes up to 53%.
2. Complete continence was achieved in rates up to 57% in 300 U onabotulinimtoxin A and 93% in abobotulinumtoxin A 250 U groups.
3. The therapeutic effect ranged from 6 to 9 months.
4. Mean cystometric capacity is increased by up to 216 mL in onabotulinimtoxin A 150 U and 259 mL in abobotulinumtoxin A 250 U.
5. Maximal detrusor pressure is reduced by up to 50 cm H_2O in onabotulinumtoxin A 150 U patients.
6. Re-injection is a valid therapeutic option and can prolonge the therapeutic effect at the same intensity level.[25]

Adverse events (AE's)

As seen in neurogenic DO, the most common AEs in idiopathic OAB patients were UTIs and increases in PVR. UTIs were present in rates up to 31% in the BoNT/A groups (onabotulinumtoxin A 200 U), with no major infectious complications being reported.[22] Increases in PVR rates were present, with CISC being necessary in up to 16% of one study group. Comparison between CISC rates is difficult for several reasons. First, there is a large inhomogeneity between the different study groups in terms of inclusion criteria, type of treatment and dose of the study drug. Second, the threshold for initiating CISC varies between authors. Chapple et al recommend CISC initiation at PVR values higher than 350 mL. For values placed between 250 mL and 350 mL, the same group recommends CISC only if the patients are

Authors	No. of patients	Change from baseline in UUI	Continence	Quality of life	MCC (mL)	pDetMax (cm H_2O)	UTIs	CISC (%)	Other adverse events (treatment related)	Duration of benefit
Chapple et al 2013#	*489*	*Week 12 daily UUI*					*Week 12*			
Placebo	239	-0.82 (-13.9%)	NA	TBS: +26.8%; I-Qol: +6.3; KHQ: -0.5 to -8.2	NA	NA	56(20.4%)	2 (0.7%)	Dysuria Bacteriuria Hematuria	NA
Botox 100U	250	-2.80 (-53.2%)	NA	TBS: +62.8%; I-Qol: +23.1; KHQ:4.4 to -26.5	NA	NA	14 (5.2%)	19 (6.9%)	Urinary retention	> 12 weeks
Fowler et al 2012#	*313*	*At 12 weeks weekly UUI*								
Placebo	44	-17.4	15.9%	I-Qol: +17.9						NA
Botox 50U	57	-20.7	29.8%	I-Qol: +29.8	NA	NA	NA	NA	NA	< 36 weeks
Botox 100U	54	-18.4	37.0%	I-Qol: +32.9	NA	NA	NA	NA	NA	< 36 weeks
Botox 150U	49	-23.0	40.8%	I-Qol: +35.2	NA	NA	NA	NA	NA	< 36 weeks
Botox 200U	53	-19.6	50.9%	I-Qol: +37.1	NA	NA	NA	NA	NA	< 36 weeks
Botox 300U	56	-19.4	57.1%	I-Qol: +39.7	NA	NA	NA	NA	NA	< 36 weeks
Tincello et al 2012	*240*	*At 12 weeks daily UI/U*	*At 12 weeks*					*6 months*		
Placebo	118	-0.87/-0.7	12 (12%)	ICIQ: -1;I-Qol:+1.7; IUSS: -0.2	NA	NA	12(11%)	4(4%)	1- general muscle weakness	NA
Botox 200U	122	-5.2/-5	36 (35%)	ICIQ: -9;I-Qol: +40.37;IUSS:-0.8	NA	NA	36(31%)	18(16%)	1- general muscle weakness	~ 6 months
Denys et al 2011	*107*	*At 90 days, 50% / 75% improvement*	*At 90 days*					*At 90 days*		
Placebo	31	29%/18%	10.7%	NA	22.9 ± 99	-3 ± 39.1	0 of 24	1 (3.2%)	0	NA
Botox 50U	23	37%/5%	15.8%	NA	38.4 ± 94.8	5.7 ± 30.2	1 of 18 (5.6%)	3 (13%)	1-Pyelonephritis 1-Bilateral UHN	~ 6 months
Botox 100U	23	65%/40%	55.0%	NA	85.5 ± 135.1	-13.8 ± 35.3	1 of 21 (4.8%)	1 (4.3%)	0	~ 6 months
Botox 150U	30	56%/40%	50.0%	NA	91.3 ± 125.2	-10.7 ± 40.1	2 of 22 (9.1%)	4 (13.33%)	0	~ 6 months
Alloussi et al 2011	*234*	*UI/6 weeks*		*AUA*						
Dysport 250U	170	-4.3 ± 1.3	93%	-2.9 ± 1.1	+258.9 ± 78.5	-9.6 ± 5.4	NA	7 (4%)	0	~ 6 months

#regulatory study; EQ-5D = EuroQol 5D visual analogue scale; I-Qol = incontinence-quality of life; IUSS = indevus urgency severity scale; ICIQ = international consultation on incontinence modular questionnaire; KHQ = king's health questionnaire; SIUP = specific impact of urinary problems quest; NA = not available; SF36 = medical outcomes study short form (36) health survey; UHN = uretero-hydro-nephrosis

Figure 2. Studies on BoNT/A use in idiopathic overactive bladder.

symptomatic. On the other hand, Alloussi et al initiate CISC at PRV values higher than 100 mL.[6,20,24]

Although rare, systemic AEs like generalized muscle weakness, sufficiently severe as to interfere with patients' everyday activities have also been reported.[22]

Detailed data on the included studies concerning BoNT/A for idiopathic OAB patients are available in Figure 2.

Common issues: choosing the right product, the right dosage and injection pattern

What to choose?

Choosing the right product is a highly debatable issue. At present time, onabotulinumtoxin A is approved by the FDA in the United States for both neurogenic and idiopathic OAB, while for the other products there are no formal indications issued from government agencies.[8] In our review, we found that onabotulinumtoxin A is a "popular" product while for abobotulinumtoxin A evidence is scarce and the existing studies are performed on a low number of patients. These studies suggest that abobotulinumtoxin A can be an efficient alternative for onabotulinumtoxin A.[6,8,24,26]

And at what dosage?

Concerning dose selection, onabotulinumtoxin A dose-ranging trials found good results when using doses equal or higher than 100 U. Although positive results were obtained in doses up to 300 U, the effect difference was not statistically significant.[8,15,20,21,23] Shenot et al in their personal experience article recommend a dose of 200 U, considering the fact that this dose was the only approved one.[27] However, AEs appeared to be in relation to the BoNT/A dose, with systemic effects being reported at 300 U.[15] For abobotulinumtoxin A, the available data suggests that 500 U can be the optimum dose for both neurogenic and idiopathic OAB management although for idiopathic OAB a dose of 250 U has also proven to be efficient.[19,24] Studies performed on higher doses of abobotulinumtoxin A (1000 U) revealed a similar effect as the 500 U dose in neurogenic OAB patients but with an increased risk of side effects and potentially severe complications.[28]

What injection pattern should I use?

Injection patterns and injection numbers are also debatable subjects. Most authors use the reconstituted drug solution for intradetrusor injecting during cystoscopy in 20 to 30 different sites. Alloussi et al

suggest using 10 sites of injection for abobotulinumtoxin A in both OAB types.[5,15,16,17,19,20,21,23,24,26,29]

Trigone-sparing or trigone-inclusion?

Early BoNT/A trials used trigone-sparing injection techniques that were adopted afterwards by many authors, with the aim of avoiding injection-related vesicoureteral reflux. However, recent studies suggest that trigone-inclusion is safe and can be performed with good results. Manecksha et al reported improved results in the trigone-inclusion group for idiopathic OAB using abobotulinumtoxin A 500 U when compared to the trigone-sparing one, with the reserve of a small, non-placebo-controlled trial.[26] Kuo et al performed a randomized, comparative trial for different onabotulinmtoxin A injection techniques. They compared detrusor, suburothelial and bladder base (trigone) injections and concluded that results were better and lasted longer in the suburothelial and detrusor groups while bladder-base injections caused less adverse events.[24,26,30]

Formal recommendations from manufacturers

As 2014 came with the introduction of formal recommendations for BoNT/A administration in both neurogenic and idiopathic DO (OAB), we consulted the official product information for onabotulinumtoxin A, which reflects the results obtained in the regulatory trials. Thus, for neurogenic DO, it is recommended to use 200 U of the product, as 1 mL injections (6.7 U) across 30 sites. For idiopathic DO, the corresponding dose is 100 U also as 1 mL injections across 20 sites.[31]

Our experience at the Clinic of Urology, Tîrgu-Mureş County Hospital

In 2012 we started an observational trial on the use of abobotulinumtoxin A at a dose of 500 U in idiopathic OAB treatment. The study protocol was approved by our local ethics committee. Study candidates were subjected to rigorous inclusion and exclusion criteria in order to avoid situations that could impair with the effect of the drug. After obtaining informed consent, the patients were included and the study drug was administered as intradetrusor injections during cystoscopy. A number of 20 injections/patient were performed in a trigone-sparing manner. To this date, the study is ongoing and preliminary results are promising (personal publication).

Conclusion

BoNT/A has been used in urology for the last 14 years, especially in patients affected by neurogenic OAB. Out of the various products available, onabotulinumtoxin A and abobotulinumtoxin A are frequently used in urologic research for treating OAB patients. Although the two products are not equivalent, the available evidence shows that onabotulinumtoxin A is an efficient treatment method for both OAB subtypes (with FDA recommendation), while abobotulinumtoxin A is a potent equivalent (although with a low degree of evidence). Therefore, there is a need for large placebo-controlled trials that could support the use of abobotulinumtoxin A in OAB patients, in countries where onabotulinumtoxin A is not available. □

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