OnabotulinumtoxinA for the treatment of overactive

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bladder

OnabotulinumtoxinA has recently been granted a license for use in overactive bladder (OAB). This review assesses the latest evidence gained from 12 randomized-controlled trials from an updated systematic review. All randomized-controlled trials have shown significant improvements in urinary symptoms. Recent Phase III studies have also shown improvements in patient satisfaction and quality of life. Significant improvements have also been reported for urodynamic parameters. The adverse events rate is low, making this form of therapy very safe. The need for intermittent self catheterization is low overall at 12% and urinary tract infection rates are between 14 and 21%. Repeated injections have been shown to be safe up to eight injection cycles and reinjection is usually required between 6–12 months. Future studies should investigate volume, site and number of injections. Electromotive and liposome methods of administration require further study.

Keywords: botox • drug safety • incontinence • onabotulinumtoxinA • overactive bladder • urgency

Overactive bladder (OAB) is a symptom syndrome complex consisting of the hallmark symptom of urinary urgency and may also include frequency and/or nocturia [1]. Urgency is described as a sudden compelling desire to void that is difficult to defer. OAB may be 'wet' or 'dry', with the former being associated with incontinence and the latter not. Detrusor overactivity is a urodynamic finding that is demonstrated in 69 and 90% of men and 44 and 58% of women with OAB dry and wet, respectively [2].

The initial management of OAB includes lifestyle changes, fluid adjustment, caffeine reduction, weight loss and bladder retraining. If these measures fail then antimuscarinic medications are utilized. These carry the unwanted side effects of dry mouth and constipation. Another medication recently licensed has been the beta-3 agonist [3]. However, long-term data regarding its efficacy, safety, pharmacokinetics and drug interactions are still awaited.

With the failure of oral agents, the next line in the treatment of OAB was traditionally surgery to augment the bladder with a portion of small bowel. Therefore the development and refinement of the use of botulinum toxin (BTX) in OAB has bought about a less invasive but highly efficacious treatment. This review will report on the use of onabotulinumtoxinA in the management of patients with OAB with particular reference to efficacy, safety and dosing. We hope to summarize the important randomized controlled trials (RCT) data obtained from an updated systematic review.

BTX-A formulations/serotypes

The bacterium *Clostridium botulinum* produces BTX, which is the most potent toxin known to man. There are seven serotypes of the toxin, BTX-A to -G. The

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most commonly used and studied is BTX-A, however, BTX-B has also been licensed in those resistant to BTX-A. BTX is a protein consisting of a light chain (50 kDa) and a heavy chain (100 kDa) bound together by a labile disulphide bond.

Different formulations of each toxin also exist due to different isolation, extraction and purification processes by the various companies that manufacture BTX. These include, Botox® (Allergan Pharmaceuticals, CA, USA), Dysport[®] (Ipsen Biopharm Ltd, Slough, UK), Xeomin[®] (Merz pharmaceuticals UK Ltd, Herts, UK), Prosigne®(Lanzhou Biological Products, Lanzhou, China) and PurTox[®] (Mentor Corporation, WI, USA). Despite being the same serotype the efficacy and safety of each formulation varies and the formulations cannot be considered as generic equivalents [4]. To reflect this the US FDA has approved new terminology for the different formulations of BTX and Botox is termed 'onabotulinumtoxinA', Dysport is termed 'abobotulinumtoxinA' and Xeomin 'incobotulinumtoxinA'. This review will focus on onabotulinumtoxinA as this is the only preparation that has sufficient evidence and thus a license for use in OAB.

Mechanism of action

BTX-A is known to block the transmission of nerve impulses wherever acetylcholine is the neurotransmitter. The heavy chain binds to complex gangliosides located in the presynaptic nerve terminals at the neuromuscular junction and facilitates the internalization of the neurotoxic light chain. This then cleaves the SNARE proteins SNAP-25, VAMP and syntaxin, which causes inhibition of vesicular SNAREdependent acetylcholine release from the presynaptic terminal of the motor end plates [5]. This in turn leads to a sustained flaccid paralysis of the innervated muscle.

Kerner first conceived a possible therapeutic role for botulinum toxin. It was first used to treat conditions of hypertonicity in striated muscle. The first use in humans, in 1980, was for the treatment of strabismus and subsequently the FDA approved its use for conditions such as strabismus, blepharospasm and hemifacial spasm in patients over 12 years old. Its indications have since expanded and it has been used successfully in many conditions characterized by muscle spasticity.

In 1996, Schurch first published the use of BTX-A, injected into the external urinary sphincter, to treat detrusor sphincter dyssynergia in patients with spinal cord injury [6]. This was followed by using local injections of BTX-A to treat neurogenic detrusor overactivity (NDO) [7]. Other urological conditions in which it has been used with varying success are bladder outflow obstruction [8] and bladder pain syndrome [9]. Clinical effects occur after 24–72 h, with the reason for this delay being unknown [10]. The defective SNARE proteins remain in the nerve terminal for a number of months and may account for the sustained action. Histological assessments have shown degeneration of intoxicated nerve terminals with eventual resprouting of axons leading to new synaptic contacts that may account for the return of muscular function after a number of months [5].

Besides affecting the efferent motor activity of the bladder, newer evidence has suggested a role for BTX-A also in the sensory afferent system. Laboratory evidence has shown that BTX-A also blocks other neurotransmitters such as ATP, substance P, P2X₃ and TRPV1 receptors [11-13]. In addition to that BTX decreases nerve growth factor, which may result in reduced afferent C-fiber hyperexcitability and thus a decrease in NDO [14].

Efficacy of onabotulinumtoxinA described in randomized clinical trials for OAB

An updated systematic review [15] has revealed that 12 randomized controlled trials (Table 1) have assessed BTX-A use in patients with OAB, all used onabotulinumtoxinA [16-27]. In total, 1237 patients have received the active drug in these trials. In addition, there are also more than 40 other publications reporting on over another 2500 patients [15]. This substantial evidence base has formed the basis for licensing by the Medicines and Healthcare products Regulatory Agency and FDA [28,29].

The development of onabotulinumtoxinA use in the bladder originated in patients with NDO due to spinal cord injury [30]. The dose initially utilized in these patients was 300 IU. Later an RCT by Cruz et al. showed similar efficacy with 200 IU, which became the licensed dose in this group of patients with NDO [31]. Based on these experiences, OAB studies initially utilized 300 and 200 IU [21], but due to the high rate of urinary retention, the dose was quickly reduced. An exploratory dosing study by Dmochowski et al. compared 50, 100, 150, 200 and 300 IU and showed a plateau in efficacy at 150 IU with a high efficacy rate at 100 IU [20]. The authors also showed that higher doses led to increased bladder paralysis and higher post-void residual urine volumes (PVR). Thus the latest Phase III RCTs have compared 100 IU onabotulinumtoxinA to placebo, which is now the licensed dose.

The two pivotal Phase III studies included 548 and 557 patients, respectively [18,25]. Patient inclusions were >3 urinary incontinence episodes in 3 days and more than 8 micturitions per day. Co-primary end points were changes from baseline in number of incontinence episodes per day and patient reported benefits on the

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Table 1. Summary of randomized controlled trials data regarding onabotulinumtoxinA use in overactive bladder.						
Study	Points in RCT (n)	Inclusions	Comparison	Primary findings	Adverse events	Ref.
Altaweel <i>et al.</i>	22	Refractory OAB	100 vs 200 IU	Bladder diary, urodynamic and QoL improvements in both 100 and 200 IU	Three patients: urinary retention	[16]
Brubaker <i>et al.</i>	43	Women Refractory detrusor overactivity > 6 UUI/3 days	Placebo vs 200 IU	Significant improvement in QoL in 60% lasting for a median of 373 days	Transient rise in residual volume (>200 ml) in 43%	[17]
Chapple <i>et al</i> .	548	Refractory OAB > 3 UUI/3 days	Placebo vs 100 IU	Significant improvements in UUI and QoL	6.9% ISC	[18]
Denys <i>et al</i> .	99	Refractory OAB > 3 UUI/3 days	Placebo vs 50 vs 100 vs 150 IU	100 and 150 IU led to significant improvements in UUI and QoL Lower risk of high residual volume in 100 IU	5% UTI 10% ISC (lower in 100-IU group)	[19]
Dmochowski et al.	311	Refractory OAB >8 UUI/week	Placebo vs 50 vs 100 vs 150 vs 200 vs 300 IU	Significant improvements in symptoms Doses greater 150 IU contributed minimal additional benefits	Doses higher than 150 IU increased risk of ISC	[20]
Flynn <i>et al</i> .	22	Women Refractory OAB >2 UUI/day	Placebo vs 200/300 IU	Significant improvements in UUI, pad changes and QoL No change in nocturia, peak pressure flow	One patient ISC 13% UTI	[21]
Gousse et al.	60	Refractory OAB >1 UUI/day	100 vs 150 IU	Significant improvements in symptom scores that continued with repeat injections	20% ISC in 150-IU group 10% ISC in 100-IU group 13% UTI	[22]
Jabs et al.	21	Women with refractory OAB and UUI	Placebo vs 100 IU	Improvement in maximum bladder capacity and UUI	Hematuria in 1 patient Constipation in 1 patient	[23]
Кио	105	Idiopathic detrusor overactivity	100 IU in different bladder regions	No difference in outcomes between bladder body only, bladder body/trigone or bladder base/trigone groups	6% Retention 21% UTI 12% Hematuria	[24]
Nitti et al.	557	Refractory OAB >3 UUI/3days	Placebo vs 100 IU	Significant improvements in UUI and QoL	5% UTI	[25]
Sahai <i>et al</i> .	34	Refractory detrusor overactivity	Placebo vs 200 IU	Significant improvements in maximum bladder capacity, frequency and UUI	6 patients ISC	[26]
Tincello <i>et al</i> .	185	Women with refractory detrusor overactivity	Placebo vs 200 IU	Significant reductions in UUI, frequency and urgency	16% ISC 31% UTI	[27]

ISC: Intermittent self catheterization; OAB: Overactive bladder; QoL: Quality of life; RCI: Randomized-controlled trials; Refractory: Persisting after treatment w anticholinergics; UTI: Urinary tract infection; UUI: Urgency urinary incontinence.

treatment benefit scale at 12 weeks. Other reported parameters were changes in urgency, frequency, nocturia and quality of life (QoL) assessments. Both studies reported a decrease in incontinence episodes by 2.6- to three-episodes per day compared with placebo,

which decreased by one episode per day (p < 0.001). This represents a 62–64% reduction in incontinence episodes. A quarter of all patients became completely dry. Also, two thirds of patients reported a positive treatment response on the treatment benefit scale.

Secondary end points also showed improvements, with 18, 45 and 25% reductions in frequency, urgency and nocturia episodes, respectively. QoL improvements assessed with the I-QoL and KHQ questionnaires also revealed significant benefits with onabotulinumtoxinA over placebo (p < 0.001).

Besides improvements in bladder diary parameters, other studies have also included urodynamic assessments pre- and post-procedure. With 100 IU onabotulinumtoxinA a 17–24% increase in maximum cystometric capacity has been reported [16,24]. This compares to a 51–72% increase with the use of 200 IU [16,26]. This shows that a patient's bladder is able to accept more volume prior to an absolute desire to void. Other parameters also shown to have improved are volume at first detrusor overactive contraction, bladder compliance and mean detrusor pressure. Urodynamic assessments provide objective data and shed light on the mechanisms by which BTX-A works on the bladder.

Safety & adverse events in OAB

Despite its high potency, BTX-A administration in to the bladder has proven to be very safe. The risk of urinary tract infection is reported in 21% of patients included in randomized controlled trials [15]. This incidence is 14% when looking at all case series reports. The differences in these outcomes are likely to represent differences in events reporting, antibiotic prophylaxis and definitions of urinary tract infection. Another adverse event is the need for temporary intermittent self catheterization (ISC) when the bladder fails to empty completely. This was required in 12% of patients in RCTs. Initial reports reported a higher rate of ISC and it must be recognized that the PVR, which instigated catheterization, was lower in those studies (100 vs 200 ml). As experience has increased with the use of BTX-A, even up to a PVR of 300 ml may be acceptable if the patient remains asymptomatic.

Systemic side effects are rare following use of the doses described for OAB. Bauer *et al.* have specifically looked at adverse events after injection of both 100 IU and 200 IU onabotulinumtoxinA [32]. Dry mouth occurred in 42% of the 200-IU group and 20% of the 100-IU group. There was a higher incidence of weakness, impaired vision and dysphagia in the 200-IU onabotulinumtoxinA group of 20%. The criticism of this study is the reliance on a questionnaire that may have introduced suggestion bias, which cannot be assessed due to the lack of a placebo arm. Other studies including the multiple RCTs have not reported such a high rate of systemic adverse events.

The other issues of concern were the long-term changes in bladder cellular architecture and formation

of antibodies to BTX-A. Biopsies post-repeat injections have not shown significant differences in inflammation, fibrosis and dysplasia in the bladder wall of patients with IDO who received onabotulinumtoxinA [33]. Antibody tests are occasionally positive in patients post-injection [34,35]. They may be responsible for failure, but some authors have shown that with time a retrial of BTX-A is feasible with good results [36].

Drug delivery

The use of a flexible cystoscope has turned intravesical BTX-A administration into an outpatient procedure that can be performed under local anesthetic. Most commonly, 0.5–1 ml containing 10 IU is administered per injection. The volume per injection and number of injection sites needs further investigation. Data from injecting guinea pig bladders has shown 2 IU dissolved in 20 ml led to increased cleaving of SNAP-25 compared with 2 IU in 2 ml both given as single injections [37]. This shows that BTX-A requires sufficient volume for distribution and it is not known, in humans, if the dilution and volume of distribution will have a significant impact on outcomes.

The depth and location of injection has been investigated by Kuo, who has shown success in 93, 80 and 67% of patients who had detrusor, suburothelial and bladder base injections, respectively [38]. The maximum cystometric capacity was increased in the detrusor and suburothelial groups but not in the bladder-base group at 3 months. There were no cases of vesicoureteric reflux. Similarly, Manecksha et al. have shown an absence of vesicoureteric reflux in patients in whom the trigone was injected as an additional site [39]. The trigone inclusion group also led to greater improvements in OAB Symptom Score scores at 6, 12 and 26 weeks. The differences in the urodynamic parameters were, however, less marked but the median duration of efficacy was 8 versus 6 months favoring the trigone injection group. These findings reflect the rich neural supply to the trigone and suggest it to be a central site for injection.

Dosing regimes

The duration of efficacy is between 6 and 12 months. Patients are often advised to contact their healthcare provider when the BTX-A effect has worn off. Thereafter repeat injections may be given. It has been shown that successive BTX-A injections have not significantly affected outcomes for up to eight consecutive injections [40,41]. However, a retrospective assessment of one hospital's care records showed that 64% of patients discontinued BTX-A treatment in the long term with infections and need for ISC cited as reasons for stopping [42].

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Executive summary

- 100 IU onabotulinumtoxinA has been shown to improve all voiding parameters in patients with overactive bladder and has now been granted a license.
- 100 IU onabotulinumtoxinA has been shown to improve quality of life and urodynamic parameters in patients with overactive bladder.
- Higher doses of onabotulinumtoxinA may be used in patients with overactive bladder but there is a higher risk of needing to
 perform intermittent self catheterization.
- OnabotulinumtoxinA administration is very safe with urinary tract infection and intermittent self catheterization being the most frequent adverse events.
- The injection volume, site and number of injections still needs further study.
- Liposome and electromotive administration may provide new routes for the future.

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