

Onabotulinum-toxin-a in urology: an update a review of recent publications about lower urinary tract dysfunction managed with botulinum toxin

Abstract

Onabotulinum toxin A (BTX-A) injection is a safe and effective treatment for adults with several conditions determining lower urinary tract dysfunctions (LUTD), such as neurogenic detrusor overactivity (NDO) and idiopathic overactive bladder (OAB) with or without urge urinary incontinence (UI), not responder to conservative treatment options, including anticholinergic drugs. This review article analyzes recent studies who were using BTX-A to treat NDO and OAB; in addition, some other conditions causing LUTDs, such as benign prostatic hyperplasia (BPH) and painful bladder syndrome/interstitial cystitis (PBS/IC) were considered, even though in these conditions larger scale trials are still mandatory to confirm its usefulness.

Keywords: detrusor over activity, overactive bladder, painful bladder syndrome, interstitial cystitis, benign prostatic hyperplasia, botulinum toxin a

Volume 2 Issue 2 - 2015

Daniele Minardi, Luigi Quaresima, Giovanni Muzzonigro

Department of Clinic and Specialist Sciences-Urology,
Polytechnic University of Marche Region, Italy

Correspondence: Daniele Minardi, Institute of Urology, AOU United Hospitals, Polytechnic University of Marche Region, via Toronto 71, Ancona, Italy, Tel +39 071 5965667,
Email d.minardi@univpm.it

Received: February 15, 2015 | **Published:** March 31, 2015

Abbreviations: BTX-A, Onabotulinum toxin a; LUTD, lower urinary tract dysfunctions; NDO, neurogenic detrusor over activity; OAB, overactive bladder; UI, urge urinary incontinence; BPH, benign prostatic hyperplasia; PBS/IC, painful bladder syndrome/interstitial cystitis; DO, detrusor over activity; LUTD, lower urinary tract dysfunctions; ROAB, refractory overactive bladder; BPH, benign prostatic hyperplasia; PRISMA, preferred reporting items for systematic reviews and meta-analyses; UI, urinary incontinence; MS, multiple sclerosis; SCI, spinal cord injury; QoL, quality of life; HR-QOL, health-related quality-of-life; BPS, bladder pain syndrome; IC, interstitial cystitis

Introduction

The use of botulinum toxin-A (BTX-A) to treat over active bladder (OAB) symptoms and detrusor overactivity (DO) is largely stated and featured in the majority of continence guideline recommendations in patients refractory to conservative treatment and to antimuscarinics. In addition to neurogenic detrusor overactivity (NDO), there have been recently reports that expand the indications to other conditions of lower urinary tract dysfunctions (LUTD), such as idiopathic OAB not responder to first-line therapy, named refractory overactive bladder (ROAB).¹ Moreover, in the last ten years some studies^{2,3} have dealt with the use of BTX-A in LUTD suggestive of benign prostatic hyperplasia (BPH) in men with moderate/severe LUTD/BPH not responding to oral therapies who refuse or resulted not suitable to surgery.⁴ More recently, some clinical trials have suggested BTX-A injections to reduce pain and LUTD in patients affected by painful bladder syndrome/ interstitial cystitis (PBS/IC).^{5,6} The aim of this review is to evaluate the most recent published article about BTX-A clinical use regarding the conditions above mentioned.

Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,⁷ studies regarding uses of BTX-A to treat LUTD in NDO, ROAB, BPH and PBS/IC in patient previously treated with other therapy were selected and systemically reviewed. Regarding the exclusion criteria, studies with a sample size less than 10 patients were not considered because the capacity to evaluate the efficacy and tolerability of BTX-A would be lowered; studies with patients age <18years or assessing mechanism of action were also excluded. With the above mentioned criteria, we conducted a review of PubMed from January 2000 to August 2014; the search keywords were: bladder, overactive bladder, detrusor, detrusor over activity, painful bladder syndrome, interstitial cystitis, benign prostatic hyperplasia, botulinum toxin.

Results

NDO secondary to multiple sclerosis or spinal cord injury

The clinical benefits of BTX-A for the treatment of urinary incontinence (UI) due to NDO in patients refractory to conservative treatment and to antimuscarinics were first demonstrated in 2000 by Schurch et al.⁸ Recently, a multicenter, double blind, randomized placebo controlled trials in 691 patients outlines significant improvements with 200 U and 300 U of Onabotulinum toxin A; 65% of patients had no involuntary detrusor contractions on urodynamics at 6weeks following treatment with Onabotulinum toxin A; improvements were seen in those despite persistent NDO in MCC (mean cystometric capacity), volume at first unstable contraction, and maximal detrusor pressure during filling cystometry; bladder

compliance also improved with Onabotulinum toxin A treatment, and low baseline pretreatment compliance did not affect clinical outcomes; it was well tolerated at both 200 U and 300 U, with no increased efficacy of 300U over 200U.⁹

Another recent study has investigated the effect of repeated Onabotulinum toxin A injections in MS (multiple sclerosis) and SCI (spinal cord injury) patients. Patients continued to receive their original treatment dose of either 200 or 300U. A total of 387, 336, 241, 113, and 46 patients received one, two, three, four and five Onabotulinum toxin A injections, respectively. The proportion of patients achieving >50% and 100% dryness by 6 weeks were 73–94% and 36–55% respectively, depending on treatment cycle. Continued improvements in Quality of Life (QoL) were observed after all cycles of Onabotulinum toxin A treatment. The UTI rate was 20% and 23.8% in patients receiving 200U and 300U in their fifth cycle of treatment.¹⁰

A recent double-blind, placebo-controlled, pivotal, phase 3 study evaluated the efficacy and safety of BTX-A 200U or 300U and concomitant use of anticholinergics drugs in a total of 691 patients affected by MS or SCI with >13 urinary incontinence (UI) episodes/week. Both MS and SCI patients demonstrated significant improvements compared with placebo in QoL total summary score and a decrease of Pd ET max. Regarding the adverse effects recorded in the study, UTIs were the most frequent ones: the proportion of MS patients who developed this side effect was 38%, 69% and 69% in the placebo, Onabotulinum toxin A 200U and 300U groups respectively, whereas in SCI patients resulted 47%, 48% and 52%.¹¹

In a randomized, double blind, placebocontrolled study focusing on treatment satisfaction and QoL after Onabotulinum toxin A treatment in patients with MS and SCI, 92 patients received 200U and 91 had 300U of BTX-A; mean improvements were seen in incontinence -QoL scores and overactive bladder-patient satisfaction with treatment questionnaire for the BTX-A treated group compared with that for the placebo group at 6 and 12 weeks.¹²

Idiopathic overactive bladder (OAB) and urge urinary incontinence (UUI)

Patients affected by idiopathic OAB inadequately managed with conservative therapy or with antimuscarinics have been evaluated for treatment with BTX-A. A phase 2, randomized, double-blind, placebo controlled, dose-ranging study has been conducted with 313 patients (288 females), with follow-up of 36 weeks, to assess disease-specific quality-of-life outcomes and general health-related quality-of-life (HRQOL) outcomes;¹³ patients received intra detrusor BTX-A (50U, 100U, 150U, 200U, or 300U) or placebo. Onabotulinum toxin A 50U did not provide adequate patient perceived benefit, whereas most doses >100U provided a meaningful and sustained benefit, with the exception of the 200-U dose, which was sometimes the outlier. The improvements in HRQOL scores observed with BTX-A in this study exceeded previously documented minimally or clinically important differences for the I-QOL and the KHQ (Kings Health Questionnaire).

A further large (557 patients) phase 3, placebo controlled trial of Onabotulinum toxin A 100U in patients with OAB and UUI inadequately managed with anticholinergics performed by Nitti et al. showed a significant decrease of UUI per day vs placebo (-2.65 vs -0.87), and 22.9% vs 6.5% of patients became completely continent.¹⁴ Regarding patient health-related quality-of-life, patients treated with OnabotulinumtoxinA 100U reported a positive response on

the treatment benefit scale vs placebo (60.8% vs 29.2%, $p < 0.001$); uncomplicated UTI was the most common adverse event reported in the trial (15.5 vs 5.9%); a 5.4% rate of urinary retention was also observed.¹⁴

The results of another recent large phase 3, international double blind, placebo controlled study led by Chapple et al.,¹⁵ concerning patients affected by idiopathic OAB inadequately managed with antimuscarinics showed just as many significant and clinically relevant improvement in all OAB symptoms, measured with KHQ scale, with uncommon adverse event, even though more prevalent compared with the placebo group, mainly upon lower urinary tract, such as UTI. The main reasons for those who dropped out of treatment are described in a report by Mohee et al.,¹⁶ 137 patients with at least 3 years of follow-up; approximately 60% had discontinued treatment, mainly as a result of intermittent catheterization related issues or UTI; interestingly, many of the patients had reverted back to conservative treatments and antimuscarinic therapy to which they were initially refractory.

Benign prostatic hypertrophy

A role for BTX-A in BPH was proposed following the increasing evidence that the pathophysiology of this disorder might relate to neural dysregulation within the prostate. A multicenter randomized double blind placebo controlled phase II trial included men over the age of 50 years with an IPSS of 12 or over, a prostatic volume of 30–100ml, and a maximum flow rate of 5–15ml/sec; patients received either trans perineal or trans rectal injection of placebo (n=94), BTX-A 100 U (n=95), 200 U (n=94), or 300 U (n=97) into the transitional zone, with almost 100 patients in each arm; at 12 weeks, there were significant improvements from baseline in IPSS, Q_{max} , total prostatic volume and transition zone volume for all groups including placebo, with no significant improvement for BTX-A over placebo patients. However, a post hoc analysis in patients with prior α -blocker treatment suggested that 200 U BTX-A might produce greater efficacy versus placebo; no changes in PSA were seen in the treatment groups; BTX-A had no negative impact on sexual function measured with the IIEF-5 questionnaire.⁴

Another study reported on ten patients with BPH and LUTS unresponsive to traditional medical therapy, who were poor surgical candidates and were treated with varying doses of transurethral BTX-A (100–300U) depending on prostatic size.¹⁷ After treatment, there were noted improvement in mean IPSS from 24.5 to 13.4, an increase in Q_{max} from 7.9 to 16.2ml/s, reduction in prostate volume from 41.5ml to 30.4ml and mean PSA from 3.1 to 1.7ng/ml. It was felt that the trans-urethral method of injection was a safe alternative method of delivery in this pilot study.

Painful bladder syndrome/interstitial cystitis

Bladder pain syndrome (BPS) includes interstitial cystitis (IC) is defined as a chronic pelvic pain, pressure or discomfort related to the bladder associated with urgency, frequency, nocturia, dysuria and sterile urine.¹⁸ Several intravesical drugs have been studied in the past, including lidocaine, heparin, pentosan polysulfate sodium, dimethyl sulfoxide, chondroitin sulfate, hyaluronic acid as well as investigational drugs such as GM-0111. Recently, intravesical submucosal injections of BTX have been studied in patients with BPS/IC. Jhang et al.,¹⁹ showed that BTX-A injection could induce peripheral desensitization, reduce bladder chronic inflammation and

decrease apoptotic signal molecules in the urothelium; it is possible therefore to have a significant improvement of symptoms such as daytime frequency, nocturia, pain, an increase of bladder capacity and a better quality of life. Dellis et al.,²⁰ confirmed that BTX-A intravesical administration in patients with BPS/IC is a safe and efficient treatment option; however they affirmed, on the basis of results from the literature, that the level of evidence of the studies available until now is not high.

Conclusion

In summary, the use of BTX-A is well established in the management of NDO in patients who were not adequately managed by anticholinergics; recent large scale placebo controlled trials have expanded the indication for the use of BTX-A to the treatment of idiopathic overactive bladder and to benign prostatic hyperplasia. Recent evidence is beginning to support use of BTX-A in the treatment of painful bladder syndrome/interstitial cystitis: however larger sample size trials are required for validate this hypothesis.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

References

1. Cox L, Cameron AP. OnabotulinumtoxinA for the treatment of overactive bladder. *Res Rep Urol*. 2014;6:79–89.
2. Maria G, Brisinda G, Civello IM, et al. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo–controlled study. *Urology*. 2003;62(2):259–264.
3. Brisinda G, Caddeu F, Vanella S, et al. Relief by botulinum toxin of lower urinary symptoms owing to benign prostatic hyperplasia: early and long–term results. *Urology*. 2009;73(1):90–94.
4. Marberger M, Chartier–Kastler E, Egerdie B, et al. A randomized double–blind placebo–controlled phase 2 dose–ranging study of OnabotulinumtoxinA in men with benign prostatic hyperplasia. *Eur Urol*. 2013;63(3):496–503.
5. Giannantoni A, Bini V, Dmochowski R, et al. Contemporary management of the painful bladder: a systematic review. *Eur Urol*. 2012;61(1):29–53.
6. Pinto R, Lopez T, Silva J, et al. Persistent therapeutic effect of repeated injections of onabotulinum toxin a in refractory bladder pain syndrome/interstitial cystitis. *J Urol*. 2013;189(2):548–553.
7. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta–analyses: The PRISMA statement. *Int J Surg*. 2010;8(5):336–341.
8. Schurch B, Stohrer M, Kramer G, et al. Botulinum–A toxin for treating detrusor hyper reflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol*. 2000;164:692–697.
9. Rovner E, Dmochowski R, Chapple C, et al. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor over activity. *Neurourol Urodyn*. 2013;32(8):1109–1115.
10. 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(3):491–497.
11. Ginsberg D, Cruz F, Herschorn S, et al. OnabotulinumtoxinA is effective in patients with urinary incontinence due to neurogenic detrusor over activity regardless of concomitant anticholinergic use or neurologic etiology. *Adv Ther*. 2013;30(9):819–833.
12. Sussman D, Patel V, Del Popolo G, et al. Treatment satisfaction and improvement in health–related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. *Neurourol Urodyn*. 2013;32(3):242–249.
13. Fowler CJ, Auerbach S, Ginsberg D, et al. OnabotulinumtoxinA Improves Health–Related Quality of Life in Patients With Urinary Incontinence Due to Idiopathic Overactive Bladder: A 36–Week, Double–Blind, Placebo–Controlled, Randomized, Dose–Ranging Trial. *Eur Urol*. 2012;62(1):148–157.
14. Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with Overactive Bladder and Urinary Incontinence: Results of a phase 3, Randomized, Placebo controlled trial. *J Urol*. 2013;189(6):2186–2193.
15. Chapple C, Sievert KD, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomized double–blind, placebo–controlled trial. *Eur Urol*. 2013;64(2):249–256.
16. Mohe 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(1):106–113.
17. Hamidi Madani A, Enshaei A, Heidarzadeh A, et al. Transurethral intraprostatic Botulinum toxin–A injection: a novel treatment for BPH refractory to current medical therapy in poor surgical candidates. *World J Urol*. 2013;31(1):235–239.
18. Seth J, Khan MS, Dasgupta P, et al. Botulinum Toxin–What Urologic Uses Does the Data Support? *Curr Urol Rep*. 2013;14(3):227–234.
19. Jhang JF, Jiang YH, Kuo HC. Potential therapeutic effect of intravesical botulinum toxin type A on bladder pain syndrome/interstitial cystitis. *Int J Urol*. 2014;(21 Suppl 1):49–55.
20. Dellis A, Papatsoris AG. Intravesical treatment of bladder pain syndrome/interstitial cystitis: from the conventional regimens to the novel botulinum toxin injections. *Expert Opin Investig Drugs*. 2014;23(6):751–757.