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Review – Benign Prostatic Obstruction

Is Botulinum Neurotoxin Type A (BoNT-A) a Novel Therapy for Lower Urinary Tract Symptoms Due to Benign Prostatic Enlargement? A Review of the Literature

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Abstract

Context: The intraprostatic injection of botulinum neurotoxin type A (BoNT-A) is a minimally invasive but still-experimental treatment of lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE) based on an off-label use of the drug. **Objective:** Report the mechanisms of action of BoNT-A on the prostate as well as the efficacy and safety of intraprostatic BoNT-A injection according to various injection protocols.

Evidence acquisition: We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) database and the abstract volumes of the 2005, 2006, and 2007 European Association of Urology (EAU), American Urological Association (AUA) and International Continence Society (ICS) meetings for studies on intraprostatic BoNT-A injection.

Evidence synthesis: Five experimental studies and 10 clinical studies were found. The level of evidence is 1b for one study and 3 for the other studies, with grades of recommendation of A and C, respectively. The experimental studies report induced relaxation of the prostate, atrophy, and reduction of its size through inhibition of the trophic effect of the autonomic system on the prostate gland. In the clinical studies, all patients had LUTS due to BPE and prostate volume varied from <20 ml to >80 ml. The dose varied from 100 U to 300 U of Botox[®]. The injection was performed transperineally, transrectally, or transurethrally under general, local, or without anesthesia. The follow-up period ranged from 3 mo to 19.8 mo. All studies reported an improvement of maximum urinary flow rate, quality-of-life index and reduction of International Prostate Symptoms Score, prostate-specific antigen (PSA) level, post-void residual volume, and prostate volume. Local or systemic side effects were rare. Only patients with retention needed a urethral drainage catheter.

Conclusions: BoNT-A intraprostatic injection provides improvement in patients with LUTS due to BPE refractory to medical treatment. However, there is a need for large placebo controlled-studies and long-term results. So far the therapy is still experimental. © 2008 European Association of Urology. Published by Elsevier B.V. All rights reserved.

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1. Introduction

During the last decade the use of botulinum neurotoxin type A (BoNT-A) became popular for a number of indications in the urological field, although it is not yet licensed for them. A large number of studies and review papers report the use of BoNT-A in the treatment of striated sphincter dyssynergia [1,2], neurogenic detrusor overactivity [3,4], idiopathic detrusor overactivity [5], and sensory bladder disorders [6].

Recently much research has been conducted into the pathophysiology, the pharmacotherapy, and the minimally invasive treatment of lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE). It is suggested that there are two main components, the static and the dynamic. The prostate has an abundance of sympathetic and parasympathetic efferent and sensory afferent nerves. Parasympathetic innervation of the prostate gland—muscarinic receptors are primarily found in the epithelial rather than the stromal cells—has an important effect on growth and secretion of the prostate epithelium [7–9]. The dynamic component, responsible for the contraction of the smooth muscle, is under sympathetic noradrenergic innervation [9]. Excessive sympathetic activity stimulates epidermal growth factor in the prostate and has a trophic function on prostate growth [10,11]. Studies also report that sensory afferent mechanisms are involved in LUTS [6]. Subsequently, it was hypothesized that BPE could originate from neural dysregulation of the prostate and alterations in local neuropeptides.

Therefore the ideal therapy for LUTS due to BPE should cause atrophy of the prostate by reducing the trophic effects of various neurotransmitters, should induce relaxation of the dynamic component by inhibition of the α_1 -adrenergic receptors, and should inhibit the afferent input.

Remembering the mechanism of action of BoNT-A, the presumed pathophysiology of LUTS due to BPE, the disadvantages of medical treatment (persistence of LUTS, side effects) [12,13], the disadvantages of operative techniques (side effects, mortality, high risk to patients) [14,15] and the disadvantages of some new, minimally invasive techniques (ineffectiveness, lack of reproducible results) [16–18], it is understandable that BoNT-A intraprostatic injection has gained the interest of urologists.

2. Methods

2.1. Search strategy

A literature search was performed in the Medical Literature Analysis and Retrieval System Online (MEDLINE) database in

December 2007 to retrieve English language studies (from 1992 to 2007) on the use of BoNT-A in the treatment of LUTS due to BPE. For retrieving the references in MEDLINE we used the following medical subject heading terms: benign prostatic hyperplasia/obstruction/enlargement, prostate, and botulinum toxin A. Furthermore, we searched the abstract volumes of the 2005, 2006 and 2007 European Association of Urology (EAU), American Urological Association (AUA) and International Continence Society (ICS) meetings.

2.2. Botulinum neurotoxin type A injection in animal models

Five studies on the use of BoNT-A in rat prostates [19–21] and dog prostates [22,23] were found. Various doses of BoNT-A were injected (5–20 U in rats and 100–200 U in dogs). Two of the studies [21,23] were vehicle controlled. The reduction of prostate volume or weight was evaluated, and a histological examination was performed for morphologic examination, apoptosis [19,21,22], and proliferation [21,22]. A Western blot analysis for α_1 -adrenoreceptors and androgen receptors was done in one study [21]. The effects of BoNT-A on prostate contractile function (prostate urethral pressure responses to electrical and pharmacological stimulation) [23], on capsaicin-induced neurogenic prostatitis, and on prostatic pain [20] were tested.

Five authors reported atrophic changes with increased apoptosis [19–23], including decreased cell proliferation [21], flattened epithelial cells [20,21], and subsequent reduction of prostate volume or weight. In the vehicle-controlled studies [21,23], in which different doses of BoNT-A were injected, similar effects were observed: there were statistically significant differences between the BoNT-A and the vehicle groups. Chuang et al [22] reported that prostate volume did not change significantly, although gross examination revealed a smaller and less indurate prostate after BoNT-A injection compared to the controls. Lin et al [23] found a significant reduction (23%) of the prostate volume only in the 200 U-dosage group. The Western blot analysis revealed a dose-dependent reduction of α_1 -adrenergic receptors in the first week, which was less obvious in the second week. There was no significant change in androgen receptors [21].

The prostate urethral pressure responses to electrical and pharmacological stimulation were decreased in a dose-dependent way (200 U dosage induced a statistically significant reduction of responses), while normal saline injection had no effect [23]. They noticed that BoNT-A does not affect nitric oxide-related relaxation of the prostate. Atrophy of the prostate, a relative increase of stromal proportion, and vacuolization in the cytosol of the smooth-muscle cells were also reported. Chuang et al [20] noticed that BoNT-A injections provide anti-inflammatory effects in a dose-dependent fashion and reduce the prostatic pain.

While in rats all the effects decreased in the second week [21], in the dog study the effects persisted for at least 3 mo [22].

Table 1 – Study design and inclusion criteria

	Study design	Number of patients	Criteria	Evidence level
Chuang et al [22]	Prospective	8	LUTS due to BPE, PV > 40 ml	3
Maria et al [31]	DBPC 1:1	30 (15:15)	LUTS due to BPE, Qmax < 15 ml/s	1b
Chuang et al [24]	Prospective	16	LUTS due to BPE, PV < 30 ml	3
Chuang et al [25]	Prospective	41	LUTS due to BPE PV < 30 ml PV > 30 ml	3
Kuo et al [26]	Prospective	10	BPO in poor surgical candidates	3
Park et al [27]	Prospective	52	LUTS due to BPE	3
Larson et al [28]	Open label	40 (10 + 30)	LUTS due to BPE	3
Guercini et al [29]	Prospective	16	LUTS due to BPE, severe voiding obstruction PV > 80 ml	3
Silva et al [30]	Prospective	21	BPE plus chronic retention (poor surgical candidates)	3
Kuo et al [32]	NRCC	60 (30:30)	LUTS due to BPE	3

DBPC, double blind, placebo-controlled; Qmax, maximum urinary flow rate; BPE, benign prostatic enlargement; BPO, benign prostatic obstruction; LUTS, lower urinary tract symptoms; NRCC, non-randomized, controlled comparative; PV, prostate volume.

2.3. Clinical studies of botulinum neurotoxin type A in the treatment of lower urinary tract symptoms due to benign prostate enlargement

Reviewing the literature, we found 10 studies [22,24–32] on the use of BoNT-A in the treatment of LUTS due to BPE.

2.3.1. Study and patient characteristics

294 patients were enrolled in the 10 studies. There was only one randomized, double-blind, placebo-controlled study [31] and one non-randomized, controlled, comparative study [32] (Table 1). Most of the studies were small-scale studies enrolling <30 patients. There were only three larger-scale studies: one with 52 patients with various prostate volumes (PV) who were treated with various doses of BoNT-A (half of them combined with α_1 -adrenergic blockers) [27]; another with 41 patients (small and large prostates) [25]; and the last by Kuo et al [32] who enrolled 60 patients (PV > 60 ml), with a suboptimal treatment outcome of combined medical therapy—half of them were treated with BoNT-A. Unfortunately this abstract provides limited information about injection protocol and results. Forty

patients had acute or chronic urinary retention and were on a urethral indwelling catheter (Table 2). Most of the patients had been treated with α_1 -adrenergic blockers alone or in combination with 5 α -reductase inhibitors with inadequate response or could not tolerate the medication.

Among the studies the baseline mean PV varied from 19.6 ± 1.2 ml to 106 ml (Table 2). In seven studies [22,26,27,29–32] the baseline mean PV was >50 ml. Chuang et al [25] and Park et al [27] determined the dose of BoNT-A according to PV. The PV was evaluated during follow-up in order to determine the BoNT-A effect.

The maximum urinary flow rate (Qmax; Table 2) and the post-void residual volume (PVR; Table 2) were evaluated at baseline and during follow-up. At baseline, the mean Qmax varied from 7 ml/s to 10.4 ml/s. Qmax <12 ml/s [22,24,25,32] or <15 ml/s [31] was an inclusion criteria. Furthermore, patients on indwelling urethral catheters due to acute or chronic urinary retention participated in the studies [22,24–26,29,30]. The mean PVR at baseline varied from 64.2 ml to 295 ml. Kuo et al [26] performed a videourodynamic study to prove bladder outlet obstruction.

Table 2 – Baseline parameters

	Patients in retention	PV (ml)	Qmax (ml/s)	IPSS	Mean PVR (ml)	QoL index	PSA level (ng/ml)	
Chuang et al [22]	2	61.6 ± 8.7	7.5 ± 1.8	19 ± 1.8	177.6 ± 71.7	1.6 ± 0.3	–	
Maria et al [31]	0	52.6 ± 10.6	8.1 ± 2.2	23.2 ± 4.1	126.3 ± 38.3	–	3.5 ± 1	
Chuang et al [24]	1	19.6 ± 1.2	7.3 ± 0.7	18.8 ± 1.6	67.7 ± 30	3.8 ± 0.3	0.8 ± 0.23	
Chuang et al [25]	5							
		PV < 30 ml	21.1	7.9	18.7	64.2	3.9	–
		PV > 30 ml	54.3	7	19.3	161.7	4.1	–
Kuo et al [26]	8	65.5 ± 19.5	7.6 ± 3.9	–	243 ± 133.9	4.5 ± 2.7	–	
Park et al [27]	0	47.2 ± 23.9	9.6 ± 6.5	24.3 ± 7.8	122.7 ± 141.2	–	2.6 ± 3.2	
Larson et al [28]	0	–	8.2	21.2	–	–	–	
Guercini et al [29]	3	106	10.4	24	295	–	9.5	
Silva et al [30]	21	70 ± 10	–	–	–	–	6 ± 1.1	
Kuo et al [32]	–	–	–	–	–	–	–	

PV, prostate volume; PSA, prostate-specific antigen; Qmax, maximum urinary flow rate; QoL, quality of life; PVR, post-void residual volume; IPSS, International Prostate Symptoms Score; AUA, American Urological Association.

Table 3 – Dosages: dilution and technique

	Dose/dilution	Route of injection	Number of injections/place	Anesthesia	Needle	Catheter after the injection
Chuang et al [22]	200 U (8 ml)	Transperineal	1 in each lobe	Propofol 50 mg i.v.	21G	For 1 wk in 2 patients with previous retention
Maria et al [31]	200 U (4 ml)	Transperineal	1 in each lobe	Without	22G	–
Chuang et al [24]	100 U (4 ml)	Transperineal	1 in each lobe	Propofol 50 mg IV.	21G	For 1 wk in 1 patient with previous retention
Chuang et al [25]	100 U (4 ml) 200 U (8 ml)	Transperineal	1–2 in each lobe	n = 20 (IV sedation) n = 20 (without)	21G	For 1–4 wk (n = 5 with previous retention)
Kuo et al [26]	200 U (20 ml)	Transurethral	4 in each lobe, 2 in the middle lobe	Light general	23G	For 1 d to every patient; 2 patients had to perform CISC for 2 wk
Park et al [27]	100 U (4 ml) 200 U (6 ml) 300 U (9 ml)	Transperineal	1 in each lobe	Without	22G	–
Larson et al [28]	100 U	Transrectal	In base and mid-prostatic area of the lateral lobes	Without	22G	Short-term catheterization in 1 patient
Guercini et al [29]	300 U	Transperineal	–	–	–	–
Silva et al [30]	200 U in 8 ml	Transrectal	1–2 in each lobe	Without	21G	For 1 mo to every patient
Kuo et al [32]	200 U	–	–	–	–	–

CISC: clean, intermittent self-catheterization.

Patient's symptoms (Table 2) were assessed with the International Prostate Symptoms Score (IPSS) in all but two studies [26,30]. Most of the patients had moderate to severe symptoms (IPSS, 18.8 ± 1.6 to 24.3 ± 7.8). A quality-of-life (QoL) index was also assessed [22,24–26,28].

Six author groups also measured PSA values before and after treatment [24,27,29–32]. Prostate biopsies were performed [24,32] after injection for morphological examination (cell apoptosis).

The mean follow-up period varied from 3 mo to 19.8 mo [22,24–32].

2.3.2. Injection protocols (Table 3)

Botox® (Allergan, Irving, CA, USA) was used in all studies. The dose varied from 100 U to 300 U dissolved in 4–20 ml of normal saline. The 100 U doses were injected in patients with small prostates (PV < 30 ml) [24,25,27]. The 200 U doses were injected in prostates with various sizes [22,25,26,30–32]. The use of 300 U was reported [27,29] in large prostates (PV > 80 ml). Authors preferred the transperineal [22,24,25,27,29,31] or the transrectal [28,30] delivery route under transrectal ultrasound (TRUS) guidance. Only Kuo et al [26] used the transurethral route. Injection of an equal amount of BoNT-A into each lobe was performed in one or two different sites [22,24,25,27,30,31]. Larson et al [28] injected BoNT-A in the base and the mid-prostatic area, and Kuo et al [26] injected it in 10 different sites, 4 in each lobe and 2 in the middle lobe. Chuang et al [22,24] initially injected BoNT-A under general anesthesia, and later without it [25]. Kuo et al [26] reported the use of light general anesthesia. The other studies [27–31] did not report any type of anesthesia. Antibiotics were used perioperatively [22,24,25] or for 7 d [26,30]. Normally the patients did not receive a urethral indwelling catheter postoperatively, except those with previous acute or chronic urinary retention [22,24–26,30].

2.3.3. Efficacy (Tables 4 and 5)

All studies showed an effectiveness of BoNT-A injection. Maria et al [31] reported that from the BoNT-A group 11 of 15 patients and 13 of 15 patients improved at the first-month and second-month evaluations, respectively, while from the placebo group 2 of 15 patients and 3 of 15 patients had improvement in the same periods, respectively. Four nonresponders from the placebo group had a BoNT-A injection subsequently with very good results. Silva et al [30] reported that 17 of 21 patients with chronic retention were able to void again. The nonresponders of this group had a middle lobe into which BoNT-A was not injected. Kuo et al [32] reported an overall improvement in the treatment group of 83% of patients versus 17% of patients in the control group. In Chuang et al [25] 31 of 41 patients (75%) had >30% overall improvement. Park et al [27] revealed that 18 of 26 patients from the BoNT-A group and 21 of 26 patients from the combination group (BoNT-A plus α_1 -adrenergic blockers) had relief of symptoms in the first and third months after injection of the control dosage. At the 6-mo follow-up 21 of 23 patients that stayed in the study had symptomatic relief. In the other studies [22,24,26,28,29] the authors reported that all of the patients were improved after BoNT-A injection.

Regarding the IPSS [22,24,25,27–29,31,32] (Table 4) and the QoL [22,24–26,28] (Table 5), there was a statistically significant reduction in IPSS which occurred 1 mo after BoNT-A injection, with further improvement in the second month. Furthermore, there was a significant difference between the BoNT-A group and the placebo group. Kuo et al [35] reported that both the BoNT-A and the control group had significant reductions in IPSS of 47% and 32.5%, respectively. Park et al [27], comparing the BoNT-A group with the combination group (BoNT-A plus α_1 -blockers), did not find any difference in the total IPSS reduction.

Table 4 – Treatment results

	Patients improved (patients treated)	Reduction of IPSS	Increase in Qmax	Reduction of PVR
Chuang et al [22] First month	8 (8)	From 19 ± 1.8 to 5 ± 2.0 (73.1%, $p < 0.05$)	From 7.5 ± 1.8 ml/s to 12.9 ± 0.5 ml/s (72%, $p < 0.05$)	From 177.6 ± 71.7 ml to 24.5 ± 4.5 ml (86.2%, $p = 0.064$)
Maria et al [31] First month	11 (15)	From 23.2 ± 4.1 to 10.6 ± 1.7 (54%, $p = 0.00001$)	From 8.1 ml/s to 14.9 ml/s ($p < 0.00001$)	From 126.3 ± 38.3 ml to 49.6 ± 13.4 ml (60%, $p = 0.00001$)
Maria et al [31] Second month	13 (15)	From 23.2 ± 4.1 to 8 ± 1.6 (65%, $p = 0.00001$)	From 8.1 ml/s to 15.4 ml/s ($p < 0.00001$)	From 126.3 ± 38.3 ml to 21 ± 16.2 ml (83%, $p = 0.00001$)
Placebo group	2 (15) 1 st month 3 (15) 2 nd month 4 (BoNT-A)	NS ($p = 0.9$)	NS ($p = 0.9$)	NS ($p = 0.9$)
Chuang et al [24] First month	16 (16)	From 18.8 ± 1.6 to 8.9 ± 1.9 (52.6%, $p = 0.0001$)	From 7.3 ± 0.7 ml/s to 11.8 ± 0.8 ml/s (39.8%, $p < 0.001$)	From 67.7 ± 30 ml to 25.1 ± 4 ml (63%, NS)
Chuang et al [25]* 100 U BoNT-A	31 (41)	From 18.7 to 9.8 (48%, $p < 0.001$)	From 7.9 ml/s to 12 ml/s (62%, $p < 0.001$)	From 64.2 ml to 35.7 ml (44%, $p = 0.3$)
200 U BoNT-A		From 19.3 to 9.5 51% ($p < 0.001$)	From 7 ml/s to 10.3 ml/s (47%, $p < 0.001$)	From 161.7 ml to 45.2 ml (72%, $p = 0.02$)
Kuo et al [26] 6 mo	10 (10)	–	From 7.6 ± 3.9 ml/s to 11.6 ± 3.5 ml/s ($p = 0.05$)	From 243.5 ± 133.9 ml to 36.8 ± 34.1 ml ($p = 0.005$)
Park et al [27] 3 mo	39 (52)	From 24.3 ± 7.8 to 16.9 ± 6.4 (30.3%, $p < 0.05$)	From 9.6 ± 6.5 ml/s to 11.1 ± 5.9 ml/s (15.5%, $p < 0.05$)	From 122.7 ± 141.2 ml to 84.7 ± 40.9 ml (34.3%, $p < 0.05$)
Larson [28] 3 mo	10 (10)	From 21.2 to 11.4	From 10.4 ml/s to 13.3 ml/s	–
Guercini [29] 6 mo	16 (16)	From 24 to 9 ($p = 0.002$)	From 8.2 ml/s to 18.1 ml/s ($p < 0.05$)	From 295 ml to 85 ml ($p = 0.05$)
Silva [30] 3 mo	17 (21)	–	From retention to 10.3 ± 1.4 ml/s	From retention to 92 ± 24 ml
Kuo [32]	–	47%	By 2.9 ml/s	–

BoNT-A, botulinum toxin type A; NS, not significant; PVR, post-void residual volume; Qmax, maximum urinary flow rate; IPSS, International Prostate Symptoms Score.
* All values reported in this study are during month 1.

Table 5 – Treatment results

	Reduction in PV	QoL score	PSA level	Safety	Biopsy
Chuang et al [22] First month	From 61.6 ± 8.7 ml to 50 ± 5.9 ml (18.8%, $p < 0.05$)	From 3.9 ± 0.3 to 2.1 ± 0.3 (61.5%, $p < 0.05$)	–	No side effects	–
Maria et al [31] First month	From 52.6 ± 10.6 ml to 23.8 ± 6.2 ml (54%, $p = 0.00001$)	–	From 3.7 ± 0.9 ng/ml to 2.1 ± 0.7 ng/ml (42%, $p = 0.00006$)	No side effects	–
Maria et al [31] Second month	From 52.6 ± 10.6 ml to 16.8 ± 7.8 ml (68%, $p = 0.00001$)	–	From 3.7 ± 0.9 ng/ml to 1.8 ± 0.7 ng/ml (51%, $p = 0.00001$)		
Placebo	NS ($p = 0.6$)	–	NS ($p = 0.8$)		
Chuang et al [24] First month	From 19.6 ± 1.2 ml to 17 ± 1.1 ml (13.3%, $p < 0.0014$)	From 3.8 ± 0.3 to 2.1 ± 0.3 (44.7%, $p < 0.0001$)	From 0.8 ± 0.23 ng/ml to 0.72 ± 0.14 ng/ml (NS)	Dysuria and minor hematuria ($n = 3$)	Increased apoptotic
Chuang et al [25]* 100 U	From 21.1 ml to 18 ml 15% ($p < 0.001$)	From 3.9 to 2.1 46% ($p < 0.001$)	–	No side effects	–
200 U	From 54.3 ml to 46.3 ml (15%, $p < 0.001$)	From 4.1 to 2 (51%, $p < 0.001$)			
Kuo et al [26] 6 mo	From 65.5 ± 19 ml to 49.6 ± 17.6 ml ($p = 0.009$)	From 4.5 ± 2.7 to 2.1 ± 1.9 ($p = 0.0000$)	–	No side effects	–
Park et al [27] 3 mo	From 47.2 ± 23.9 ml to 42 ± 19 ml (13.1%, $p < 0.05$)	–	From 2.6 ± 3.2 ng/ml to 2.4 ± 3.1 ng/ml (NS)	No side effects	–
Larson et al [28] 3 mo	–	From 4.1 to 1.7	–	Acute epididymitis ($n = 1$), urinary retention ($n = 1$)	–
Guercini et al [29] 6 mo	From 106 ml to 53 ml ($p < 0.0001$)	–	From 9.5 ng/ml to 2.5 ng/ml ($p < 0.05$)	No side effects	–
Silva et al [30] 3 mo	From 70 ± 10 ml to 47 ± 7 ml ($p < 0.001$)	–	From 6 ± 1.1 ng/ml to 5 ± 0.9 ng/ml ($p = 0.04$)	No side effects	–
Kuo et al [32]	23.5% ($p < 0.05$)	–	35.4% ($p < 0.05$)	–	–

QoL, quality of life; PV, prostate volume; PSA, prostate-specific antigen; NS, not significant.

* All values reported in this study are during month 1.

Table 6 – Onset, time to maximum effect, and duration of effect

	Onset	Maximum	Duration*
Chuang et al [22]	1 wk	1 mo	8 mo
Maria et al [31]	1 mo	2 mo	>12 mo (mean, 19.8 mo)
Chuang et al [24]	1 mo	1–3 mo	6–12 mo
Chuang et al [25]	1 wk	1–3 mo	12 mo
Kuo et al [26]	1–2 d	1 wk	6–12 mo
Park et al [27]	During first month	3–6 mo	6 mo
Larson et al [28]	1 wk	During first month	3 mo
Guercini et al [29]	1 mo	2 mo	6 mo
Silva et al [30]	1 mo	3 mo	6 mo
Kuo et al [32]**	2 wk	–	6 mo

* The duration of response was calculated according to the follow-up. There was no long-term follow-up. The longest follow-up was up to 19.8 mo (Maria et al) without determined an important deterioration of outcomes during this follow-up.

** Onset and duration only for histological changes.

Qmax (Table 5) was significantly increased in seven studies [22,24–26,28,29,31] during the first month after BoNT-A injection. Maria et al [31] reported a statistically significant difference in the BoNT-A group between the baseline and after treatment, as well as between the BoNT-A group and the placebo group. Park et al [27] reported that Qmax was statistically significantly increased only in the third month. Kuo et al [32] showed a significant increase in Qmax (2.9 ml/s) only in the BoNT-A group. Patients with previous urinary retention [30] reached a Qmax of 9 ± 1.2 ml/s and 10.3 ± 1.4 ml/s 1 mo and 3 mo after injection, respectively.

In the only urodynamically controlled video study Kuo et al [26] revealed a statistically significant reduction of voiding pressure and post-void residual with a statistically significant increase of Qmax.

All studies demonstrated a statistically significant reduction of PV (Table 5) of various degrees after BoNT-A injection. Maria et al [31] showed a statistically significant difference in the reduction between BoNT-A-treated patients and placebo-treated patients. Similar results were demonstrated between BoNT-A group and the control group [32]. In Chuang et al's study [25], although 12 of 41 patients had no change of PV, the overall reduction was statistically significant.

Regarding PVR (Table 4), some studies demonstrated a significant reduction [26,29,31] and some [22,24] demonstrated a reduction that was not statistically significant. In Maria et al's study [31], there was a significant reduction of PVR in the BoNT-A group (before and after treatment) in comparison with the placebo group. Chuang et al [25] reported a significant reduction in the small-prostates group (100 U BoNT-A dosage) only at third month evaluation, however there was a significant reduction of PVR in the large-prostates group (200 U dosage), which appeared during the first month and was maintained during the 12-mo follow-up period. PVR was significantly reduced 3 mo after injection, although the reduction was not significant during the first-month evaluation [27]. Kuo et al [26] reported that after the removal of the catheter two patients had to perform clean, intermittent self-catheterizations for 2 wk. Patients with previous urinary retention [30] had a mean PVR of 92 ± 24 ml after the removal of the catheter 1 mo postoperatively.

PSA levels (Table 5) were significantly reduced [31] when baseline values were compared with after-treatment values and BoNT-A values were compared with placebo group values. Three studies [29,30,32] reported a significant reduction in PSA, and two studies [24,27] reported reduction in PSA that was not significant.

2.3.4. Onset, time to maximum effect, and duration of effect (Table 6)

The study by Maria et al [31] noticed significant improvement in baseline versus placebo within 1 mo after BoNT-A injection. The maximum effects were achieved between the first and second months. These benefits were maintained in 17 of 19 patients (who received BoNT-A) for >12 mo (mean follow-up period, 19.6 ± 3.8 mo). In the other studies benefits appeared within the first days [26], the first week [22,25,28], or the first month [24,27,29,30,32]. The maximal effects were noticed during the first week [26], the first month [22,24,25,28], or later [24,25,27,29,30]. The duration of the benefits varied according to the study period between 3 mo and >12 mo without any deterioration during this period.

2.3.5. Safety (Table 5)

BoNT-A was well tolerated in all studies. There were minor local adverse events like acute epididymitis in one patient [28] and dysuria and minor hematuria in three patients [24]. Kuo et al [32] did not report any side effects, although he repeated the injections of 200 U within 3 mo. The authors did not report any systemic BoNT-A-related adverse effects. Furthermore, there was no need for postoperative analgesia.

3. Discussion

The feasibility of intraprostatic injection through various routes has been tested with many injectable agents [33].

Regarding the animal studies, three [19,21,22] showed atrophy of the prostate and reduction of the prostate size. BoNT-A obviously disrupted the trophic effect of the autonomic system on the

prostate gland by inhibiting the influence of acetylcholine on the muscarinic receptors (mostly in the epithelial cells), which seems to be of primary importance in the genesis of prostatic secretions and growth. This chemical denervation induces cellular apoptosis and decreases cell proliferation. These effects were dose dependent. Some of the animal studies have proven relaxation of the prostate [21,23] due to the down-regulation of the α_1 -adrenergic receptors, vacuolization of the stromal smooth-muscle cells, and impaired release of norepinephrine from adrenergic nerve endings. BoNT-A might reduce LUTS through a sensory mechanism [20] by blocking neurotransmitter release from peripheral afferent nerve terminals (in the bladder and in the prostate). A major concern is the fact that dogs are the only animals that develop BPE and also have structural similarity to human prostates, but that is not the case with rats [34–37]. The doses injected into dogs and rats were comparatively higher than in humans relative to their body weight. According to studies [7,8] in humans the average muscarinic receptor density is 2.1 fmol/mg wet weight and is of the same range as those of rat, rabbit, and pig prostates. Somewhat lower values were found in normal or enlarged canine prostates. Although the doses used in rats were higher [19–21], the effects on the rat prostate were shorter than the effects on the human prostate. This is obviously due to the fact that the rat prostate consists primarily of epithelium with a higher turnover rate.

In the clinical studies various parameters were evaluated (Tables 4 and 5). There are definitely beneficial effects with BoNT-A therapy, but there are variations. The increase of Qmax (15.5–120%) and the decrease in IPSS (30.3–73.1%) are statistically significant in all studies [22,24–32]. These results are in accordance with and justify the significant reduction of QoL [22,24–26,28]. There is a statistically significant reduction of PV which varies from 13.1% to 68% [22,24–27,29–32]. The shrinkage of the prostate seems to be more prominent in patients with larger prostates [29–31]. However, the patients with small prostates also report symptomatic relief after BoNT-A injection [24]. An important issue in Chuang et al's [25] study is that symptomatic relief was revealed in patients without shrinkage of their prostates, which can be explained by the induced relaxation of prostatic smooth muscle by BoNT-A. Furthermore, all studies [22,24–27,29–31] show a reduction, significant or not significant, of PVR (34.3–86.2%). In patients with small prostates and small PVR (<100 ml) at baseline [24,25], the reduction of PVR was not statistically significant. Almost all the

patients with previous urinary retention were able to void, however they had postoperative urinary catheter drainage for 1 d to 7 d [22,24–26] or for 1 mo [30].

Although the main cause for LUTS is focused today on the bladder and BoNT-A has proved to be effective in reducing detrusor overactivity, the studies of BoNT-A treatment of LUTS due to BPE also demonstrate its effectiveness. The only randomized, double-blind, placebo-controlled study [31] showed “resection-like” results, but these results were critically commented upon in a letter to the editor as being “even too good to be true.” Open-label, α_1 -blocker studies [38,39] have generally yielded similar effect as strong as BoNT-A for most parameters including IPSS, Qmax and PVR, whereas they are known not to affect PV. As long as there are no head-to-head comparative studies, it would be premature to state that BoNT-A is superior to α_1 -blockers, 5 α -reductase inhibitors and their combination, or almost equal to transurethral resection of the prostate (TUR-P) and open prostatectomy.

BoNT-A effects appeared during first month [22,24–32] and were maintained for up to 12 months (the study period) [22,24–31]. A comparison with the known therapeutic options with regard to long-term results is not yet possible. There are also no data on the risk for acute urinary retention and for BPE-related surgery in the long run. Although repeated intradetrusor BoNT-A injections are a safe and valuable treatment option for neurogenic detrusor overactivity over a period of several years [40], there is no evidence about how the prostate behaves with repeated BoNT-A injections. Only Kuo et al [32] reported repeated injections of 200 U, mostly in patients with large prostates within 3 mo, but without reporting further details regarding indications, efficacy, duration, or side effects. Since we do not know yet whether and at which intervals the BoNT-A injections have to be repeated, the cost-effectiveness of this treatment cannot yet be calculated.

Different therapeutic doses and dilutions have been reported in various studies but not systematically tested. The minimum dose was 100 U, and the maximum dose was 300 U. BoNT-A was effective in both small (PV < 30 ml) [24,25], medium (PV = 30–80 ml) [22,25–27,30–32], and large (PV > 80 ml) [26,29,32] prostate sizes. The ideal dose of BoNT-A for PV is not yet established. PV influences the dosage of BoNT-A, but whether larger prostates require higher doses has actually not been tested. If PV < 30 ml, the injection of 100 U of BoNT-A seems to be adequate. In medium-sized prostates (PV = 30–

80 ml), authors preferred a 200 U dosage of BoNT-A. If PV > 80 ml, the injection of 300 U looks more reasonable and provides better results. In four of these studies [26,29–31] higher doses of BoNT-A injection achieved a higher percentage of PV shrinkage. There is no evidence about whether the severity of LUTS play a role in the selection of the optimal dose.

Depending on the preferences of the authors, BoNT-A was injected into the prostate through three different routes. The transperineal approach was the most frequently used. Most of the studies, regardless of the injection route, report similarly favorable results. Larson et al [28] (transrectal approach) demonstrated the least favorable results regarding Qmax, although there was symptomatic relief (decrease in IPSS of 50%). On the other hand, Silva et al [30] reported favorable results in patients with chronic urinary retention who were injected transrectally. All of the approaches seem to have advantages and disadvantages. The transurethral injection of BoNT-A needs light general anesthesia or sedation [26]. In contrast, transperineal and transrectal approaches can be used without even local anesthesia and do not need postoperative analgesia. Transrectal injections [28,30] were performed as an outpatient procedure. The transurethral route allows to injection of the BoNT-A into the transitional zone and into the median lobe, while with transperineal and transrectal approaches the median lobe may be missed. After transurethral injection [26], urethral catheter drainage should be applied for 1 d. It cannot yet be decided which approach is the one that is going to be the most appropriate. There is no evidence so far for the optimal sites of BoNT-A injection.

Seven studies [22,24–27,30,32] reported that patients had symptoms refractory to medical treatment or had intolerable side effects. In the other three studies [28,29,31] this issue was not clarified. There was no comparison with BoNT-A between responders and nonresponders to α_1 -blockers.

The procedure is considered safe since local or systemic side effects were rare [24,28]. However, recently the FDA released a warning based on observations of adverse reactions, especially in children with cerebral palsy. The agency noted that these reactions may be related to overdosing and did not advise health care professionals to discontinue prescribing BoNT-A. The absence of side effects and the fact that BoNT-A can be injected without anesthesia seem to be important advantages. Only patients with previous acute or chronic urinary retention need a temporary catheter drainage postoperatively [22,24–26,30].

The potential effects of BoNT-A on erectile function, the risk of retrograde ejaculation, and sperm abnormalities were not evaluated. Finally, due to its action in cell proliferation/apoptosis [19–23] and sensory afferents [6], the potential role of BoNT-A in the treatment of chronic pelvic pain syndrome and prostate cancer should be considered as an area for future investigation.

The level of evidence (LoE) for this new type of therapy must still be regarded as low. There is only one randomized, double-blind, placebo-controlled study [31] with a LoE of 1b and a grade of recommendation A. All the others are case-controlled studies with a small number of patients and short follow-up periods, corresponding to an LoE of 3 and a grade of recommendation C.

4. Conclusions

The experimental studies have revealed the possible mechanism of action of BoNT-A on prostate. The results of the clinical studies are encouraging for the further use of BoNT-A in the treatment of LUTS due to BPE refractory to medical treatment. However, the level of evidence is 1b for only one study [31] and 3 for all the other studies. What we need are large scale, clinical, placebo-controlled, randomized studies, including long-term surveillance, in order to determine the best delivery route, the best sites within the prostate for BoNT-A injections, the suitable dosing and dilution, the long-term effects, and safety. Moreover, comparative studies with α_1 -blockers, 5 α -reductase inhibitors, and TUR-P are required. So far BoNT-A therapy for LUTS due to BPE must be regarded experimental.

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Study concept and design: Oeconomou, Madersbacher

Acquisition of data: Oeconomou, Kiss, Berger

Analysis and interpretation of data: Oeconomou, Rehder, Berger

Drafting of the manuscript: Oeconomou, Kiss, Rehder

Critical revision of the manuscript for important intellectual content:

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Editorial Comment on: Is Botulinum Neurotoxin Type A (BoNT-A) a Novel Therapy for Lower Urinary Tract Symptoms Due to Benign Prostatic Enlargement? A Review of the Literature

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Recently, botulinum toxin has been used for several urological indications, including striated sphincter dyssynergia and neurogenic and idiopathic detrusor overactivity [1–4]. It shows good efficacy and a favorable profile of adverse events.

Oeconomou et al performed a systematic review of the literature aiming at evaluating the available evidence in favor of the use of botulinum toxin A (BoNT-A) in the field of lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE) [5]. Five preclinical and ten clinical studies were identified. The best evidence was the randomized placebo-controlled trial from Maria et al. which enrolled 30 patients evaluated at 2-mo

follow-up (reference 31 in Oeconomou et al [5]). The study showed that BoNT-A reduced the American Urological Association (AUA) symptom score by 65% and serum prostate-specific antigen (PSA) level by 51% compared to baseline values. Although the study was methodologically accurate, the limited number of patients and the short follow-up were considerable drawbacks.

The available literature assessing BoNT-A in patients with LUTS due to BPE probably does not justify a systematic review. To date, BoNT-A should not be considered a novel therapy for BPE and no guidelines in the field include BoNT-A as a possible treatment [6]. Clearly, large-scale, placebo-controlled randomized trials are needed to evaluate the short- and long-term efficacy of BoNT-A as well as maintenance such as the need for repeated injections in patients with LUTS due to BPE. Moreover, due to the availability of several efficacious treatments for BPE, the possible role for BoNT-A should be addressed in further randomized trials that compare BoNT-A to α -blockers, 5- α reductase inhibitors, minimally invasive treatments, and maybe even traditional surgery. Although BoNT-A is really precious for patients with storage LUTS due to neurogenic and

idiopathic detrusor overactivity or for those patients with striated sphincter dyssynergia, I am a little bit skeptical about whether it is what we need the most for the patients with BPE.

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Editorial Comment on: Is Botulinum Neurotoxin Type A (BoNT-A) a Novel Therapy for Lower Urinary Tract Symptoms Due to Benign Prostatic Enlargement? A Review of the Literature

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Medical treatment of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) has been primarily based on α_1 -adrenoceptor (AR) antagonists, 5α -reductase inhibitors, and phytotherapy. Only a few new drug classes have been added, which is probably because the pathophysiology of LUTS is multifactorial and treatment targets are difficult to define. It is currently unclear whether the most relevant target is within the prostate or whether extraprostatic sites are more important. Many patients with benign prostatic obstruction still experience persistent storage symptoms after prostatectomy, which should relieve obstruction. Furthermore, LUTS also occur in women. Therefore, focus has shifted from the prostate to the bladder as the source of some LUTS and as a therapeutic target [1].

Botulinum neurotoxin type A (BoNTA) has been recently introduced not only for the treatment of LUTS but also for neurogenic and idiopathic detrusor overactivity (DO) [2]. Oeconomou et al present a timely review of the current knowledge of BoNTA as a novel therapeutic option in the treatment of LUTS [3]. Intraprostatic injection of BoNTA

results, with few side effects, in significant improvements in urinary flow rate, Quality of Life Index, reduction of International Prostate Symptoms Score, prostate-specific antigen (PSA), postvoid residual volume, and prostate volume. Although the mechanism of action leading to these improvements is not completely clarified, next to atrophy of the prostate and relaxation of prostatic smooth muscle, afferent signaling pathways might be of importance. After intradetrusor BoNTA injection, a decrease of transient receptor potential vanilloid type 1 (TRPV1) and P2X3-immunoreactive positive nerve fibers was observed [4]. TRPV1 and purinergic receptors are expressed by urothelial cells as well as by afferent nerves in proximity to urothelial cells in the urinary bladder, whereas intravesical adenosine triphosphate (ATP) induces detrusor overactivity in conscious rats [5]. It remains to be determined whether other factors that influence bladder function are modulated by BoNTA.

Further randomized controlled studies with longer follow-up are needed to evaluate the potential of BoNTA. Based on the current findings, however, BoNTA seems to be a promising new option for the treatment of LUTS.

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