



## Platinum Priority – Incontinence

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# Efficacy and Safety of Low Doses of OnabotulinumtoxinA for the Treatment of Refractory Idiopathic Overactive Bladder: A Multicentre, Double-Blind, Randomised, Placebo-Controlled Dose-Ranging Study

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## Abstract

**Background:** In the treatment of patients with idiopathic overactive bladder (iOAB), high doses of botulinum toxin type A (BoNTA) were often associated with complications resulting from high postvoid residuals (PVR), leading to clean intermittent catheterisation (CIC) and urinary tract infections (UTI).

**Objective:** Evaluate the efficacy and tolerability of low doses of onabotulinumtoxinA compared to placebo in patients with iOAB.

**Design, setting, and participants:** Between 2005 and 2009, adults with persistent iOAB were included in a prospective, randomised, double-blind, placebo-controlled comparative trial.

**Intervention:** Patients were randomised to undergo a single intradetrusor injection procedure of either placebo or onabotulinumtoxinA (50 U, 100 U or 150 U).

**Measurements:** The initial evaluations (ie, clinical and urodynamic variables as well as quality of life [QoL]) were repeated at day 8 and months 1, 3, 5, and 6.

**Results and limitations:** Ninety-nine patients were included in the efficacy analysis. Three months after the procedure, we observed >50% improvement versus baseline in urgency and urge urinary incontinence (UUI) in 65% and 56% of patients who respectively received 100 U ( $p = 0.086$ ) and 150 U ( $p = 0.261$ ) BoNTA injections and >75% improvement in 40% of patients of both groups (100 U [ $p = 0.058$ ] and 150 U [ $p = 0.022$ ]). Complete continence was observed in 55% and 50% patients after 100 U and 150 U BoNTA treatment, respectively, at month 3. Frequency symptoms and QoL improved up

<sup>1</sup> Other participants are listed in the appendix.

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to the 6-mo visit. We observed only three patients with a PVR >200 ml in the 150 U group and a few UTIs.

**Conclusions:** 100 U and 150 U BoNTA injections were well tolerated and have both shown to improve symptoms and QoL in patients with iOAB. Nevertheless, 100 U injections showed a reasonable efficacy, with a lower risk of high PVR.

**Trial registration:** ClinicalTrials.gov NCT00231491.

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## 1. Introduction

*Overactive bladder* (OAB), defined as lower urinary tract symptoms of urgency with or without urge urinary incontinence (UUI), usually with frequency and nocturia [1], affects approximately 17% of adults in European countries [2] and has a substantial impact on different parameters, including quality of life (QoL) [3]. Conservative treatments (ie, lifestyle modifications, pelvic floor exercises, bladder training, and anticholinergic regimens) may result in insufficient improvements and in low compliance because of bothersome adverse events [4,5]. For idiopathic OAB (iOAB) patients, sacral neuromodulation is the only approved second-line treatment. Botulinum toxin type A (BoNTA), another minimally invasive option, is currently under evaluation.

BoNTA injections have largely been studied in patients with neurogenic OAB [6]. However, only a few articles described the effect of onabotulinumtoxinA in patients with iOAB [7], and only four randomised, placebo-controlled studies reported either the effect of 200 U BoNTA injections [8,9] or compared the efficacy of different BoNTA doses (50, 100, 150, 200, and 300 U) [10–12]. These data demonstrated significant improvements in OAB symptoms and QoL, but they also showed increased postvoid residual (PVR), acute urinary retention (AUR), and symptomatic urinary tract infections (UTI). A dose-related effect was observed in urodynamic measures and safety outcomes; QoL improved for most patients. The optimal dosing of BoNTA still remains to be defined [13].

Our objective was to evaluate, in a placebo-controlled, dose-ranging study, the efficacy and tolerability of a single intradetrusor injection procedure of low doses of onabotulinumtoxinA (50, 100, or 150 U) in patients with iOAB refractory to anticholinergics and in patients who discontinued anticholinergics.

## 2. Patients and methods

### 2.1. Patients

Between October 2005 and March 2009, patients >18 yr of age with iOAB that lasted for >6 mo were recruited from 11 centres in France. Patients were included if they had three or more episodes of urgency with or without UUI per 3 d; eight or more voidings per 24 h; a proven detrusor overactivity (DO); and were refractory, had contraindications to, or discontinued anticholinergics because of adverse events. Before inclusion, patients had used anticholinergics for at least 3 mo and for up to 12 mo. All patients were trained or willing to perform clean intermittent catheterisation (CIC) for prophylactic use and were able to fill in a bladder diary. In case of anticholinergics use, a stable regimen was maintained during the

study period. Patients were not included if they had symptomatic UTI, a urinary flow rate <15 ml/s, a PVR >150 ml, predominant stress urinary incontinence, a 24-h urinary production >3 l, an allergy or contraindication to study medication, an ongoing anticoagulant or antineoplastic treatment, or if they had been exposed to BoNTA in the past 3 mo.

### 2.2. Study design

We set up a double-blind, multicentre, prospective, randomised phase 2 trial to compare the efficacy and tolerability of a single intradetrusor injection procedure of different doses of onabotulinumtoxinA with placebo in adults with refractory iOAB and DO (confirmed by cystometry). The follow-up lasted 6 mo, with visits at day 8 and months 1, 3, 5, and 6. The study was approved by the Local Research Ethical Committee (Boulogne Billancourt, 25 November 2004) and was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients. The study was registered at ClinicalTrials.gov (NCT00231491).

### 2.3. Product and injection technique

At inclusion, patients were randomised on a 1:1:1:1 basis to undergo a single-injection procedure of either onabotulinumtoxinA (50 U, 100 U, or 150 U-Botox, Allergan, Irvine, CA, USA) or placebo. The randomisation was performed by an independent statistician and was stratified by centre. One dose of prophylactic antibiotics was orally administered 90 min before injection. BoNTA was injected at cystoscopic guidance after the bladder was distended using approximately 100 ml of normal saline solution. Study drugs were injected under cystoscopic guidance after local (lidocaine gel) or general anaesthesia. OnabotulinumtoxinA was reconstituted using 15 ml of normal saline solution. A single-injection procedure of 15 injections was performed in the detrusor, sparing the trigone. The distribution of injection sites was homogeneous, defined on a bladder model, and adopted by all centres.

### 2.4. Patient assessment

Baseline information was gathered using a physical examination, a 3-d micturition diary, a urodynamic examination, a lower urinary tract ultrasound, and QoL questionnaires. Patient data were collected 15 d before inclusion (day – 15); at inclusion; on day 8; and at months 1, 3, 5, and 6.

The primary end point of the study was the proportion of patients showing >50% improvement compared to baseline of both urgency and UUI episodes at month 3. Secondary endpoints included changes in symptoms, urodynamic measures, and QoL. Individual symptom evaluation included 24-h frequency of micturition, mean UUI, and urgency episodes/d and pads/d recorded on a 3-d micturition diary. Urodynamic measures consisted of volume at first and at strong contraction, detrusor pressure (DP), maximum DP, maximum cystometric capacity (MCC) measured by cystometry, and PVR and voided volume evaluated through noninvasive uroflowmetry. QoL was assessed using the Incontinence Quality of Life (I-QoL) questionnaire, a validated disease-specific 22-item score [14,15] evaluating both the distress and impact of urinary incontinence, and the EQ-5D visual analogue scale

(VAS) [16], measuring the patient's current health-related QoL state; both scales range from 0 to 100 (worst to best).

Tolerability and safety were evaluated at each visit using the PVR, the maximal flow rate, the perisurgical VAS pain score, vital signs, and the presence of UTI and BoNTA antibodies. UTIs were evaluated using a urine strip test; if positive, a complete laboratory culture test was performed. All asymptomatic UTIs were treated for 7 d using prophylactic antibiotics. BoNTA antibodies were measured at day – 15 and at month 6 as previously described [17].

### 2.5. Statistical analysis

A sample calculation of 38 patients per group was based on a 50% reduction in primary outcome criteria after BoNTA injection, a 20% reduction in the placebo group, an  $\alpha$ -risk of 5%, and a power of 80%, resulting in a total of 160 inclusions. An interim analysis was planned at mid-inclusion.

Intergroup comparisons were performed using the Kruskal-Wallis test for quantitative variables and the  $\chi^2$  test for qualitative variables. The dose-response relationship for BoNTA was assessed by logistic regression stratified by centre, with 50% reduction of primary outcome. Because of missing data, we also used the last observation carried forward (LOCF) method to improve the robustness of the analyses on the main criterion. Tolerability evaluations and changes in secondary endpoints from baseline were compared between each dose and placebo using the Man-Whitney test. A  $p$  value  $<0.05$  was considered statistically significant.

The data were double-entered and held by the principle investigator. Analysis was performed by a blinded statistician from the Department of Clinical Research, Ambroise Paré Hospital, Boulogne, France, using SAS statistical software (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Participation flow and patient characterisation

Because of slow recruitment, an interim analysis by an independent data-monitoring committee (IDMC), and early discontinuation, only 107 patients were included. The

patient flow is illustrated in Figure 1. Moreover, two centres were excluded from the study because of major protocol deviations, resulting in a statistical analysis being conducted on 99 patients. Eighty-five patients were followed up to 6 mo. There were no statistically significant differences in baseline characteristics between groups (Table 1). Most patients were women (87.9%), and the mean age was 61.6 yr of age. Eight patients restarted anticholinergic agents at month 3, one of whom started earlier (50 U group).

### 3.2. Efficacy

#### 3.2.1. Clinical variables

Seventy-seven patients had a complete set of primary outcome data both at baseline and at day 90 (Table 2). The overall test hardly reached significance ( $p = 0.08$ ), and the post hoc power was 62%. Taking into account the IDMC recommendations, the high placebo effect, and a potentially subjective evaluation [18], we also considered  $>75\%$  reduction in urgency and UII symptoms as a coprimary outcome. When considering LOCF data calculation in 92 patients, we observed  $>50\%$  reduction in symptoms from baseline in 65% and 58% of patients who respectively received 100 U and 150 U BoNTA (Table 3). When considering  $>75\%$  reduction, the overall treatment effect was significant ( $p = 0.03$ ), with a 42% success rate in the 100 U and 150 U BoNTA groups versus 22% in the placebo group (Table 2). Results were confirmed by the LOCF analysis (Table 3).

Improvement in urgency or UII episodes was observed in most patients at the first visit (day 8) and was significantly different from placebo at month 1 in the 150 U BoNTA group (Fig. 2). Results at month 1 in the 100 U and 150 U groups were comparable; however, only 150 U

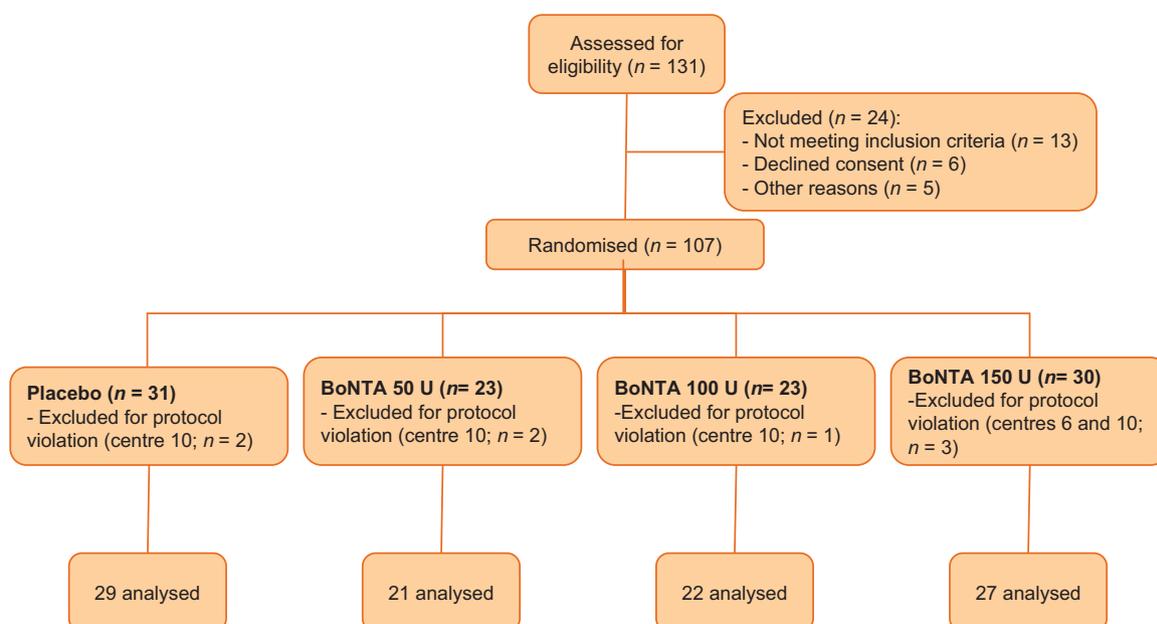


Fig. 1 – Patient flow chart.  
BoNTA = botulinum toxin type A.

**Table 1 – Demographic, clinical, and quality of life baseline characteristics (mean plus or minus standard error of the mean)**

	Total	Placebo	BoNTA			p
			50 U	100 U	150 U	
<b>No. of patients</b>	99	29	21	22	27	–
No. of female (%)	87 (87.9)	27 (93.1)	20 (95.2)	18 (81.8)	22 (81.5)	0.440
Age, yr	61.6 ± 14.0	61.7 ± 13.9	62.3 ± 12.8	62.5 ± 17.5	60.3 ± 12.8	0.723
<b>OAB symptoms/d<sup>a</sup></b>						
24-h frequency	12.3 ± 4.2	11.2 ± 2.3	12.7 ± 6.4	12.6 ± 4.6	12.8 ± 3.2	0.227
Urgency episodes	8.0 ± 4.8	7.0 ± 3.5	6.8 ± 5.3	8.7 ± 6.1	9.3 ± 4.6	0.089
UUI episodes	5.0 ± 4.3	5.9 ± 4.6	3.9 ± 2.4	5.9 ± 6.3	3.9 ± 2.7	0.439
Pads	3.6 ± 2.1	4.0 ± 2.1	3.3 ± 1.6	4.2 ± 3.0	3.2 ± 1.9	0.573
<b>Urodynamic scores</b>						
Voided volume, ml	168.9 ± 99.4	207.5 ± 152.8	156.4 ± 71.3	144.6 ± 54.5	155.2 ± 53.8	0.068
Volume at first contraction, ml	129.4 ± 72.6	130.1 ± 66.4	110.6 ± 76.6	158.4 ± 83.2	118.8 ± 64.0	0.210
Volume at strong desire to void, ml	202.8 ± 104.9	189.0 ± 79.0	203.7 ± 126.2	228.5 ± 130.1	192.7 ± 83.4	0.769
Detrusor pressure, cm H <sub>2</sub> O	42.7 ± 32.5	46.7 ± 33.2	29.3 ± 21.2	49.3 ± 40.1	42.4 ± 30.4	0.175
MCC, ml	227.9 ± 120.0	229.3 ± 102.2	212.2 ± 141.7	249.3 ± 129.0	220.5 ± 116.5	0.723
PVR, ml	9.6 ± 20.4	7.3 ± 13.1	14.6 ± 34.2	6.9 ± 13.5	10.4 ± 17.1	0.750
<b>QoL</b>						
EQ-5D VAS	54.9 ± 23.7	60.2 ± 20.6	47.3 ± 22.8	58.1 ± 24.7	52.2 ± 26.7	0.301
I-QoL	32.6 ± 19.0	33.2 ± 15.9	36.6 ± 19.8	31.0 ± 22.5	29.9 ± 19.6	0.567

BoNTA = botulinum toxin type A; OAB = overactive bladder; UUI = urge urinary incontinence; MCC = maximum cystometric capacity; PVR = postvoid residual; QoL = quality of life; VAS = visual analogue scale; I-QoL = Incontinence Quality of Life.

<sup>a</sup> Reported on 3-d voiding diary.

**Table 2 – Primary criteria: percentage of patients with >50% or 75% improvement in urgency and urge urinary incontinence episodes at month 3**

		Placebo	BoNTA		
			50 U	100 U	150 U
<b>Reduction &gt;50%</b>	No.	23	16	19	19
	Success rate, %	30	37	68	58
	p (compared to placebo)	–	0.46	0.06	0.49
	Overall p	–	0.08		–
<b>Reduction &gt;75%</b>	Success rate, %	22	6	42	42
	p (compared to placebo)	–	0.05	0.06	0.06
	Overall p	–	0.03		–

BoNTA = botulinum toxin type A.

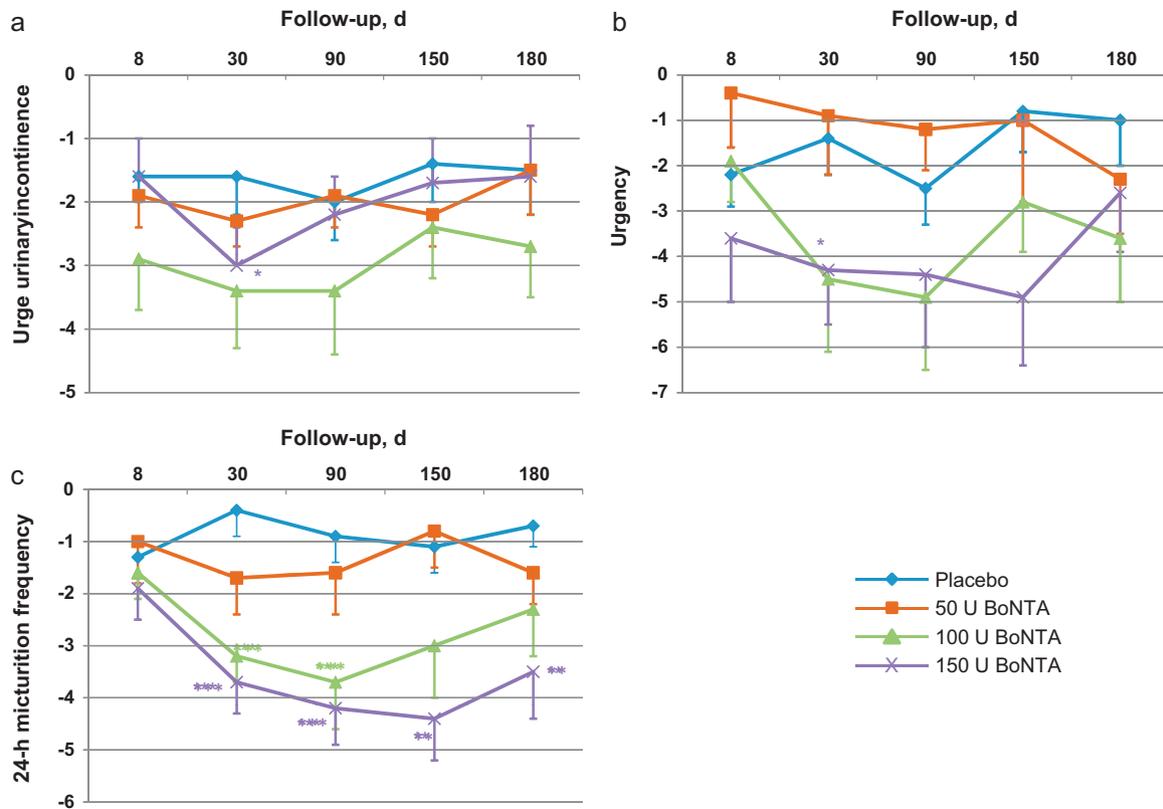
**Table 3 – Primary criteria: percentage of patients with >50% or 75% improvement in urgency and urge urinary incontinence episodes at month 3 calculated with the last observation carried forward method**

		Placebo	BoNTA		
			50 U	100 U	150 U
<b>Reduction &gt;50%</b>	No.	28	19	20	25
	Success rate, %	29	37	65	56
	p (compared to placebo)	–	0.39	0.09	0.2691
	Overall p	–	0.06		–
<b>Reduction &gt;75%</b>	Success rate, %	18	5	40	40
	p (compared to placebo)	–	0.04	0.06	0.02
	Overall p	–	0.01		–

BoNTA = botulinum toxin type A; LOCF = last observation carried forward.

BoNTA results were significantly different from placebo. Symptom reduction benefits showed a slight trend towards decrease after 5–6 mo. The decrease in 24-h frequency in the 150 U group remained significantly different from placebo for up to 6 mo. The number of patients achieving complete continence was significantly higher than placebo after 100 U and 150 U BoNTA. At month 3, 15.8%, 55.0%,

50.0%, and 10.7% ( $p < 0.001$ ) and at month 5, 15.8%, 45.0%, 45.8%, and 7.1% ( $p < 0.009$ ) achieved complete continence after respectively 50 U, 100 U, 150 U, and placebo. For patients on 50 U BoNTA, symptom improvement was never significantly different from placebo; the proportion of patients who experienced >75% symptom improvement was lower than in the placebo group.



**Fig. 2 – Mean difference (plus or minus standard error) from baseline in the number of (a) urge urinary incontinence episodes, (b) urgency episodes, and (c) 24-h frequency in the different treatment groups (placebo, botulinum toxin type A [BoNTA] 50 U, 100 U, or 150 U). P values were calculated for each BoNTA dosage compared to the placebo group at each time point.**

\*  $0.01 \leq p < 0.05$ .

\*\*  $0.001 \leq p < 0.05$ .

\*\*\*  $p < 0.001$ .

### 3.2.2. Urodynamic variables

We observed a small placebo effect in the urodynamic results (Table 4). Significant improvements compared to placebo were observed at month 3 after 150 U BoNTA treatment for all measured volumes (voided volume,

volume at first contraction, volume at first desire to void) and for MCC. Slight improvements were observed after 50 U BoNTA treatment. These urodynamic improvements showed a tendency to decrease at month 6 (data not shown).

**Table 4 – Mean absolute difference of several urodynamic measures at month 3 from baseline**

		Placebo	BoNTA		
			50 U	100 U	150 U
Voided volume, ml	<i>n</i>	23	18	18	20
Versus day 0 plus or minus SE		$-32.5 \pm 164.7$	$13.5 \pm 46.1$	$47.9 \pm 47.6$	$48.5 \pm 64.6$
	<i>p</i>	–	0.351	0.002	0.007
Volume at first contraction, ml	<i>n</i>	20	14	20	20
Versus day – 15 plus or minus SE		$17.5 \pm 68.1$	$76.1 \pm 90.4$	$75.7 \pm 90$	$110.3 \pm 109.9$
	<i>p</i>	–	0.052	0.047	0.005
Volume at strong desire to void, ml	<i>n</i>	19	14	19	18
Versus day – 15 plus or minus SE		$20.3 \pm 91.3$	$75.6 \pm 70.5$	$82.1 \pm 136.5$	$122.8 \pm 107.7$
	<i>p</i>	–	0.058	0.120	0.004
Detrusor pressure, cm H <sub>2</sub> O	<i>n</i>	23	15	18	21
Versus day – 15 plus or minus SE		$-3 \pm 39.1$	$5.7 \pm 30.2$	$-13.8 \pm 35.3$	$-10.7 \pm 40.1$
	<i>p</i>	–	0.846	0.16	0.084
MCC, ml	<i>n</i>	24	17	20	21
Versus day – 15 plus or minus SE		$22.9 \pm 99$	$38.4 \pm 94.8$	$85.5 \pm 135.1$	$91.3 \pm 125.2$
	<i>p</i>	–	0.634	0.112	0.043

BoNTA = botulinum toxin type A; SE = standard error; MCC = maximum cystometric capacity.

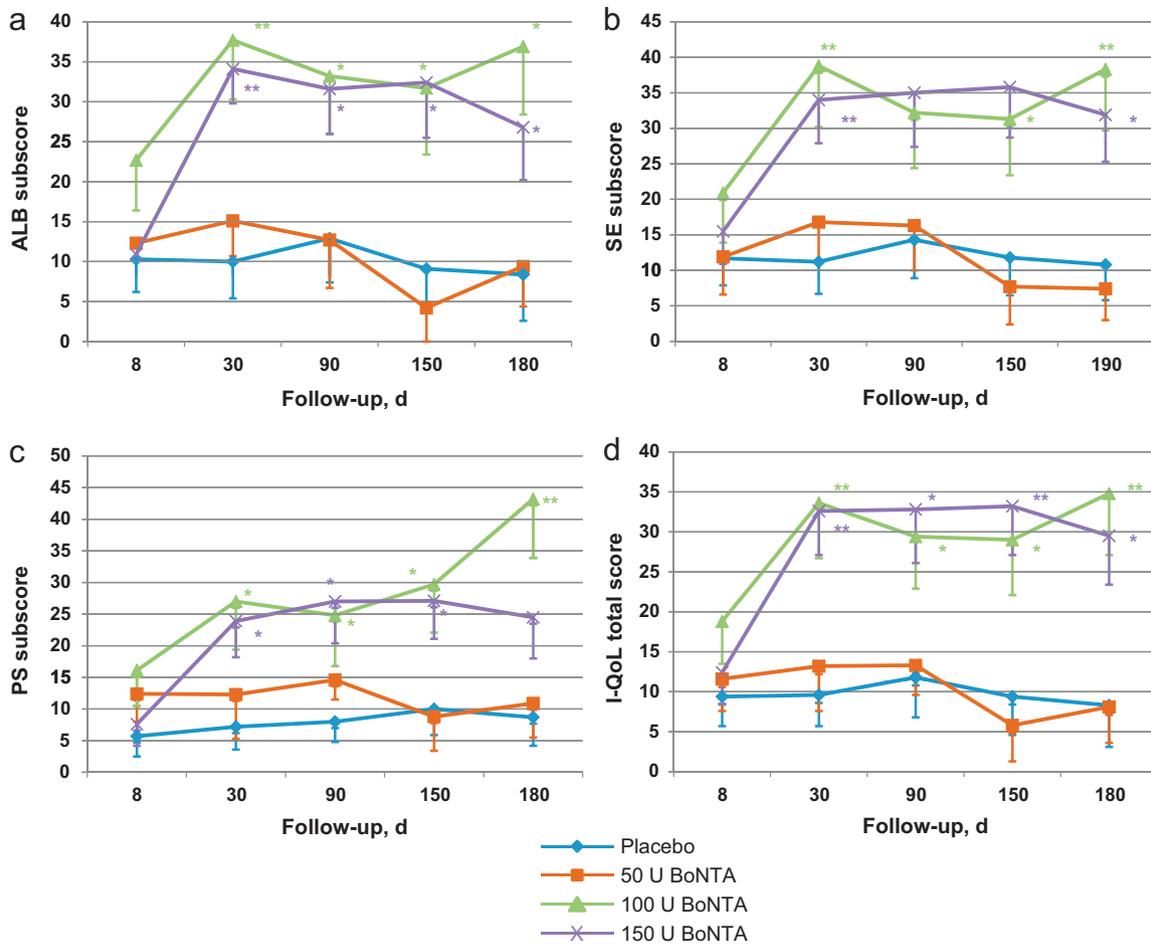


Fig. 3 – Mean differences in Incontinence Quality of Life (plus or minus standard error) questionnaire subscale scores (a) avoidance and limiting behaviour, (b) social embarrassment, (c) psychosocial impacts, and (d) total score from baseline according to the treatment group. P values are the comparison between placebo and botulinum toxin type A treatment.

ALB = avoidance and limiting behaviour; SE = social embarrassment; PS = psychosocial impacts; I-QoL = Incontinence Quality of Life; BoNTA = botulinum toxin type A.

\* 0.01 ≤ p < 0.05.

\*\* 0.001 ≤ p < 0.05.

\*\*\* p < 0.001.

3.2.3. Quality of life

In most patients receiving 100 U and 150 U BoNTA, QoL had improved at month 1, though not all results were significantly different from placebo (Fig. 3). The general health status, as measured by the EQ-5D VAS, had also improved at month 1 in those two groups and was significantly different from placebo (Fig. 4).

3.3. Safety and tolerability

UTIs were identified in 4 of 84 and 6 of 82 patients at month 3 and month 6, respectively (Table 5). Perisurgical VAS pain score was around 4 out of 10 and was comparable in all groups (Fig. 5). Six severe adverse events were reported, two of which were related either to disease progression or to study drug administration (Table 6).

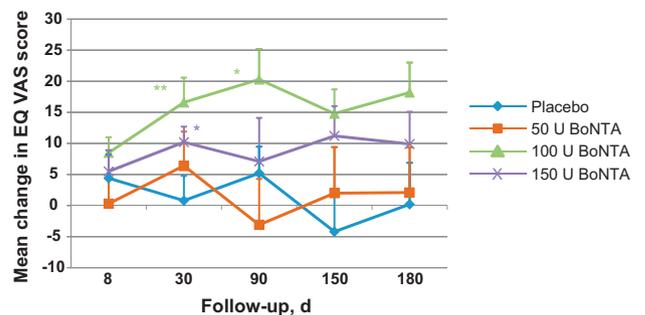


Fig. 4 – Mean difference in the EQ visual analogue scale plus or minus standard error from baseline in the different treatment groups. P values were calculated for each botulinum toxin type A dosage compared to the placebo group at each time point.

EQ VAS = EQ-5D visual analogue scale; BoNTA = botulinum toxin type A.

\* 0.01 ≤ p < 0.05.

\*\* 0.001 ≤ p < 0.05.

**Table 5 – Adverse events**

		Total	Placebo	BoNTA		
				50 U	100 U	150 U
UTI						
No. of total (%)	D0	1 of 97	0 of 29 (0%)	0 of 21 (0%)	1 of 22 (4.5%)	0 of 25 (0%)
	M3	4 of 85	0 of 24 (0%)	1 of 18 (5.6%)	1 of 21 (4.8%)	2 of 22 (9.1%)
	M6	6 of 82	2 of 23 (8.7%)	2 of 18 (11.1%)	0 of 19 (0%)	2 of 22 (9.1%)
Perisurgical VAS pain scale						
	<i>n</i>	85	28	15	19	23
Mean plus or minus SD		4.1 ± 2.5	4.0 ± 2.6	3.9 ± 2.4	4.2 ± 2.5	4.2 ± 2.5
	<i>p</i>	0.984	–	–	–	–

BoNTA = botulinum toxin type A; UTI = urinary tract infection; D = day; M = month; VAS = visual analogue scale; SD = standard deviation.

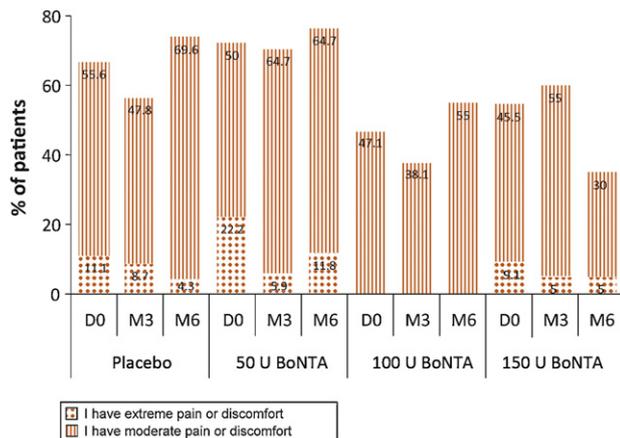
**Table 6 – Severe adverse events leading to hospitalisation**

Study drug	Description
50 U BoNTA	Breast cancer Pyelonephritis <sup>*</sup> Bilateral hydronephrosis at month 6 in patient with low compliance and severe DO*
100 U BoNTA	Hydrocephalus Depression
150 U BoNTA	Cardiac arrhythmia

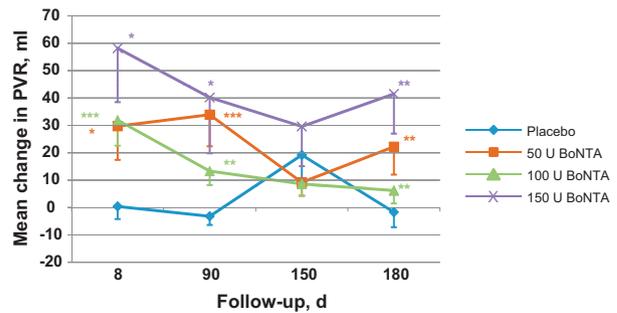
BoNTA = botulinum toxin type A; DO = detrusor overactivity.  
\* Adverse event related to disease progression or study drug intervention.

PVR increased in all treatment groups and was significantly different from placebo at day 8, month 3, and month 6 (Fig. 6). We observed a slight dose-response relationship in the 100 U and 150 U BoNTA groups.

The proportion of patients with a high PVR was low in all groups (Fig. 7). In the 150 U group, three patients had a PVR >200 ml at day 8 and only one patient at month 6. Few patients needed CIC (Table 7). BoNTA antibodies were found in two patients who received 150 U; the presence of antibodies had no significant impact on efficacy.



**Fig. 5 – Level of pain assessed by the patient according to the treatment: (a) placebo, (b) 50 U botulinum toxin type A (BoNTA), (c) 100 U BoNTA, and (d) 150 U BoNTA at day 0, month 3, and month 6. D = day; M = month.**



**Fig. 6 – Mean difference from baseline (plus or minus standard error) in postvoid residual. PVR = postvoid residual; BoNTA = botulinum toxin type A.**

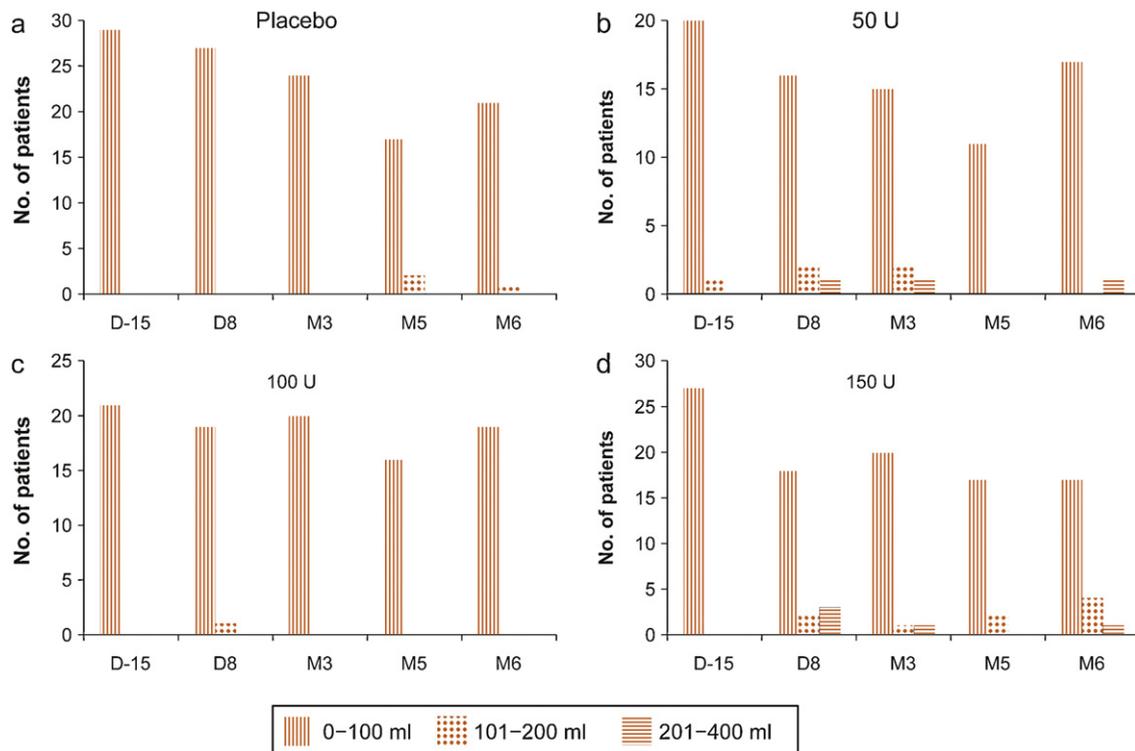
**Table 7 – Number of patients requiring clean intermittent catheterisation**

Group	Number of patients	CIC
Placebo	1	- Inclusion
50 U BoNTA	3	- D30 (PVR 5ml) - D8, D30, D90, D150, D180 - Inclusion (PVR 120 ml)
100 U BoNTA	1	- D90, D150, D180 (PVR 80 ml)
150 U BoNTA	4	- Inclusion, D8 (PVR 100 ml), D30 - D8 (PVR 300 ml), D30, D150 (PVR 180 ml) - D30, D90, D150 (PVR 200 ml), D180 - D30, D90 (PVR 50 ml)

CIC = clean intermittent catheterisation; BoNTA = botulinum toxin type A; D = day; PVR = postvoid residual.

**4. Discussion**

To our knowledge, this is the first study evaluating low doses of a single intradetrusor injection of BoNTA in a placebo-controlled, double-blind, dose-ranging study with a 6-mo follow-up in patients with iOAB and confirmed DO. We observed promising success rates in improvement of both urgency and UII episodes at month 3 after 150 U BoNTA; success rates >50%; and >75% improvement in 56% (not shown) and 40% (*p* = 0.022) of patients, respectively. Success rates were comparable in the 100 U BoNTA group but not significantly different from placebo.



**Fig. 7 – Repartition of the postvoid residual at each time point according to the treatment group: (a) placebo, (b) 50 U botulinum toxin type A (BoNTA), (c) 100 U BoNTA, (d) 150 U BoNTA. D = day; M = month.**

The 150 U BoNTA dosage demonstrated a slightly higher trend in overall symptom improvement in urgency and UUI episodes and 24-h micturition frequency than 100 U BoNTA, without a pronounced dose-response relationship. We also observed a slightly higher and consistent improvement in QoL after 150 U BoNTA treatment compared to the 100 U dosage. The number of adverse events remained low but was observed more frequently after 150 U treatment. The more objective urodynamic measures revealed a higher trend in dose-response relationship changes between 100 U and 150 U, especially for measures performed at first contraction and at first desire to void and for the MCC. These effects clearly demonstrated BoNTA action on afferent nerve systems in blocking neural transmission and consequently affecting positively urgency and frequency, as it was largely studied by Schmid et al. [19].

Our results were comparable to those of Brubaker et al. [8]; they observed a significant 60% response rate in Patient Global Impression of Improvement (PGI-I) score  $\geq 4$  compared to placebo at least 2 mo after the initial 200 U BoNTA injection. Recently, Dmochowski et al. [10] reported a mean decrease in UUI episodes for seven consecutive days of  $-17.4$  (placebo),  $-20.7$  (50 U),  $-18.4$  (100 U),  $-23.0$  (150 U),  $-19.6$  (200 U), and  $-19.4$  (300 U). In addition, they reported 37% and 41% of incontinence-free patients after 100 U and 150 U BoNTA, respectively, at month 3; these values are slightly lower than those observed in our study. Doses  $>150$  U did not provide additional benefit in iOAB patients.

The 50 U dose clearly demonstrated a lower symptom improvement than the 100 U and 150 U doses. In addition, we observed a high placebo effect, a phenomenon that is often observed in OAB studies, using patient-reported data [20,21]. This observation was strengthened by the double-blind setting of the study. The important placebo effect of symptom improvement could also be related to symptom severity and high patient expectations. The observation that the proportion of patients experiencing  $>75\%$  symptom improvement in the 50 U group was lower than placebo might be related to the relatively low baseline values in this specific group. Urodynamic results and other clinical evaluations confirmed the low efficacy of placebo and of the 50 U dose.

Overall, QoL in patients with iOAB was improved after a BoNTA injection [9–11,22,23]. Using the King's Health Questionnaire, Dmochowski et al. [10] observed an improved QoL with 100 U and 150 U BoNTA injections at month 6, whereas no improvement could be observed with a 50 U dose. Using a VAS, Cohen et al. [23] observed no difference between 100 U and 150 U at month 3. In our study, QoL improvements were maintained for up to 6 mo and were generally longer lasting than clinical and urodynamic improvements.

We observed only minimal complications, and the number of adverse events was lower than the one observed by others. An increased PVR was noticed at several time-points, but the number of patients with a PVR  $>200$  ml was

low. Only 1 of 23 patients required CIC at months 3 and 6 after 150 U BoNTA treatment. The 100 U dose showed a non-negligible efficacy, even if not significantly different from placebo, a good efficacy–tolerability ratio, and no patients with a high PVR. Dmochowski et al. [10] reported PVR-related CIC in 5 of 80 patients after 100 U or 150 U BoNTA treatments. Cohen et al. [23] reported that 2 of 44 patients needed CIC because of AUR. In our study, we observed a low incidence of UTI. Cohen et al. reported 7 of 40 patients with UTI [23]. Noteworthy, we only included patients with a PVR <150 ml at baseline versus PVR <200 ml in other trials. It may have reduced the risk of increased PVR. The good tolerability–safety observations may also be explained by the use of lower BoNTA concentrations and of higher injection volume compared to Dmochowski et al. [10]. The relation between the injected concentration (or volume) and tolerability was not often studied and would be interesting. However, at the 2005 International Continence Society congress, Gilles Karsenty [24] reported that this type of relationship did not exist in neurogenic bladder patients. The DO inclusion criteria may also explain other differences from previous studies.

There are limitations to this study. We had a slow recruitment, protocol violations, and an early study interruption by the IDCM committee, resulting in a lower study population than expected. It is worth recalling that BoNTA started to be used in patients with iOAB only recently. Patients, investigators, and centres might have been sceptical to envisage using BoNTA injections to treat iOAB: less evidence, less experience, the potential need for catheterisation, and fewer pathology-related safety issues than in neurogenic bladder cases. This could partially explain the slow recruitment between 2005 and 2009. These points resulted in a lack of power of the primary endpoint. Finally, by considering the >75% improvement in urge incontinence and urgency at month 3, we improved the statistical power.

## 5. Conclusions

A single-injection procedure of 100 U or 150 U onabotulinumtoxinA is an effective treatment for patients with iOAB who failed anticholinergic regimens. Following the procedure, 24-h micturition frequency and QoL were improved for 6 mo; 100 U BoNTA injections seemed to have a better efficacy–safety ratio. Further studies will be needed to confirm the effectiveness of 100 U and 150 U doses. They might also consider evaluating the efficacy and tolerability of repeated injections of onabotulinumtoxinA to optimise the risk–benefit ratio. This would help to introduce onabotulinumtoxinA as a treatment of choice in patients with refractory iOAB.

**Author contributions:** Pierre Denys had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Other (specify):** None.

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## Appendix A

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