Onabotulinum toxin A Injections in Men With Refractory Idiopathic Detrusor Overactivity

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OBJECTIVE To establish the effectiveness and safety profile of Onaboulinum toxin A (BTX-A) in men with idiopathic detrusor overactivity and compare with the outcomes observed in women. Several randomized trials have demonstrated the effectiveness of intradetrusor BTX-A injections in improving symptoms and quality of life in patients with overactive bladder (OAB) symptoms. Most trials however contained relatively few men or excluded men altogether.

MATERIALS AND METHODS Data patient undergoing BTX-A for refractory OAB with idiopathic detrusor overactivity on urodynamics were extracted from our center's prospectively maintained database. Incontinence impact questionnaire-7 and urogenital distress inventory-6 scores were collected at baseline and 4-12 weeks together with data regarding urinary retention requiring clean intermittent self-catheterization (CISC) and urinary tract infection (UTI). Urodynamic studies were assessed where available to see if voiding dysfunction and CISC were predictable.

RESULTS Sixty-five men received 133 BoNT-A treatments in the 15-year period representing 27.8% of those with refractory OAB. Baseline urogenital distress inventory-6 and incontinence impact questionnaire-7 fell by 4.2 ($P = .00$) and 6.0 ($P = .00$) points for men and by 6.0 ($P = .00$) and 11.1 ($P = .00$) for women, respectively. De novo CISC was required in 46 (42.6%) men and 107 (35.3%) women ($P = .10$). UTI was reported in 36 (29.0%) men and 86 (27.0%) women ($P = .73$). The bladder outflow obstruction index and the bladder contractility index did not reliably predict CISC requirement.

CONCLUSION Men with refractory OAB experience significant improvement in quality of life scores following BTX-A, though the benefit appears greater in women. The requirements for CISC and UTI rates were similar between sexes. UROLOGY 123: 242–246, 2019

Overactive bladder (OAB) symptoms were present in 10.8% of men and 12.8% of women in the EPIC study.[1] While OAB symptoms were more common in women under 60, OAB correlates strongly with age in men such that 73.9% of men over 60 reported storage symptoms.[1]

When patients with OAB remain symptomatic despite conservative measures, such as behavioral therapy, antimuscarinic, and beta-3 agonist medication, BTX-A injections have been shown in several randomized controlled trials (RCT) to reduce incontinence episodes and improve quality of life (QoL) outcome measures compared to placebo.[2-6]

The main adverse events associated with BTX-A injections are urinary tract infection (UTI) and urinary retention requiring clean intermittent self-catheterization (CISC) in the idiopathic OAB population. The rates of UTI in randomized trials varied between 24.1% and 44% though some studies did not require culture confirmation of UTI.[4,5,7] UTI rates were also higher in trials that used 200-300 U.[6] The need for de novo CISC during these studies, which contained very few or no men at all, varied between 6.9% and 42% though different criteria were used to assess when to initiate CISC in the different studies.[3-5,7] The larger phase III RCTs contained between 0% and 11.9% men.[4-7] The only published study to specifically address men's response to BTX-A reported long-term success in 25% of men at 69-month follow-up where success was defined as continuing with BoNT-A injections.[8] They did not report specific QoL outcomes. Their patient population was also heterogenous and included a significant number of men with neurogenic lower urinary tract dysfunction. There remains an absence of evidence regarding QoL

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outcomes and the safety profile of BoNT-A for men when they constitute a significant proportion of patients with OAB. This study aims primarily to establish the clinical effectiveness in terms of QoL outcomes measures as well as adverse event frequency for BTX-A in men with OAB and idiopathic detrusor overactivity (IDO) and compare these outcomes to women. The study also aims to analyze the urodynamic profiles of men who require CISC after BTX-A injections to establish whether there are any urodynamic features that predict CISC requirement.

MATERIALS AND METHODS

Male subjects, over 18 years of age with confirmed detrusor overactivity on urodynamic studies who received intradetrusor BoNT-A injections from 2004 were identified from our institution's database. Patients with neurogenic detrusor overactivity, painful bladder syndromeor interstitial cystitis, and patients with OAB symptoms without detrusor overactivity on their urodynamics (ie, bladder oversensitivity) were excluded. The study was registered as a clinical audit within our local trust (project 6708). The data for women with refractory OAB and IDO were also extracted for comparison.

At our center, all patients who are being considered for BTX-A intradetrusor injections undergo an International Continence Society (ICS) standard urodynamic test following ICS good urodynamic practices.[9] Those meeting the criteria for BTX-A intradetrusor injections are seen in a dedicated clinic. Once a specialist has discussed the benefits and risks of the procedure, an appointment is made for the patient to be shown CISC by a specialist nurse. Patients are asked to complete baseline urogenital distress inventory-6 (UDI-6)[10] and incontinence impact questionnaire-7 (IIQ-7) questionnaires. The UDI-6 and IIQ-7 are both validated and abbreviated questionnaires with grade "A" recommendations by the ICS. The UDI-6 is a 6-item inventory which aims to quantify symptoms associated with lower urinary tract dysfunction.[11] The IIQ-7 is a 7-item questionnaire which focuses on the impact of urinary incontinence on QoL including physical activity, travel, social relationships, as well as emotional health.[11]

On the day of injection, a urine dipstick test and a pregnancy test in women of childbearing age are carried out. If no active infection is present, patients are consented and 500 mg of Ciprofloxacin is administered orally. BTX-A injections are injected in a trigone sparing technique as previously described.[12,13] The vast majority of injections were performed in an outpatient setting under local anaesthetic. After instillation of 10-mL Instillagel (lidocaine 2% + chlorhexidine gluconate 0.25%, Clinimed, UK), 10-20 injections of BTX-A in saline are given evenly around the bladder using a flexible cystoscope if under local anesthetic and a rigid cystoscope if under general anaesthetic. Following injections, patients are observed for 30 minutes.

We initially injected 200 U BTX-A in 2004 based on the limited available evidence. Following the BTX-A licensing change, patients with IDO were started at 100 U. Subsequent doses were escalated up to a maximum of 300 U or reduced after further discussion with the patient.[14] All patients are reviewed 2 weeks later by a specialist nurse with a urine dip to screen for infection and for a postvoid residual (PVR) volume measurement. CISC was recommended to PVR's over 150 mL who reported symptoms such as difficulty voiding, frequency, or urgency. At their next appointment 2 weeks later, patients were asked to complete follow-up UDI-6 and IIQ7 questionnaires and the results were entered into a prospectively maintained database.

Information regarding adverse events including UTI and urinary retention requiring de novo CISC was added retrospectively by review of patients' electronic records if not already in our prospective database. UTI was defined as symptoms of UTI requiring antibiotic treatment but did not necessarily require culture confirmation.

Baseline urodynamic data including the detrusor pressure at maximum flow rate (PdetQmax) and the maximum flow rate (Qmax) were extrapolated from the patients' urodynamic traces to enable calculation of the bladder outflow obstruction index (BOOI) and the bladder contractility index (BCI) in a retrospective fashion.

Statistical analysis and production of figures was done using Microsoft Excel Version 2016. *T* tests were used for continuous variables and results considered statistically significant if $P < .05$.

RESULTS

Of 672 injections identified on the database, 478 (71.1%) patients (male and female) had IDO. Of these, 133 (27.8%) BoNT-A treatments were given to 65 men with IDO. Individual men had received between 1 and 12 treatments at the time of analysis. Previous bladder outflow obstruction surgery had been performed in 6 men and 9 men had undergone radical prostatectomies. The mean age of the male patients at the time of their treatment was 57.1 years (SD 13.0) compared to 53.5 years (SD 11.2) for women ($P = .02$). Treatment doses for men varied between 100 U and 300 U and the distribution is shown in Table 1. The most common dose for men was 100 U, which was used in 58 (43.6%) treatments. A higher proportion of women (48.1%; n = 166) vs men (33.1%; n = 44) men received 200 U.

Table 2 and Figure 1 show the QoL outcomes for men and women whose outcomes were assessed with the

Table 1. Baseline data

Total BoNT-A Treatments	1	2	3	4	5	6	7	8	9	10	11	12	Total Subjects
Men (n)	37	16	4	2	2	2	0	0	0	1	0	1	**65**
Women (n)	128	76	51	41	5	4	2	0	0	1	0	1	**128**
BoNT-A Dose	**100 U**	**150 U**	**200 U**	**250 U**	**300 U**	**Not Known**	**Total**						
Men													
Treatments (n)	58	12	44	12	3	4	133						
%	43.6	9.0	33.1	9.0	2.3	3.0	100						
Women													
Treatments (n)	115	34	166	12	2	16	345						
%	33.3	9.9	48.1	3.5	0.6	4.6	100						

Table 2. Treatment outcomes

	All BoNT-A Treatments Men n = 133	Women n = 374	*P* (Men Vs Women)
Baseline UDI-6 (n)	10.3 (80)	10.2 (232)	.87
4-12-week FU UDI-6 (n)	6.1 (47)	4.2 (149)	.00
Δ Symptom score	−4.2	−6.0	.01
P (paired t)	.00	.00	
Baseline IIQ-7 (n)	12.3 (73)	17.0 (233)	.00
4-12-week FU IIQ-7 (n)	5.7 (43)	5.9 (169)	.78
Δ Symptom score	−6.6	−11.1	.00
P (paired t)	.00	.00	
	Men 100 U n = 57	**Men 200 U n = 44**	***P* (100 U vs 200 U)**
Baseline UDI-6	13.1	10.2	.22
4-12-week FU UDI-6	5.9	8.0	.01
Δ Symptom score	−7.2	−2.2	
P (paired t)	.00	.02	
Baseline IIQ-7	15.2	12.6	.07
4-12-week FU IIQ-7	7.7	6.1	.26
Δ Symptom score	−7.6	−6.6	
P (paired t)	.00	.01	
Adverse events			
	Men	**Women**	***P*(men vs women)**
Urinary retention requiring ISC			
All doses	46/108 (42.6%)	107/303 (35.3%)	.10
100 U	23/47 (48.9%)	-	-
De novo ISC (200 U)	17/37 (45.9%)	-	-
P (100 U vs 200 U)	.79	-	-
UTI			
Follow-up	124 (93.2%)	318 (85.0%)	-
UTI (all doses)	36 (29.0%)	86 (27.0%)	.73
UTI (100 U)	16/51 (31.4%)	-	-
UTI (200 U)	11/44 (25%)	-	-
P (100 U vs 200 U)	.42	-	-

FU, follow up; IIQ-7, incontinence impact questionnaire-7; ISC, intermittant self-catheterisation; UDI-6, urogenital distress inventory-6; UTI, urinary tract infection.

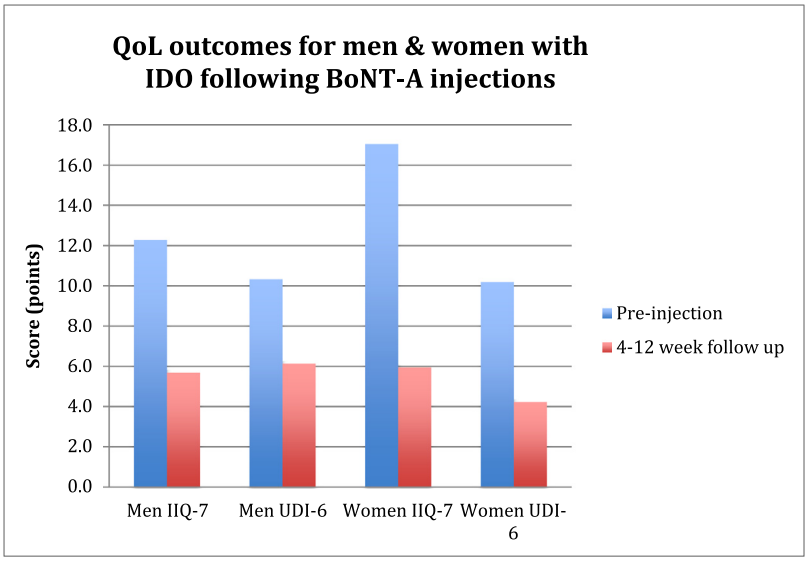

Figure 1. QoL outcomes for men and women with IDO undergoing intravesical BTX-A injections. (Color version available online.)

Table 3. Adverse events by urodynamic parameters in male patients

	n	Already Using CISC	De Novo CISC Required	No Data Re CISC	*P*
All	43	1 (2.3%)	23 (60.5%)	3	
Qmax* < 10 mL/s	11 (25.6%)	1 (10%)	5 (55.6%)	1	.65 (vs Qmax > 10 mL/s)
10 mL/s < Qmax < 15 mL/s	15 (34.9%)	0	8 (57.1%)	1	
Qmax > 15 mL/s	17 (27.9%)	0	10 (66.7%)	1	.43 (vs Qmax < 15 mL/s)
BOOI** < 20	24 (55.8%)	0	12 (57.1%)	2	.40 (vs BOOI > 20)
BOOI 20-40	17 (39.5%)	1 (6.3%)	10 (66.7%)	1	
BOOI > 40***	2 (4.6%)	0	2 (100%)	0	.26 (vs BOOI < 40
BCI*** < 100	12 (27.9%)	1 (9.1%)	6 (60%)	1	.87 (vs BCI > 100)
BCI 100-150	19 (44.2%)	0	13 (76.5%)	1	
BCI > 150	12 (27.9%)	0	4 (40%)	1	.10 (vs BCI 0.13 < 150)

* Qmax, maximum flow rate during voiding phase of urodynamics.
** BOOI, bladder outflow obstruction index = $P_{Det}Q_{max} - 2 \times Q_{max}$.
*** BCI, bladder contractility index = $P_{Det}Q_{max} + 5 \times Q_{max}$.

UDI-6 and IIQ-7. Men and women had similar baseline UDI-6 scores but women had higher baseline IIQ-7 scores (17.0 vs 12.3, $P = .00$).

The UDI-6 and IIQ-7 scores of men fell by 4.2 and 6.0 points ($P = .00$ for both) at 4-12-week follow-up. Women experienced greater improvement in both UDI-6 and IIQ-7 scores (−6.0 and −11.1, $P = .00$ for both). The QoL outcomes for men given 100 U and 200 U are shown in Table 2. The fall in UDI-6 score was greater for the men who received 100 U than 200 U and the fall in IIQ-7 score was similar for both doses.

One male and 1 female patient were using CISC before their first BTX-A injection. Urinary retention requiring de novo CISC was required by 46 (42.6%) men and 107 (35.3%) women ($P = .10$). For men, there was no statistical difference in de novo CISC when comparing 100 U and 200 U. UTI was reported in 36 (29.0%) men and 86 (27.0%) women ($P = .73$). The adverse events for 100 U and 200 U are also shown in Table 3. The UTI rate for men injected with 100 U or 200 U was not statistically significant ($P = .42$).

Baseline urodynamic studies before first injection were available for review in 43 men. Table 3 shows baseline BOOI and BCI for men before their first injection. Only 2 (4.7%) had a BOOI > 40 representing obstructed flow, but both these men had problems completing the voiding stage of their urodynamic study. In both cases the PVR was less than 50 mL. Both these patients were treated for their OAB symptoms and accepted the higher risk of voiding dysfunction post-treatment. Of the remaining patients, 24 (55.8%) were unobstructed (BOOI < 20) and the remaining 17 (39.5%) had equivocal obstruction. De novo CISC was seen in 12 of 21 (57.1%), 10 of 15 (66.7%), and 2 of 2 (100%) of the unobstructed, equivocal, and obstructed groups based on BOOI, although the differences were not statistically significant. The 12 men who had good bladder contractility (BCI > 150) had a lower de novo CISC rate than those with normal or poor bladder contractility, but this did not reach statistical significance ($P = .13$). The preinjection PVR was also not found to be predictive of the need for de novo CISC.

DISCUSSION

This is the first study to specifically report on QoL outcomes of intradetrusor BTX-A in men with IDO in a "real life" clinical setting. Men experienced significant improvements in QoL measured with UDI-6 and IIQ-7 scores at 4-12-week follow-up after BTX-A injections, though their QoL improvements were not as great as those observed in women.

The baseline UDI-6 of the men and women were similar in our study implying that they had similar levels of symptoms associated with their lower urinary tract dysfunction. However, the women in our cohort had higher preinjection IIQ-7 scores implying that their urinary symptoms had a more detrimental effect on their QoL. Although the great majority of men in this study were not obstructed on urodynamics, the authors hypothesize that men are more likely to have underlying voiding as well as storage symptoms. These voiding symptoms would likely persist following BTX-A injections which may explain the greater improvements in QoL scores observed in women.

The de novo CISC requirement rates (42.6% for men and 35.3% for women) appear quite significant. In a large phase III RCT for example, 6.9% of those given 100 U BTX-A required CISC compared to 0.7% given placebo.[4] In this particular study, patients with a PVR's > 350 mL were all started on CISC and those with a PVR between 200 and 350 mL only started CISC if they were symptomatic. In a phase II dose ranging trial, 18.2% of those given 100 U, 23.1% of those given 200 U, and 25.5% of those given 300 U developed urinary retention and 10.9%, 21.2%, and 16.4% required a catheter after their BTX-A.[3] Other Botulinum toxin studies in women have been stopped early owing to retention rates over 40%.[7] In the only study specifically looking at male patients, Rahnama'i et al found that 24% of men required CISC after BTX-A injections though their population included 27% neuropathic patients and 19% of their combined cohort were using CISC before their injections.[8] Clearly, the rate of de novo CISC requirement varies from study to study due to the differing protocols employed by the individual centers. In our own experience, the majority of patients

with a PVR >150 mL are symptomatic and hence are instigated on CISC, which often leads to an improvement in their symptoms. Furthermore, our data include patients who have received a variety of BTX-A doses and not only the lowest dose of 100 U, which has typically been associated with the lowest CISC rates.

Our data suggest men with a BCI over 150 were less likely to need de novo CISC ($P = .10$). A previous study in men with IDO who required CISC after 200 U BTX-A were observed to have a lower pretreatment BCI and Qmax than those who did not require CISC.[15] UTI rates were less than those observed in a recent dose ranging RCT where 48.1% of those receiving 200 U were treated for UTI.[3] UTI following this treatment is clearly a problem with uncertain etiology at this current time.

Unexpectedly, men who received 200 U appeared to have less improvement in UDI-6 scores than those who received 100 U. Men who received 200 U also experienced less need for de novo CISC and UTI. Dose escalation in poor responders may partly explain this but there appears no advantage in giving 200 U over 100 U to men either in terms of symptom improvement or prevention of adverse events.

Rahnama'i et al found that only 22/88 (25%) of patients continued with their BTX-A injections at mean follow-up of 69 months.[8] Of those who stopped, 35 of 88 (39.8%) stopped due to insufficient effect and 27 of 88 (30.7%) stopped as they had tolerability issues.

The study is limited by relatively poor follow-up of some QOL measures and baseline urodynamics for men. Furthermore patients received different doses and this was not a placebo-controlled study. The BCI has been criticized as an indicator of bladder contractility as it is both flow and volume dependent.[16] Although information was collected in a prospective fashion, missing data and urodynamic information were collected retrospectively. The study nevertheless represents patients in a "real life" setting and is one of very few studies to report on men treated with BTX-A for refractory OAB.

CONCLUSION

Men with refractory OAB experienced significant gains in QoL following BTX-A injections though the improvements were less than those observed in women. UTI and de novo CISC rates were similar in men and women. Neither the BOOI or BCI on urodynamics could reliably predict the need for CISC in men.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urology.2018.09.016.

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