Outcomes for Intravesical Abobotulinumtoxin A (Dysport) Treatment in the Active Management of Overactive Bladder Symptoms—A Prospective Study

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OBJECTIVE To present the results our active management protocol for bothersome overactive bladder (OAB) symptoms using abobotulinumtoxinA (Dysport) over a 9-year period.

MATERIAL AND METHODS Data from consecutive patients with OAB symptoms due to urodynamically-proven idiopathic detrusor overactivity who had failed maximum-dose pharmacotherapy and bladder drill were reviewed. All patients completed the Overactive Bladder Symptom Score (OABSS) and Likhart quality of life indices before treatment and again at review 6 weeks post-treatment. Two hundred and fifty units of abobotulinumtoxinA were injected under general anaesthesia. Repeat treatment was offered only after failed resumption of pharmacotherapy with bladder drill.

RESULTS The results of 299 treatments in 170 patients were reviewed. OABSS and quality of life indices improved by a mean of 35% (P <.001) and 41% (P <.001), respectively, with the OABSS improving by 2 or more points in 65% of cases. While urgency incontinence was completely abolished in 26%, the severity of incontinence was reduced in 44%. Pharmacotherapy was resumed after a mean of 10.2 months, and the mean interval between repeat abobotulinumtoxinA injection treatments was 21.3 months. De-novo self-catheterization was required in 18.2% of cases due to high postvoid residuals.

CONCLUSION The use of abobotulinumtoxinA is safe and highly effective treatment option for patients with refractory OAB symptoms. Our data show similar outcomes to onabotulinumtoxinA in terms of symptom score improvement and self-catheterization rates. UROLOGY 130: 54–58, 2019.

Overactive bladder (OAB) is a chronic condition that affects over 17% of British adults over 40 years of age[1] with estimated 29.8 million of US population having bothersome OAB symptoms.[2] OAB is defined as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia.[3]

The symptoms of OAB can affect the patient's quality of life and have a negative impact on sleep, social life, productivity, and relationship.[4] While lifestyle modifications, bladder drill, and pharmacologic treatment usually improve OAB symptoms significantly, a proportion of patients remain refractory to conservative OAB management. In addition, up to 70% of patients with OAB discontinue antimuscarinic treatment within a year of initiation, either due to insufficient efficacy or due to side effects.[5] Botulinum toxin A is recommended to patients with OAB symptoms due to idiopathic detrusor overactivity (IDO) that have failed to respond to conservative treatment including pharmacologic treatment.[6-7]

Two preparations of botulinum toxin A are available: onabotulinumtoxinA (onaBTX) (Botox, Allergan, Inc., Irvine, CA) and abobotulinumtoxinA (aboBTX) (Dysport, Ipsen Biopharm Ltd, Slough, UK). Both are the same serotype, but they differ in their dose and efficacy and they are not interchangeable[8]; they are derived from different bacterial strains and different fragments of the toxin are isolated during purification and extraction processes. It has been suggested a conversion of 2-3 to 1 for aboBTX to onaBTX.[9] Most published studies on botulinum toxin A in OAB treatment have focused on onaBTX. However, aboBTX has been shown to

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be very effective on patients with neurogenic detrusor overactivity[10-11] but there are only a small number of published articles on its use in IDO treatment.[12]

Since introducing botulinum toxin-A treatment on our unit we have adopted an active management protocol for OAB. This involves clear instruction of lifestyle modification, commencement of modified-release once-daily antimuscarinic therapy with the subsequent addition of mirabegron 50 mg as necessary, plus clear instruction on the performance of bladder drill/bladder retraining. Those patients whose OAB symptoms persist despite these measures are offered a urodynamic study with a view to subsequent intravesical botulinum toxin-A injection treatment. Patients are reviewed 6 weeks post-treatment and complete an Overactive Bladder Symptom Score (OABSS) PRO to assess response; postvoid residual (PVR) urine is measured by ultrasound at this visit. Those patients whose symptoms have resolved or improved significantly and who have no voiding dysfunction are discharged back to primary care with clear written instructions (to both patient and primary care physician) that resumption of pharmacotherapy and bladder drill must begin when bothersome OAB symptoms recur. Patients are listed directly for repeat aboBTX treatment (without need for a clinic appointment) if a subsequent referral letter indicates refractory bothersome OAB symptoms despite full compliance with these instructions.

The aim of this study was to evaluate the efficacy and duration of action of aboBTX as part of our active management protocol for OAB patients.

MATERIALS AND METHODS

We analyzed our prospectively-collected data of patients with refractory OAB symptoms who were treated with aboBTX as part of an active management protocol in our unit. Patients' case notes were reviewed if any information was missing. All patients had urodynamically-proven IDO and all had failed conservative measures (lifestyle modifications, bladder drill in addition to maximum-dose pharmacotherapy—at least 2 oral anticholinergics with or without mirabegron). Patients with Bladder Pain Syndrome, neurogenic detrusor overactivity or who were already fitted with long-term catheters were excluded.

Baseline Assessment

A frequency-volume diary was completed over 3 days prior to urodynamics only. All patients were asked to complete an OABSS questionnaire and IPSS Quality of Life (QoL) Likert score, and their PVR was recorded. The OABSS is a validated self-reporting questionnaire that quantifies OAB symptoms—daytime frequency, nocturia, urgency, and urgency incontinence.[13]

Injection Technique

Intravesical aboBTX injection was performed as a day case procedure under general anaesthesia with the patient in lithotomy position, using a 22.5 French rigid cystoscope with a 12° telescope; a single dose of prophylactic antibiotic was used as per local antimicrobial prophylaxis policy (co-amoxiclav, cefuroxime or teicoplanin etc). Two hundred and fifty units of aboBTX (Dysport) diluted in 40 mL normal saline were injected in a variable number of sites into the detrusor and suburothelium, sparing the trigone. We have shown in a previous study that the injection pattern does not influence patient's response to botulinum toxin.[14] All patients were asked to discontinue their OAB medication post-injection.

Follow-Up

Patients were reviewed in a dedicated nurse led clinic at 6 weeks after treatment and asked to complete the OABSS and Likert QoL questionnaire again and had their PVR checked. Our policy is to initiate clean intermittent self-catheterization (CISC) if the PVR was more than 150 mL and patients had associated voiding dysfunction symptoms. Patients whose symptoms improved were discharged to their primary care physician and advised to restart their pre-aboBTX OAB medication at a later date if their OAB symptoms recurred. Patients were relisted directly for repeat intravesical aboBTX treatment if their OAB symptoms remained bothersome despite resumption of maximum-dose pharmacotherapy.

The primary outcome was change from baseline in OABSS; secondary outcomes were changes in postoperative PVR, interval between injections, change in QoL, and CISC rate. An improvement in the total OABSS score of 2 or more points (13%) was considered a meaningful change.[15]

Statistical Analysis

The results were analyzed using Statistical Package for Social Science (SPSS version 20) and the graphs were produced using Microsoft Excel. A P value less than .05 was considered statistically significant. Wilcoxon signed-rank test was used to assess the statistical difference between pre- and post-treatment scores and the Mann-Whitney test was used to assess differences between male and female scores.

RESULTS

A total of 172 patients received 306 treatments with aboBTX for proven IDO between September 2008 and December 2018. Seven treatment episodes were eliminated due to incomplete data or lack of follow-up. Overall, 299 treatment episodes in 170 patients were analyzed. The patient demographics are shown in Table 1. The mean time to follow-up appointment was 48 days (range = 6-169).

Baseline OABSS and QoL score and their improvements after aboBTX are presented in Table 2. OABSS improved by 2 or more points following 65% of treatments, remained unchanged in 20% and was worse in 14% of treatments (including 7 episodes of urinary retention). Overall, the OABSS and QoL indices improved by a mean of 35% and 41%, respectively (P <.001) following treatment, and in 55% of cases, the OABSS improved by 3 or more points. While complete resolution of urgency incontinence was achieved following only 77 treatments (26%), the severity of the incontinence improved significantly,

Table 1. Patient demographics

	Male	Female	Overall
No. patients	45	125	170
Median age (range)	72 (20-95)	61 (22-89)	67 (20-95)
No. of treatments (mean and range)	1.34 (1-4)	1.93 (1-7)	1.77 (1-7)

Table 2. Mean (± SD) overactive bladder symptom scores (OABSS) and individual OAB domain scores pre- and post-treatment

Parameter	Pre-aboBTX	Post-aboBTX	Difference	Improvement %	*P* Value
OABSS overall	11.09 ± 2.55	7.21 ± 4.15	3.87 ± 4.39	34.9	<.001
Frequency	1.2 ± 0.61	0.7 ± 0.68	0.5 ± 0.752	42	<.001
Nocturia	2.28 ± 0.91	1.69 ± 1.04	0.59 ± 1	26.1	<.001
Urgency	4.15 ± 1.08	2.72 ± 1.74	1.42 ± 1.93	34	<.001
Urgency incontinence	3.67 ± 1.36	2.03 ± 1.72	1.63 ± 1.89	44.3	<.001
QoL	5.44 ± 0.77	3.2 ± 2.09	2.23 ± 2.19	40.7	<.001

indicated by a 44.4% improvement in the mean OABSS score for urgency incontinence (P <0.001). The scores for daytime frequency, nocturia, and urgency also improved significantly after treatment, by 41.7%, 26.1% and 34.1%, respectively (P <.001).

The number of treatments varied from 1 to 7 per patient (median = 1, mean = 1.77). Of the 299 individual treatments, 202 were repeat treatments. The mean interval between repeat injection treatments overall was 21.3 months (range = 2-82 months) (Fig. 1). The mean interval of time to resumption of pharmacotherapy post-treatment was 10.2 months (range 1-42 months).

In terms of the QoL Likert scores, there was a mean overall improvement from 96.6% of patients who answered: "mostly dissatisfied," "unhappy," or, "terrible," to 47.3% postoperatively.

There was gender difference between pre-op OABSS and QoL score with women having a higher OABSS and QoL score than men (P = .003 and P = .001, respectively). However, women obtained a better overall response to aboBTX than men (P = .005) (Table 3). Treatment with aboBTX was associated with an increase in mean PVR (51 ± 112 mL), but clinically this was not significant. Again, there was a gender difference between mean PVR preinjection and postinjection, men having a significantly larger PVR than women (P <.001). In 51 cases (18.2%) CISC was initiated in patients who were not already performing self-catheterization and again this was more common in men compared to women (42% vs 14%, respectively). CISC was discontinued at 3 months except in one case in whom it was continued for 9 months.

Two patients developed an uncomplicated urinary tract infection after aboBTX which responded to antibiotics. One patient developed suprapubic pain that settled with simple analgesia in a few days and in one case the daytime frequency has worsened.

COMMENT

To our knowledge this is the largest series of patients with urodynamically-proven IDO treated with aboBTX where patients receive 250 units of aboBTX as part of an active management program for OAB.

Urgency is the OAB symptom with the major impact on the patient QoL and is the strongest predictor of OAB associated bother.[16-17] In our cohort, aboBTX significantly reduced the urgency score in 74 % of cases; in 55% this (urgency score) fell by 3 or more points. These results compare favorably with those reported for onaBTX for which the success ranges from 40% to 87% depending on dose used.[18-21] Complete resolution of incontinence was achieved in 26% of cases, similar results being reported by Tincello for onaBTX.[20]

In our study, women had a better response to botulinum toxin than men. Women had significantly higher OABSS scores than men preinjection, in keeping with the findings from the EpiLUTS study which found that OAB symptoms are more bothersome for women than for men.[22] QoL scores likewise improved more significantly in females compared to males following injection treatment. These gender differences might be due to associated or coexisting voiding LUTS in men.

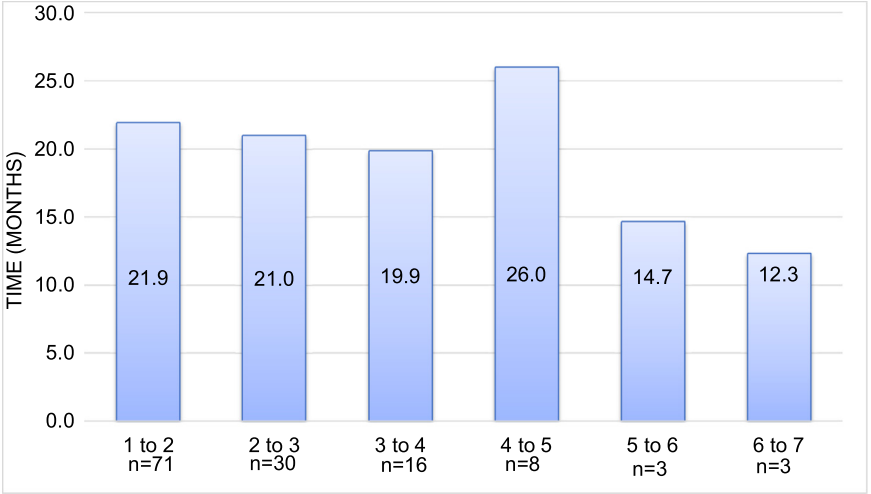

Figure 1. Mean interval (months) between repeat injection treatments. (Color version available online.)

Table 3. Comparison of individual OABSS domain responses, QoL, and PVR between male and female patients, pre- and post-treatment

Parameter	Male treatments ($n = 56$)				Female treatments ($n = 243$)				Male vs female improvement
	Pre-aboBTX	Post-aboBTX	Improvement %	*P* Value	Pre-aboBTX	Post-aboBTX	Improvement %	*P* Value	*P* Value
OABSS overall	10.0 ± 2.679	8.02 ± 3.563	19.8	<.001	11.31 ± 2.53	7.00 ± 4.238	38.1	<.001	.005
Frequency	1.07 ± 0.768	0.70 ± 0.599	34.8	.001	1.24 ± 0.587	0.71 ± 0.703	42.7	<.001	.2
Nocturia	2.05 ± 1.022	1.91 ± 0.996	6.8	.294	2.33 ± 0.898	1.63 ± 1.052	30	<.001	.001
Urgency	4.00 ± 1.134	3.40 ± 1.417	15.1	.008	4.17 ± 1.09	2.58 ± 1.781	38.1	<.001	.002
Urgency incontinence	2.95 ± 1.495	2.35 ± 1.717	20.5	.023	3.81 ± 1.302	1.96 ± 1.719	48.6	<.001	<.001
QoL	5.07 ± 0.884	3.75 ± 1.683	26	<.001	5.53 ± 0.725	3.10 ± 2.143	43.9	<.001	<.001
PVR	29.75 ± 35.07	182.3 ± 180.09		<.001	24.9 ± 29.22	64.11 ± 101.71		<.001	-

aboBTX, abobotulinumtoxinA; PVR, postvoid residual; QoL, quality of life.

The de-novo CISC rate in our cohort is 18.2%, compared to reported ISC rate in other studies which varies from 1.6% to 45% and is dependent on botulinum toxin A dose.[18-19] This large variation is mainly due to lack of consistent criteria on initiation of CISC. Some authors suggest that raised PVR can be safely managed by observation and need for CISC should be guided on patient symptoms rather than the PVR value.[19,23] We also found that, in contrast to Khan et al the need for ISC is not related to previous botulinum toxin injection[24]. Seventy-six percent of treatments that required de-novo ISC were after the first aboBTX injection. Male gender and a preoperative PVR in excess of 100 mL have been identified as potential risk factors for adverse effects post-botulinum toxin injection.[25] In our study men had a significant increase in their PVR compared to women, with 42% of men needing to perform ISC compared to only 14% of women. This is probably due to different anatomy and the possibility of concomitant subclinical bladder outlet obstruction in men.

The interval between repeat injection treatments varies greatly among reported series and ranges from 7.6 months to 17.2 months.[26-30] Most studies have employed onaBTX-A and it is unclear whether resumption of pharmacotherapy and bladder drill was initiated between injections. In our study the interval between injections is significantly prolonged (21.2 months) compared to other studies.[27-29] While this may be due to possible superior efficacy of aboBTX-A over onoBTX-A, it is more likely due to our active management protocol which insists of resumption of maximum-dose pharmacotherapy and bladder drill when OAB symptoms recur.

CONCLUSION

The use of aboBTX-A as part of an active management protocol for refractory OAB symptoms due to IDO is a safe and highly effective treatment option. Our data show similar outcomes to onaBTX-A in terms of both symptom score improvement and self-catheterization rates.

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