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Effects of 100 and 300 Units of Onabotulinum Toxin A on Lower Urinary Tract Symptoms of Benign Prostatic Hyperplasia: A Phase II Randomized Clinical Trial

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Abstract

Purpose—We conducted a 2-stage, multicenter, double-blind, randomized phase II clinical trial of 100 and 300 unit doses of onabotulinum toxin A to treat the lower urinary tract symptoms of benign prostatic hyperplasia.

Materials and Methods—Men 50 years old or older with clinically diagnosed benign prostatic hyperplasia, American Urological Association symptom index 8 or greater, maximum urinary flow rate less than 15 ml per second, voided volume 125 ml or greater, and post-void residual 350 ml or less were randomized to prostatic transrectal injection of 100 or 300 units of onabotulinum toxin A. The primary outcome was at least 30% improvement from baseline to 3 months in American Urological Association symptom index and/or maximum urinary flow rate and safety. The men were followed for 12 months.

Results—A total of 134 men were randomized and treated (68 with 100 units, 66 with 300 units), with 131 assessed at 3 months and 108 assessed at 12 months. Each dose met the 3-month primary outcome criteria. In the 100 unit arm the mean baseline American Urological Association

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symptom index of 18.8 decreased by 7.1 and 6.9 at 3 and 12 months, respectively. In the 300 unit arm the baseline of 19.5 decreased by 8.9 and 7.1, respectively. In the 100 unit arm the mean baseline maximum urinary flow rate of 10.0 ml per second increased by 2.5 and 2.2, respectively, and in the 300 unit arm the baseline of 9.6 increased by 2.6 and 2.3, respectively.

Conclusions—The intraprostatic injection of 100 or 300 units of onabotulinum toxin A passed predetermined criteria for treatment efficacy and safety, and a randomized trial with either dose is warranted. The 100 unit dose may be preferable due to similar efficacy with reduced costs and adverse effects.

Keywords

prostatic hyperplasia; onabotulinum toxin A

Benign prostatic hyperplasia and lower urinary tract symptoms are bothersome and costly conditions affecting nearly half of men older than age 50 years and 90% of men older than age 80.^{1,2} In the search for more effective noninvasive therapies, the role of the neural activity in BPH has been studied.³

Botulinum toxin was first used in the 1970s for strabismus. Thereafter, botulinum toxin has been used safely for numerous other disorders characterized by excessive or inappropriate muscle contraction, including muscular dystonia and axillary hyperhidrosis.⁴ Onabotulinum toxin A blocks acetylcholine release at neuromuscular junctions and in autonomic neurons.⁴ Botulinum toxin can induce prostatic involution in rats.⁵ This effect was thought to be secondary to altered neurotropism of the epithelial cells rather than a direct toxic effect. It has been demonstrated that this toxin can induce changes without causing local inflammation or significant systemic side effects. It is possible that BPH and related LUTS would be ameliorated by prostatic injection with botulinum toxin by the mechanisms of neuromuscular junction blockade, and stromal and/or epithelial involution.

Botulinum toxin injection has been used for several urological conditions including voiding dysfunction,⁶ and studies have shown that intraprostatic injection may be beneficial in LUTS secondary to BPH.^{7–10} However, the optimum dose is uncertain. To better characterize the appropriate dose of onabotulinum toxin A we evaluated the treatment success and safety of botulinum toxin prostatic injection in a 12-month, 2-stage, multi-center, double-blind, randomized, phase II clinical trial of 2 doses of onabotulinum toxin A in men with BPH. We report outcomes at 3 and 12 months after treatment.

MATERIALS AND METHODS

We used a noncomparative, 2-stage, phase II study design with treatment success and safety evaluated against predetermined criteria. The primary objective was to determine whether 2 different doses (100 U and 300 U) of onabotulinum toxin A (marketed in the United States as BOTOX® by Allergan Pharmaceuticals, Irvine, California) injected into the prostate gland demonstrated significant improvement and safety to warrant a sham controlled phase III clinical trial. The protocol was approved by the institutional review boards of the participating clinical centers. An independent Data and Safety Monitoring Board, established by the National Institute of Diabetes and Digestive and Kidney Diseases, monitored study progress and safety.

Patients were recruited at 7 clinical centers (Baylor College of Medicine, Houston, Texas; Cornell University, New York, New York; Mayo Clinic, Rochester, Minnesota; Medical College of Wisconsin, Milwaukee, Wisconsin; Northwestern University, Chicago, Illinois; University of Colorado Denver, Aurora, Colorado; and University of Texas Southwestern

Medical Center, Dallas, Texas). Eligible subjects were male, at least 50 years old, provided informed consent, had no prior surgical treatment for BPH and no prior use of botulinum toxin, underwent an appropriate washout period for any prescription BPH medical therapy, had an AUASI of 8 or greater administered once at initial screening and again after appropriate BPH drug washout when applicable, voided volume 125 ml or greater, and Qmax less than 15 ml per second. Men were not asked to discontinue BPH herbal preparations. Men were excluded from participation based on medical history, conditions and medications that would interfere with the evaluation of treatment. Men were randomized in a 1:1 ratio to a 100 or a 300 U dose of onabotulinum toxin A. The study was double-blind as to the toxin dose. The drug was injected transrectally into the prostatic peripheral transitional zone with ultrasound guidance. It was administered as 2 cc per lobe in 1 ml aliquots at 2 injection sites for a total of 4 sites. The urologists administering the onabotulinum toxin A followed a predetermined and uniform protocol for injection.

The primary efficacy outcome was treatment success defined as improvement in AUASI by at least 30% and/or improvement in Qmax by at least 30% from baseline to 3 months after injection. In addition, 2 safety criteria also had to be met. A dose failed if 1) a life threatening, disabling or fatal event was determined to be related to the onabotulinum toxin A injection, or 2) 40% or more of the participants reported a moderate or severe side effect related to the botulinum toxin injection. Treatment efficacy and safety were evaluated at the end of stage 1, and each dose was required to meet or exceed criteria to proceed with enrollment of additional patients into stage 2. If primary outcome and safety were inconclusive at 3 months, then additional safety, function and satisfaction outcome criteria were evaluated in men followed to 12 months after treatment.

Data Collection

Men were contacted by telephone at 1 week after treatment, and evaluated in person at 1, 2, 3, 6, 9 and 12 months. Uroflowmetry, vital signs, AUASI and medical conditions were collected or performed at baseline and each visit; transrectal ultrasound and questionnaires on the impact of BPH, bladder function, erectile function and ejaculatory function were administered at baseline, and 3 and 12 months; bladder ultrasound was performed at baseline and 12 months; and physical and digital rectal examination, and prostate specific antigen were determined at baseline, and at 3, 6 and 12 months.

Statistical Methods

Patients were assigned to dose arm using block randomization. Simon's optimal 2-stage design was applied to determine whether there was sufficient activity at either of the 2 dose levels to warrant further investigation.¹¹ Each case was considered a success or failure based on the primary outcome criteria. The response rate or proportion of patients treated successfully was examined in 2 stages. At both stages the 2 dose levels were compared not to each other but to predetermined cutoff values. The trial was designed to enroll 24 patients per arm in stage 1, follow to 3 months and compare each dose arm to established passing criteria (treatment response rate at least 9 of 24 and no safety issues). Each dose arm that passed stage 1 continued in stage 2 to enroll an additional 39 patients who were followed to 3 months. Each dose arm was again evaluated by applying to all patients the predefined criteria (treatment response rate of at least 25 of 63 and no safety issues). The sample size was based on significance level $\alpha = 0.05$ and power 90%. For this phase II trial withdrawals and dropouts were tracked if possible but missing outcome data were not imputed.

RESULTS

The figure shows the consort diagram with a total of 134 patients enrolled and treated (68 at dose 100 U and 66 at dose 300 U). In stage 1, 53 patients were treated and recruitment was halted to allow for a 3-month evaluation. Of these patients 1 withdrew and 52 were evaluated at 3 months. At the 100 U dose 22 of 27 patients passed treatment response criteria and at the 300 U dose 23 of 25 passed. Each dose passed the predetermined efficacy criteria (at least 9 of 24) with no safety issues and recruitment was reinstituted for stage 2. At 3 months 67 patients in the 100 U dose arm and 64 in the 300 U dose arm were evaluated. Each arm passed the treatment response criteria of at least 25 of 63 (46 men at 100 U and 50 at 300 U) with no safety issues.

By the last 12-month followup visit 11 men (16.2%) in the 100 U dose arm and 8 (12.1%) in the 300 U dose arm had withdrawn due to dissatisfaction with treatment results or continued to attend study followup but received an alternate treatment before 12 months. Additional treatments administered included laser and photovaporization of the prostate, and medical and complementary therapies such as tamsulosin, finasteride, alfuzosin, dutasteride, tolterodine, stinging nettle, *Serenoa repens* (saw palmetto) and *Pygeum africanum* (pygeum). A total of 108 patients (53 in the 100 U and 55 in the 300 U dose groups) were followed to 12 months without additional treatment for LUTS/BPH. Longitudinal outcome data are presented for this group of 108 men (table 1).

Selected clinical and demographic characteristics of enrolled men by dose arm are shown in table 2. Generally the men were in their mid 60s, mainly white nonHispanic, married or in a committed relationship, and reported having symptoms of BPH for about 8 years. At baseline, mean AUASI was 19.2 and 20.1, and mean prostate volume was 51.1 and 48.1 cc for the 100 U and 300 U doses, respectively. Table 3 summarizes the baseline differences in men who completed the 12 months of study and in those who dropped out. Men completing the study had a slightly smaller prostate, slightly greater Qmax and slightly lower total symptom scores.

Table 1 presents AUASI and Qmax by dose arm at followup points for the 108 men who were evaluated 12 months after treatment. On average the AUASI for men in the 100 U dose arm improved by 7.1 points at 3 months and by 6.9 points at 12 months, and for men in the 300 U dose arm AUASI improved by 8.9 points at 3 months and 7.2 points by 12 months. Qmax in men in the 100 U dose arm increased by 2.5 and 2.2 ml per second at 3 and 12 months, respectively. In men treated with 300 U, Qmax improved by 2.6 and 2.3 ml per second for the 3 and 12-month evaluations, respectively.

Table 4 summarizes the AEs, including those considered serious, during the 12 months of the trial for all patients by dose arm. The frequencies of AEs and serious AEs were similar for the 2 dose arms, with 10% (7 of 68) at the 100 U and 8% (5 of 66) at the 300 U dose reporting a serious AE, and 68% (46 of 68) at the 100 U and 62% (41 of 66) at the 300 U dose reporting an AE. On average the AE rate was 2.5 per subject treated with 100 U and 2.7 per subject treated with 300 U.

Following injection of the 100 unit dose 1 death was observed at 12 months, and was considered by the study physician and confirmed by the Data and Safety Monitoring Board not to be related to the onabotulinum toxin A injection. Among the serious AEs 3 cases of urosepsis were reported related to the onabotulinum toxin A injection and the remaining events were judged not related to the injection.

DISCUSSION

The 100 U and 300 U doses of onabotulinum toxin A met our predefined criteria for the primary outcome of treatment success, that is a 30% improvement in AUASI and/or Qmax, and demonstrated safety from baseline to 3 months after injection. The proportion of men with improvement in AUASI and/or Qmax was approximately equal for each dose at 12-month followup. Both treatment doses achieved the 12-month safety criteria. Consistent with our primary outcome for treatment success, significant improvements in mean AUASI and mean Qmax from baseline to 3 and 12 months after treatment were observed in both dose arms. There were small differences in baseline characteristics for those men completing 12 months of study compared to those not completing the study, as shown in table 3.

Since the 100 U and 300 U doses of onabotulinum toxin A met our predefined criteria for treatment success and safety at 3 months which were sustained at 12 months, either dose may be a candidate for further study comparing toxin to placebo. The 100 unit dose may be preferable for a randomized trial because of similar efficacy, and the potential for reduced costs and adverse effects.

There are few reports on botulinum toxin to treat BPH. In a randomized, placebo controlled study 30 men with symptomatic BPH were randomized to receive prostatic injection of saline or 200 U botulinum toxin.⁷ For the 200 U dose AUASI decreased from 23.2 to 8.0 from baseline to 2 months after injection, Qmax increased from 8.1 to 15.4 ml per second and PVR decreased from 126.3 to 21.0 ml. In our study AUASI and Qmax changes from baseline to 2 months were not as great as for this placebo controlled trial. During 2 months in the 100 U arm AUASI changed from 18.8 to 11.1 and Qmax changed from 10.0 to 11.3. In the 300 U arm AUASI changed from 19.5 to 12.4 and Qmax changed from 9.6 to 12.8. We observed an increase from baseline to 2-month PVR in the 100 U dose arm from 79.5 to 102.3 ml and in the 300 U dose arm from 89.5 to 111.4 ml (data not presented in tables).

Chuang et al stratified patients in whom medical treatment failed based on prostate size.⁸ Patients with a prostate smaller than 30 cc were treated with 100 U botulinum toxin while those with a prostate larger than 30 cc were treated with 200 U by transperineal prostatic injection. At 12 months the improvements in the study by Chuang et al in AUASI, Qmax and PVR were similar to those reported by Maria et al,⁷ but the percent decrease in prostate size was substantially smaller (13% to 19% vs 61%). In 12 of 41 men (29%) there was no change in prostate volume. Of these 12 men 7 (58%) had more than 30% improvement in International Prostate Symptom Score, Qmax and PVR, suggesting that botulinum toxin may relieve BPH symptoms in ways other than reducing prostate size. Published studies have generally documented prostate size reductions from 16% to 68%.^{7-10,12,13}

Our results are consistent with those of other clinical studies of botulinum toxin in BPH, although the 3-month improvements in AUASI (39.1% for 100 U, 42.6% for 300 U) and Qmax (25.6% and 28.5%, respectively) demonstrated in our study were smaller than those previously published, which listed symptom index decreases of 61% to 73% and Qmax increases of 53% to 92%.⁷⁻¹⁰

Our results suggest that the mechanism of action of onabotulinum toxin A is not through denervation of parasympathetic nerves. The decrease in prostate size that is known to occur following parasympathetic nerve denervation was not observed in our single injection study.^{14,15} Additional investigation into the mechanism of action of onabotulinum toxin A in prostate tissues is appropriate, particularly in view of clinical evidence in the human bladder that onabotulinum toxin A can modulate the expression of sensory nerve receptors and the release of nerve growth factor.¹⁶⁻¹⁸

Other investigators have used transurethral injection as opposed to the transrectal route used in our study. It is possible that the route of injection may have a bearing on efficacy. Theoretically transurethral injection might have a more central effect, and a differing symptom and urodynamic effect.

Our phase II study has several important limitations. It was not designed to compare the effect of onabotulinum toxin A to placebo or as a dose ranging study with a placebo control group. There is a substantial placebo effect in the medical treatment of BPH which may be exaggerated by injection therapy. In addition, we assessed our primary outcome at 3 months after injection. Because LUTS associated with BPH can be chronic, the long-term effects and safety of a single injection of onabotulinum toxin A need to be determined.

CONCLUSIONS

We showed that a single injection of a 100 U or a 300 U dose of onabotulinum toxin A met the primary outcome for treatment efficacy and safety. Future studies of onabotulinum toxin A should include a randomized clinical trial with the 100 U or 300 U dose compared to placebo.

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Abbreviations and Acronyms

AE	adverse event
AUASI	American Urological Association symptom index
BPH	benign prostatic hyperplasia
LUTS	lower urinary tract symptoms
PVR	post-void residual
Qmax	maximum urinary flow rate

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Consort diagram

Figure.
Consort diagram

Table 1

AUASI and Qmax at baseline and followup

	AUASI		Qmax (ml/sec)	
	100 U	300 U	100 U	300 U
Baseline	18.8	19.5	10.0	9.6
1 Mo	12.0	12.5	12.6	12.1
2 Mos	11.1	12.4	11.3	12.8
3 Mos	11.7	10.6	12.5	12.2
6 Mos	12.0	12.3	12.4	12.9
9 Mos	12.2	13.2	13.0	12.1
12 Mos	11.9	12.4	12.2	11.9

Table 2

Baseline clinical and demographic characteristics

	100 U	300 U
Mean $\pm$ SD age	67.0 $\pm$ 8.6	65.3 $\pm$ 7.7
% Race/ethnicity white nonHispanic	92.6	86.2
% Education beyond high school	86.7	87.7
% In married or committed relationship	77.9	78.5
Mean $\pm$ SD yrs with BPH symptoms	7.9 $\pm$ 6.1	8.3 $\pm$ 6.3
Mean $\pm$ SD AUASI	19.2 $\pm$ 5.9	20.1 $\pm$ 6.5
Mean $\pm$ SD ml/sec Qmax	10.0 $\pm$ 3.0	9.7 $\pm$ 2.5
Mean $\pm$ SD mm prostate length	44.4 $\pm$ 15.4	45.0 $\pm$ 15.1
Mean $\pm$ SD cc prostate vol	51.1 $\pm$ 24.2	48.1 $\pm$ 26.7
Mean $\pm$ SD cm ² max sagittal area	15.3 $\pm$ 5.8	14.0 $\pm$ 6.3

Table 3

Baseline comparison of completers vs dropouts

	Mean $\pm$ SD 12-Mo Completers (108)	Mean $\pm$ SD Dropouts (26)
Age	66.0 $\pm$ 8.2	67.0 $\pm$ 8.3
AUASI	19.2 $\pm$ 6.0	21.5 $\pm$ 6.8
Qmax (ml/sec)	9.8 $\pm$ 2.7	10.1 $\pm$ 3.1
Prostate vol (cc)	50.1 $\pm$ 26.7	47.7 $\pm$ 19.8

Table 4

Serious adverse events by dose arm

	Serious AEs		AEs*	
	100 U	300 U	100 U	300 U
No. pts reporting	7	5	46	41
No. events reported	7	6	116	109
Events with relationship to study treatment/procedures:				
None	4	5	64	64
Remote	1	0	1	3
Unlikely	1	0	12	8
Possible	1	0	18	20
Probable	0	1	13	5
Definite	0	0	8	9
No. event outcome:				
Complete recovery	5	4	91	84
Recovery with residual effect	1	2	25	27
Recovery with persistent effect	0	0	0	0
Death	1	0	0	0
No. event severity/toxicity grade:				
1-Mild	0	0	78	69
2-Moderate	3	4	35	38
3-Severe	2	1	3	2
4-Life threatening or disabling	1	1	0	0
5-Fatality	1	0	0	0

* Included documented urinary tract infection without sepsis in 4 patients; pelvic pain which resolved in 1; 3 instances of urinary retention, 1 of which did not resolve and required ongoing catheterization; gross hematuria reported 14 times; hematospermia reported 6 times; 1 diagnosis of prostate cancer during the 12-month followup; 2 patients with an increase in prostate specific antigen without a diagnosis of prostate cancer; increased urinary symptoms, primarily nocturia, frequency and urgency reported 9 times and dysuria 2 times; a weak urinary stream in 3 patients and urinary leakage including post-void dribble 3 times; and erectile dysfunction or altered ejaculation recorded 6 times.