THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH & REVIEWS

ERECTILE DYSFUNCTION

Long Term Effectiveness and Safety of Intracavernosal Botulinum Toxin A as an Add-on Therapy to Phosphosdiesterase Type 5 Inhibitors or Prostaglandin E1 Injections for Erectile Dysfunction

Francois Giuliano, MD, PhD,[1,2] Charles Joussain, MD, PhD,[1,2] and Pierre Denys, MD, PhD[1,2]

ABSTRACT

Background: Some evidence suggests that intracavernosal botulinum toxin A (BTX-A IC) injections administered in addition to phosphodiesterase type 5 inhibitors (PDE5-Is) or prostaglandin E1 intracavernosal injections (PGE1 ICI) could effectively treat erectile dysfunction (ED) in non−responders, or insufficient responders to these pharmacologic treatments.

Aim: To determine the long-term effectiveness and safety of combined treatment involving a single injection of BTX-A IC as an add on therapy to PDE5-Is or PGE1-ICI for the treatment of ED of different etiologies.

Methods: A retrospective, uncontrolled, single center study was conducted. Data from 123 consecutive patients with ED who were insufficient responders to PDE5-Is or PGE1-ICI and who received onabotulinumtoxinA 100 U, abobotulinumtoxinA 250 U or 500 U IC as an add on to their current pharmacologic treatment were analyzed. All analyses were exploratory. Qualitative data were compared using the Fisher's exact test. Univariate and multivariate analysis were performed using logistic regression with Odds Ratios (OR). Only variables with $P < .05$ in the univariate analysis were selected for multivariate analysis.

Results: The minimally clinically important difference (relative to baseline severity of ED) in the International Index of Erectile Function-Erectile function domain (IIEF-EF) score was achieved in 50% of patients at 34 (27 −42) days and in 41% at 5.9 (3.9 − 8.1) months following BTX-A IC in combination with PDE5-Is or PGE1 ICI. The severity of ED influenced response to BTX-A IC according to the multivariate analysis (OR = 0.3, IC (95%]) = (0.16 − 0.56). Neither being post prostatectomy nor the type of BTX-A affected the response. Effectiveness tended to decrease more over time with abobotulinumtoxinA 250 U than 500 U.

The only side-effects were mild penile pain on injection (n = 1) and mild penile pain for 3 days following injection (n = 1); no systemic effects were reported.

Clinical implications: BTX-A IC (all types) administered as an add on to registered pharmacologic treatments improved erectile function for at least 6 months in 41% of patients with ED of varying etiologies, and was safe.

Strengths & Limitations: A relatively large cohort of patients with ED was included, with a long follow-up period, however the study was retrospective, and uncontrolled.

Conclusion: This study provides preliminary evidence that BTX-A IC administered as an add-on therapy for ED that is insufficiently responsive to standard therapy is effective for at least 6 months, and is safe. Randomized clinical trials are now needed to fully confirm these results. **Giuliano F, Joussain C, Denys P, Long Term Effectiveness and Safety of Intracavernosal Botulinum Toxin A as an Add-on Therapy to Phosphosdiesterase Type 5 Inhibitors or Prostaglandin E1 Injections for Erectile Dysfunction. J Sex Med 2022;19:83−89.**

Key Words: OnabotulinumtoxinA; Abobotulinumtoxin A; Combined Treatment; Non−responders; Pharmacology; Duration of Action

Received June 30, 2021. Accepted October 31, 2021.

[1]Neuro-Uro-Andrology R.Poincare academic hospital, Garches, France;

[2]Faculty of Medicine, U1179 Inserm / Versailles Saint Quentin University, Montigny le Bretonneux, Paris Saclay, France

https://doi.org/10.1016/j.jsxm.2021.10.011

INTRODUCTION

There is an unmet medical need for the treatment of erectile dysfunction (ED) in non−responders or, more accurately, insufficient responders to phosphodiesterase type 5 inhibitors (PDE5-

Is).[1] To our knowledge, 2 studies have reported the short-term efficacy of combined therapy involving intracavernosal (IC) injections of botulinum toxin A (BTX-A IC) as an add on to standard therapy in these patients. The first was a randomized placebo-controlled trial that included 24 patients with severe vasculogenic ED who were non−responders to PDE5-Is or IC injections of tri-mix (a custom-prepared mixture of prostaglandin E1 (PGE1) with papaverine and phentolamine).[2] At the 4-week follow-up, erectile function, and penile rigidity were significantly more improved in the treatment group. The second study was a retrospective, uncontrolled study of 47 patients who were insufficiently responsive to PDE5-Is or PGE1 IC, and who received IC injections of abobotulinumtoxinA (Dysport; Ipsen, Paris, France) 250 or 500U as an add on therapy.[3] The results showed a 54% response rate at 6-weeks.

Although the results of both these studies are encouraging, both only assessed the short-term effectiveness and tolerance of BTX-A IC injections (at 4^2 and 6^3 weeks, respectively). More recently, the group who performed the first randomized placebo-controlled trial performed a second randomized placebo-controlled trial also in patients with severe vasculogenic ED, who were non responders to PDE5-Is and to IC injections of tri-mix. This second trial was large, with 176 patients randomized to receive either onabotulinumtoxinA 50 U, 100 U or placebo IC injections. Forty percent of patients were responders, with a maximal improvement at 3 months post BTX-A IC.[4] At 6 months, the effectiveness of onabotulinumtoxinA 100 U was superior to that of onabotulinumtoxinA 50 U. To our knowledge, these are the only data available regarding the effect of onabotulinumtoxinA at 6 months.

It is believed that BTX-A reduces ED by decreasing sympathetic activity within the cavernous and penile nerves that supply the arteries and smooth muscle of the penis.[5] This mechanism likely functions by the partial blocking of norepinephrine release of the normal vesicular dependent release of norepinephrine from the sympathetic nerve terminals into the neuromuscular junction.[6] This putative mechanism of action is similar to that of BTX-A intradetrusor injection for the treatment of overactive bladder and neurogenic detrusor overactivity.[7] To initiate voiding, parasympathetic postganglionic nerves release acetylcholine in the neuromuscular synapse which binds with the muscarinic receptor in the detrusor muscle and generates muscle contraction.[8] BTX-A injected in the detrusor muscle prevents acetylcholine release, reducing detrusor overactivity. Studies have shown that for optimal effectiveness, intradetrusor onabotulinumtoxinA injections should be administered every 5 (200U dose) or 6 months (300U dose),[9] and the overall median duration of the effect is 9 months.[10] Such data do not currently exist for BTX-A IC injections for the treatment of ED. The primary aim of the present retrospective case series study was therefore to assess the duration of effect of BTX-A IC injection in patients with ED of various etiologies. The secondary aims were to evaluate the type and rate of side effects at the time of BTX-A IC injection and during the follow-up, and the proportion of responders at the 2-month follow-up.

MATERIALS AND METHODS

We conducted a retrospective, single center study of medical files from consecutive patients who responded insufficiently to pharmacologic treatment for ED and who received BTX-A IC as an add-on therapy between October 2017 and November 2020.

Eligibility Criteria

Male patients were included if they were aged >18 years, diagnosed with ED, in a stable heterosexual relationship and had a history of insufficient effectiveness of at least 1 marketed PDE5-I at the highest approved dose, or PGE1 IC injections with a dose up to 60 μg. Current highest approved doses of PDE5-Is on demand are 100 mg for sildenafil and 20 mg for tadalafil or vardenafil, and 5 mg for daily tadalafil. Insufficient effectiveness was defined by an EF domain score of the IIEF < 26 with standard treatment. Exclusion criteria were contra-indications to BTX-A determined by abobotulinumtoxinA and onabotulinumtoxinA monographies.[11,12] Patients were categorized according to their etiology(ies) and/or risk factor(s) for ED based on their medical history and routine laboratory investigations, including glucose fasting, and lipid profiles. Patients with endocrinopathies (apart from diabetes mellitus), sleep apnea or no organic etiology and/or risk factors identified (thus ED of likely psychogenic origin) were categorized as "other." Since our sexual medicine clinic is situated within a hospital that is specialized in the treatment of neurologic disorders, the cohort was composed of a large proportion of patients with spinal cord-injury (SCI).

Intracavernosal Injection of BTX-A

The intracavernosal injection technique has been described elsewhere.[2] Briefly, an adjustable penile loop ring was placed at the penoscrotal junction for 30 minutes prior to the injections. Then, 250 or 500 Speywood units of abobotulinumtoxinA or 100 units of onabotulinumtoxinA were injected via a 13 mm long 29 $^1/_2$ G needle: 0.5 mL into each corpus cavernosum. The choice of BTX-A type (abobotulinumtoxinA or onabotulinumtoxinA) was not related to ED severity or to ED risk factors and/or etiologies. The first 32 patients who were administered abobotulinumtoxinA received a dose of 250 units and the following 37 patients received a dose of 500 units to ensure safety, as previously reported.[3]

Patient Follow-Up

Following BTX-A IC injection, patients were advised to attempt sexual intercourse using their usual pharmacologic treatment. An early follow-up assessment was scheduled during the second month after the BTX-A IC injection. Responders (see endpoints) attended a second assessment session during the

seventh month after the BTX-A IC injection or upon their request if the effectiveness decreased.

Endpoints

The primary endpoint was the proportion of responders at the first assessment. A patient was classified as a responder to BTX-A IC if the minimum clinically important difference (MCID) in the IIEF-EF score relative to their baseline severity of ED was achieved. The MCIDs according to ED severity are as follows: mild: 2 points, moderate: 5 points and severe: 7 points.[13] Baseline severity of ED was measured using the IIEF-EF during treatment with PDE5-Is or PGE1 IC injections but before BTX-A IC, and thus provided a score for the severity of persisting ED with standard treatment. Severity was classified as mild (EF score 17−30), moderate (EF score 11−16) or severe (EF score 0−10).[13]

The secondary endpoints were (i) side effects identified by patient self-report at the time of the BTX-A IC injection and during the follow-up and (ii) effectiveness at the 2-month follow-up. Data from the early assessment (2 months post BTX-A IC) of some patients in the present series treated with abobotulinumtoxinA IC have previously been reported.[3]

Statistical Analyses

Continuous variables were expressed as means with standard deviations. IIEF-EF score, time elapsed between BTX-A IC and duration of ED were expressed as medians (first-third quartile). No formal sample size calculation was performed, and all analyses were exploratory. Comparisons of qualitative data were performed using a Fisher's exact test (Prism V5, GraphPad software − La Jolla, CA, USA). Odds Ratios (OR) were calculated from logistic regressions in both the univariate and multivariate analysis to determine risk factors for non−response to BTX-A IC. (Stata/MP 16.0 [Timberlake - Richmond upon Thames UK]). The variables included in the univariate logistic regression at 34 (27−42) days were: age, ED duration, comorbidities, ED treatment prior to BTX-A IC, type of BTX-A, IIEF-EF score at baseline, and ED severity. The variables with a P value <.05 were entered into a multivariate logistic regression analysis.

Ethics

In accordance with French legislation for retrospective studies, the database was approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés) under the registration number 2209010v0. Patients' medical files were anonymized, and patients were informed they could deny access to their personal and medical data at any time. Written informed consent was obtained from all patients whose data were included in the study.

RESULTS

One hundred and thirty-one patients with ED were treated with BTX-A IC during the study period: data from 123 files were analyzed (inclusion flow chart is shown in Figure 1). Mean age was 53 ± 14 years and median duration of ED prior to

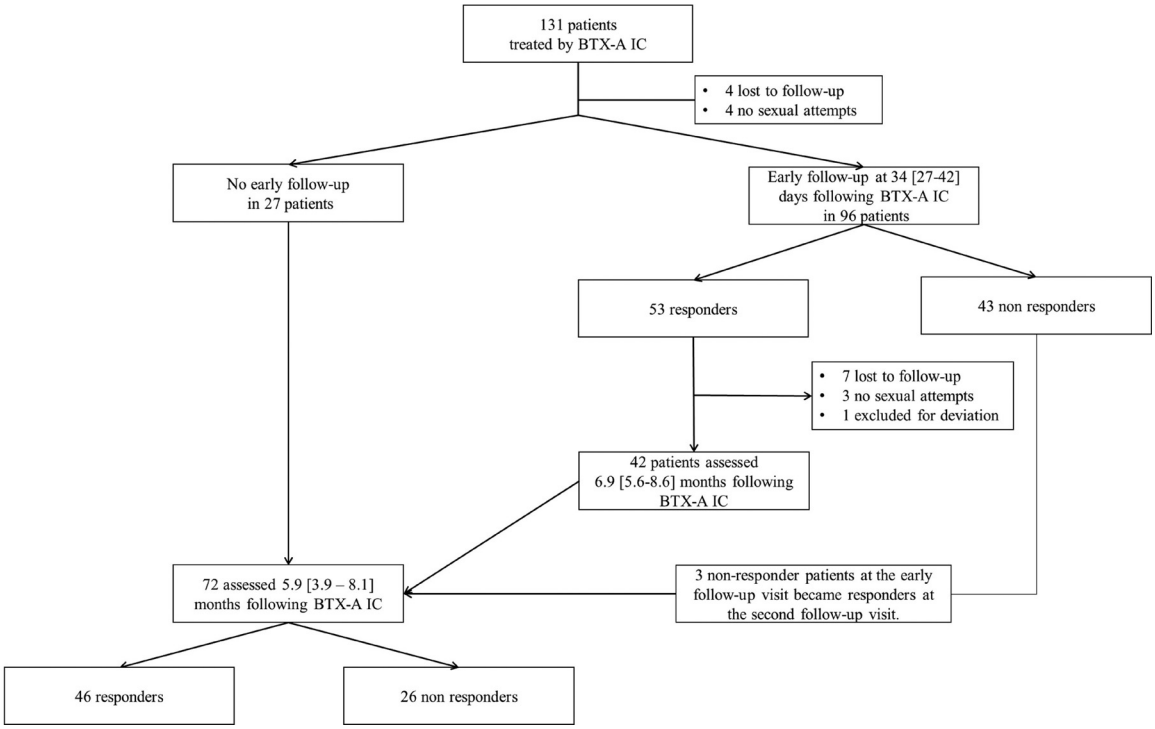

Figure 1. Flow chart of patients treated by BTX-A IC.

Table 1. IIEF-EF at baseline and post BTX-A IC, increase in IIEF-EF and responder rate according to ED severity in 96 consecutive patients who were insufficient responders at baseline to phosphodiesterase type 5 inhibitors or PGE1 IC injections assessed 34 (27-42) days post-BTX-A IC as an add on therapy to their current pharmacologic treatment

ED severity according to IIEF-EF [13]	Early assessment at 34 [27-42] days post- BTX-A IC in 96 patients		
	Severe (n = 42)	Moderate (n = 24)	Mild (n = 30)
IIEF-EF at baseline (median [1st quartile - 3rd quartile])	6 [6−7]	13 [12−14]	19 [18−20]
IIEF-EF post BTX-A IC (median [1st quartile - 3rd quartile)	9 [6−17]	18 [12.−24]	26 [23−28]
Increase in IIEF-EF (median [1st quartile - 3rd quartile)	2 [0−8.5]	5 [−1−11]	6 [3−9]
Responders (n [%])	14 (33.3%)	12 (50%)	27 [90%]

BTX-A IC was 5 (2−10) years. The risk factors and etiologies for ED were as follows: cardio-metabolic for 49 (39.8%) patients, spinal cord injury for 50 (40.7%) patients, radical prostatectomy for 27 (22%) patients and for 19 (14.4%) patients categorized as "other," no organic etiology or risk factor was identified for the majority. Prior to BTX-A IC, 77% of patients were treated with highest dose PDE5-Is and 29% by PGE1 IC injections (mean dose: 38 ± 18 μg). Eight patients (6%) were treated with PDE5-Is combined with PGE1 IC injections. Median baseline IIEF-EF score (ie, with standard treatment) was 11 (6−17) points prior to BTX-A IC; 35 (%) patients had mild, 26 (%) had moderate and 59 (48%) had severe ED. Fifty-eight patients (47%) were treated with onabotulinumtoxinA 100 U and 65 patients (53%) with abobotulinumtoxinA (32 patients (26%) with 250 Speywood U and 33 patients (27%) with 500 Speywood U).

Early Assessment

Ninety-six patients underwent early assessment, 34 (27−42) days following BTX-A IC. Of these, 53 (55.2%) were classed as responders, with an increase in median IIEF-EF score from 17 (10−19) to 26 (22−28) points (Table 1). The response rate was 90% in those with mild baseline ED, 50% in those with moderate ED and 33% in those with severe with ED; and was 56.8% in patients treated with PDE5-Is and 51.9% in patients treated with PGE1-IC injections (Table 2). Of the 39 patients treated by PDE5-Is, none switched to PGE1 IC injections. Of the 11 patients treated by PGE1 IC injections, the dose of PGE1 was reduced for 5, and 1 patient switched to PDE5-Is. The response rate according to ED risk factors and/or etiologies is shown in Figure 2. Response rate was lower in patients with post-radical prostatectomy and SCI compared to patients with other comorbidities ($P = .002$ and $P = .0045$ respectively). There was no difference in the proportion of responders between abobotulinumtoxinA (250 or 500 U) and onabotulinumtoxinA 100 U (47% and 54% respectively, $P = .67$) (Table 2). The univariate logistic regression identified the following factors as associated with the response to BTX-A IC: other comorbidities ($P = .01$), SCI ($P = .047$), post-prostatectomy ($P = .04$) and ED severity ($P < .01$). EF-score at baseline was also identified but is has the same signification as ED severity and thus was not selected for multivariate analysis. After multivariate analysis, only ED severity was identified as a risk factor OR = 0.3, IC (95%) = (0.16 − 0.56) for non−response to BTX-A IC(Table 3).

Late Assessment

Among all the patients treated, 46 (41%) were categorized as responders at the late assessment (median 5.9 [3.9 − 8.1] months post BTX-A-IC). Of the 42 initial responders (ie, among those who underwent early assessment and who were re-assessed at the late assessment), 32 remained responders (76%). Three non−responder patients at the early visit were responders at the late visit. The effectiveness of the treatment did not decrease significantly from the early to the late assessment in any of the ED risk factor and/or etiology groups (Figure 2). The decrease in effectiveness over time was not different between the types of BTX-A IC (Figure 3). The univariate analysis did not show any association between the type of standard treatment for ED, type of BTX-A or ED severity, and response to BTX-A IC.

Side Effects

One patient reported mild penile pain during BTX-A IC injection and a second patient reported mild penile pain for 3 days following BTX-A IC, with no need for pain medication. No systemic effects (generalized muscle weakness, dysphonia, diplopia, dysphagia, and respiratory function impairment[14]) were reported.

DISCUSSION

This retrospective case study confirmed that BTX-A IC is an effective add-on therapy to PDE5-Is or PGE1 IC injection, with an effect that lasted for at least 6 months: 41% of patients with ED who responded insufficiently to PDE5-Is or PGE1 IC injection responded at 6 months with BTX-A IC. In addition, both abobotulinumtoxinA (250 and 500 U) and onabotulinumtoxinA 100U IC appeared to be safe. The only side effect reported was mild pain during or after the IC injection in less than 1% of patients; no systemic side effects of BTX-A were reported. Such a high level of safety was also found in a study of onabotulinumtoxinA 100U injection in the detrusor muscle (also smooth

Table 2. ED severity according to IIEF-EF [13], risk factors, and etiologies of ED, treatment prior to BTX-A IC, type of botulinum toxin A IC delivered and IIEF-EF at baseline and time from injection to early assessment according to the response to botulinum toxin A (BTX-A) IC as an add on to their current pharmacologic treatment in 123 consecutive patients who were insufficient responders at baseline to phosphodiesterase type 5 inhibitors or PGE1 intracavernosal injections and assessed at least once post-BTX-A IC

	Early assessment post- BTX-A IC in 96 patients	
	Responders (n = 53)	Non responders (n = 43)
Age (mean +/- standard deviation) y	53 +/-13.5	55.9 +/-14.4
ED duration (median [1st quartile - 3rd quartile]) y	5 [2-10]	5 [2-10]
ED Severity according to IIEF-EF [13]		
Severe n (%)	14 (26.4)	28 (65.1)
Moderate n (%)	12 (22.6)	12(27.9)
Mild n (%)	27 (50.9)	3 (7)
ED risk factors and etiologies		
Other comorbidity(ies) n (%)	20 (37.8)	3 (7)
Cardiometabolic n (%)	16 (30.2)	13 (30.2)
Spinal cord injury n (%)	17 (32)	22 (51.2)
Post-prostatectomy n (%)	8 (15.1)	15 (34.9)
Treatment prior to BTX-A IC		
PDE5-I n (%)	42 (79.2)	32 (74.4)
PGE1 n (%)	14 (26.4)	13 (30.2)
mean dose PGE1 (mean +/- standard deviation) μg	36.4 +/-18.2	38.5 +/-19.1
PDE5-I + PGE1 n (%)	3 (5.7)	2 (4.7)
Botulinum toxin type		
onabotulinumtoxinA 100 U n (%)	24 (45.3)	17 (39.5)
abobotulinumtoxinA 250 Speywood U n (%)	15 (28.3)	13 (30.2)
abobotulinumtoxinA 500 Speywood U n (%)	14 (26.4)	13 (30.2)
BTX-A ICI result		
EF at baseline (median [1st quartile - 3rd quartile])	17 [10–19]	7 [6–11 .5]
EF post injection (median [1st quartile - 3rd quartile)	26 [22–28]	8 [6–12]
Time between injection and assessment (median [1st quartile - 3rd quartile]) d	33 [27–42]	36 [28–43.5]

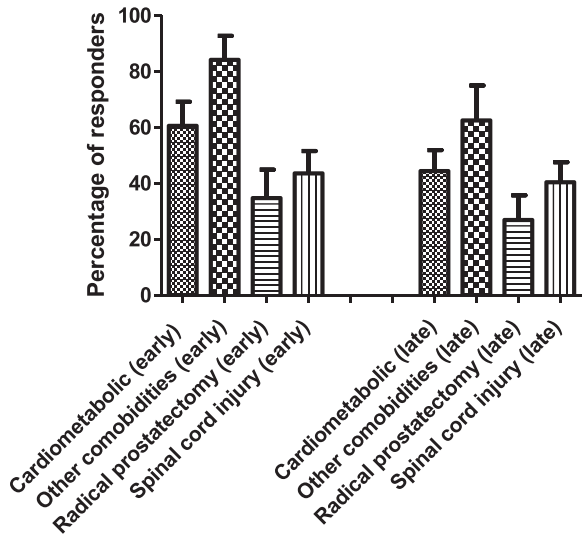

Figure 2. Percentage of responders to BTX-A IC at the early assessment (median 34 [27 – 42] days) (n = 96) and at the late assessment (median 5.9 [3.9 – 8.1] months) (n = 112) according to ED risk factors and/or etiologies.

muscle) in patients with neurogenic detrusor activity caused by multiple sclerosis.[15]

The primary endpoint of this study was a clinically meaningful improvement in the IIEF-EF score. This is commonly referred to as the minimal clinically important difference (MCID), and has been defined as the smallest change in a score in the domain of interest that patients perceive as beneficial and that would indicate a need for change in the patient's treatment, in the absence of side effects.[16] The MCID was achieved in 41% of patients at 6 months. At the time of writing, 22 of the 46 responder patients at 6 months had undergone further follow-up visits. In 18 (82%) of these patients, the response to BTX-A IC was sustained up to 11.2 (9.2–19.4) months post BTX-A IC (data not shown).

Not surprisingly, the short-term response rate to BTX-A IC was higher in patients with mild baseline ED. In patients with ED caused by radical prostatectomy or SCI, BTX-A IC was less effective than in patients with ED associated with cardio-metabolic conditions (ie, cardiovascular diseases and diabetes or other comorbidities. However, baseline ED (ie ED with standard treatment)

Table 3. Odds ratios for non–response to treatment from the univariate and multivariate analyses for the following variables: age, ED duration, IIEF-EF at baseline, ED severity, ED risk factors and etiologies, treatment prior to BTX-A IC and type of BTX-A IC. Response to treatment was defined as achievement of the MCID[13] at the early assessment post BTX-A IC

	Univariate analysis		Multivariate analysis	
	P value	OR (95% Conf. Interval)	*P* value	OR (95% Conf. Interval)
Age	*P* = .57	0.99 (0.96 – 1.02)		
ED duration	*P* = .22	0.96 (0.92 – 1.02)		
IIEF-EF at baseline	*P* < .001	1.24 (1.13 – 1.37)		
ED severity according to IIEF-EF [13]	*P* < .001	0.27 (0.15 – 0.48)	*P* < .001	0.30 (0.16 – 0.56)
ED risk factors and etiologies				
Other comorbidity(ies)	*P* = .01	5.1 (1.5 – 20.9)	*P* = .39	2.1 (0.38 – 12.2)
Cardiometabolic	*P* = .35	1.5 (0.6 – 3.6)		
Spinal cord injury	*P* = .047	0.43 (0.2 – 0.99)	*P* = .10	0.30 (0.07 – 1.25)
Post-prostatectomy	*P* = .04	0.35 (0.13 - 0.95)	*P* = .10	0.26 (0.05 – 1.29)
Treatment prior to BTX-A IC				
PDE5-Is	*P* = .72	1.19 (0.4 – 3.1)		
PGE1 IC injections	*P* = .81	0.9 (0.4 – 2.2)		
Type of botulinum toxin				
onabotulinumtoxinA 100 U	*P* = .48	1.34 (0.6 – 3.1)		
abobotulinumtoxinA 250 or 500 (Speywood U)	*P* = .48	0.74 (0.3 – 1.7)		

was more severe in patients with radical prostatectomy or SCI than in those with cardio-metabolic conditions or other co-morbidities. The response to BTX-A IC therefore seemed more influenced by the severity of the ED than by its etiology. However, this result was not confirmed at the late follow-up evaluation, probably due to a lack of statistical power resulting from the retrospective nature of the study. Of note is that most of the patients in the "other comorbidity(ies)" group who responded insufficiently to PDE5-Is or PGE1 IC injection had ED of psychogenic origin with no identified organic risk factors for ED.

PDE5-Is is the first-line treatment for ED caused by either psychogenic or organic factors, however around 25 to 35% of patients do not respond to this treatment.[17-19] Second-line therapy for these non–responders consists of local pharmacologic treatment.[20] It has been postulated that BTX-A IC has a chemical sympathectomy-like effect on the cavernosal nerve; by reducing the anti–erectile effect of cavernosal sympathetic innervation,[21,22] BTX-A IC enhances the pro-erectile effect of PDE5-Is or PGE1 ICI.[3] In the case of ED of vascular origin, it has been proposed that BTX-A IC increases the cavernosal expression of VEGF and CD31 which could be involved in vasodilation and endothelial cell proliferation.[4]

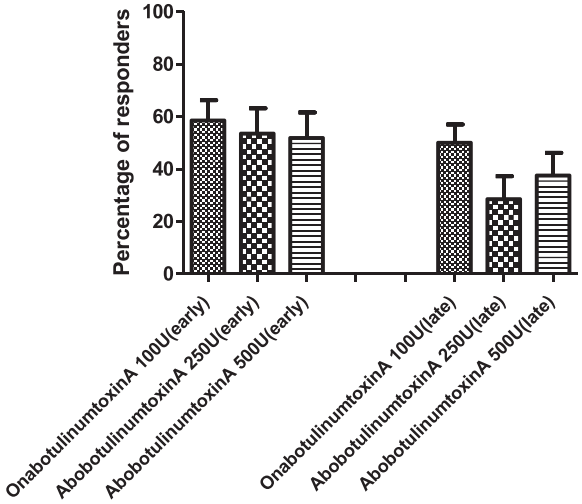

Figure 3. Decrease in effectiveness over time according to the type of BTX-A. Early: 34 [27 – 42] days post-BTX-A IC (n = 96), late: 5.9 [3.9 – 8.1] months post-BTX-A IC (n = 112).

Three preparations of botulinum toxin A (BTX-A) are commercially available and approved by the United States Food and Drug Administration and European Medicines Agency: onabotulinumtoxinA, abobotulinumtoxinA and incobotulinumtoxinA (Xeomin, NT 201; Merz Pharmaceuticals GmbH, Frankfurt, Germany). These preparations differ from each other and are not interchangeable. The main difference between onabotulinumtoxinA and the other 2 types is the purification procedure. OnabotulinumtoxinA is purified by repeated precipitation and redissolution, whereas abobotulinumtoxinA is purified by a column separation method.[23] Dose ratios between onabotulinumtoxinA and abobotulinumtoxinA are the subject of debate,[23] nevertheless, in the present study the effectiveness was not influenced by the type of BTX-A, either with a ratio of 2.5 or a ratio of 5 between ona, and abo-botulinumtoxinA. In addition, we have recently found similar results for the early (2 months) effectiveness of incobotulinumtoxinA 100U IC in 35 patients using the same treatment paradigm (unpublished data).

As described in the introduction, the only large, randomized placebo-controlled clinical trial in patients with severe vasculogenic ED suggested that the duration of effectiveness of onabotulinumtoxinA was dose-dependent.[4] Similar findings have been reported

for intradetrusor injections of BTX-A to treat neurogenic detrusor overactivity. In the present study, there was a trend toward a more pronounced decrease in effectiveness for abobotulinumtoxinA 250 U (relative decrease in effectiveness of 46% over time) when compared to 500 U (relative decrease in effectiveness of 28% over time). It is unlikely that this was influenced by severity, since around 50% of patients in each group had severe baseline ED (ie, ED with standard treatment) (data not shown). The lack of statistical significance may be due to the small sample size.

The main limitation of this study is that it was uncontrolled and retrospective. However, the large randomized, placebo-controlled trial described above found no placebo effect in patients with severe ED of vascular etiology treated by BTX-A IC.[4]

CONCLUSIONS

This study provides preliminary evidence to support the use of BTX-A IC as an add-on therapy to treat ED in insufficient responders to PDE5-Is or PGE1 ICIs: the duration of action was at least 6 months in 41% of patients with ED of varying etiologies and the treatment was safe. These results justify further assessment of the effectiveness and safety of BTX-A IC in randomized clinical trials. Such clinical trials are particularly important to determine the effectiveness of this add-on treatment in difficult to treat patients with ED of various etiologies, including radical prostatectomy.

Corresponding Author: Francois Giuliano, MD, PhD, Neuro-Uro-Andrology R.Poincare academic hospital, AP-HP, 104 bvd R. Poincare, 92380, Garches, France. Tel: +33147107832; E-mail: francois.giuliano@uvsq.fr

REFERENCES

1. Munk NE, Knudsen JS, Comerma-Steffensen S, et al. Systematic review of oral combination therapy for erectile dysfunction when phosphodiesterase type 5 inhibitor monotherapy fails. **Sex Med Rev 2019;7:430–441.**
2. Ghanem H, Raheem AA, AbdelRahman IFS, et al. Botulinum neurotoxin and its potential role in the treatment of erectile dysfunction. **Sex Med Rev 2018;6:135–142.**
3. Giuliano F, Joussain C, Denys P. Safety and efficacy of intracavernosal injections of abobotulinumtoxin A (Dysport®) as add on therapy to phosphosdiesterase type 5 inhibitors or prostaglandin E1 for erectile dysfunction-case studies. **Toxins (Basel) 2019;11:E283.**
4. El-Shaer W, Ghanem H, Diab T, et al. Intra-Cavernous Injection of BOTOX® (50 and 100 Units) for Treatment of Vasculogenic Erectile Dysfunction: Randomized Controlled Trial. Andrology; 2021.
5. Giuliano F, Brock G. Botox for erectile dysfunction. **J Sex Med 2017;14:177–178.**
6. Morris JL, Jobling P, Gibbins IL. Botulinum neurotoxin A attenuates release of norepinephrine but not NPY from vasoconstrictor neurons. **Am J Physiol Heart Circ Physiol 2002;283:H2627–H2635.**
7. Weckx F, Tutolo M, De Ridder D, et al. The role of botulinum toxin A in treating neurogenic bladder. **Transl Androl Urol 2016;5:63–71.**
8. Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. **Nat Rev Neurosci 2008;9:453–466.**
9. Joussain C, Popoff M, Phé V, et al. Long-term outcomes and risks factors for failure of intradetrusor onabotulinumtoxin A injections for the treatment of refractory neurogenic detrusor overactivity. **Neurourol Urodyn 2018;37:799–806.**
10. Rovner E, Kohan A, Chartier-Kastler E, et al. Long-term efficacy and safety of onabotulinumtoxin A in patients with neurogenic detrusor overactivity who completed 4 years of treatment. **J Urol 2016;196:801–808.**
11. Dysport Therapeutic. Available at: https://ipsen.com/websites/IPSENCOM-PROD/wp-content/uploads/sites/18/2018/11/08151628/dysport-therapeutic-pm-Oct.24.2018_EN.pdf. Accessed October 24, 2018.
12. Botox Therapeutic; Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5236lbl.pdf.
13. Rosen RC, Allen KR, Ni X, et al. Minimal clinically important differences in the erectile function domain of the international index of erectile function scale. **Eur Urol 2011;60:1010–1016.**
14. Ruet A, Durand MC, Denys P, et al. A. Single-fiber electromyography analysis of botulinum toxin diffusion in patients with fatigue and pseudobotulism. **Arch Phys Med Rehabil 2015;96:1103–1109.**
15. Tullman M, Chartier-Kastler E, Kohan A, et al. Low-dose onabotulinumtoxin A improves urinary symptoms in noncatheterizing patients with MS. **Neurology 2018;91:e657–e665.**
16. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. **Control Clin Trials 1989;10:407–415.**
17. Hatzimouratidis K. Non-responders to phosphodiesterase type 5 inhibitors: is there a second chance? **J Men's Health Gender 2006;3:342–349.**
18. Huang SA, Lie JD. Phosphodiesterase-5 (PDE5) inhibitors In the management of erectile dysfunction. **P T 2013;38:407–419.**
19. Yuan J, Zhang R, Yang Z, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. **Eur Urol 2013;63:902–912.**
20. Montorsi F, Adaikan G, Becher E, et al. Summary of the recommendations on sexual dysfunctions in men. **J Sex Med 2010;7:3572–3588.**
21. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. **Urol Clin North Am 2005;32:379–395.**
22. Andersson KE, Hedlund P, Alm P. Sympathetic pathways and adrenergic innervation of the penis. **Int J Impot Res 2000;12:S5–12.**
23. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. **J Clin Aesthet Dermatol 2014;7:31–39.**