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EFFICACY AND SAFETY OF LOW DOSES OF ONABOTULINUMTOXINA FOR THE TREATMENT OF REFRACTORY IDIOPATHIC OVERACTIVE BLADDER: A MULTICENTER, DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED STUDY.

Hypothesis / aims of study

BotulinumtoxinA (BONT-A) has shown to be effective for the treatment of patients with idiopathic detrusor overactivity (IDO), however, often high doses of BONT-A were evaluated and these were associated with complications due to high post-voided residual (PVR) leading to Intermittent Self Catheterisation (ISC) and Urinary Tract Infection (UTI). The aim of the study was to evaluate the efficacy and tolerability of low doses of anobotulinumtoxinA and compare to placebo in patients with IDO.

Study design, materials and methods

Between Oct 2005 and March 2009, adults with persistent IDO were included in a prospective, randomised, double-blind, placebo-controlled, independent, comparative trial. Patients were centrally randomised to receive a single intradetrusor injection of placebo, 50U, 100U and 150U onabotulinumtoxinA. The initial evaluation (i.e. clinical, 3 days micturition diary, flow rate, Post void residual urine (PVR), urodynamic variables and quality of life using IQol and EDQ5 was repeated at day 8, month 1,3,5 and 6. Primary outcome was >50% reduction of urgency and urge urinary incontinence (UUI) at month 3. Secondary outcomes were voiding symptoms, urodynamics and QoL. Patients were included if they had ≥3 episodes of urgency and/or urge incontinence (UUI) and ≥8 voidings on a 3 days micturition diary, had proven detrusor overactivity (DO) and were refractory, had contraindications or discontinued anticholinergics due to adverse events. All patients were trained or willing to perform ISC and able to fill in a bladder diary. Patients were mainly excluded in case of symptomatic UTI, flow rate <15mL/sec and PVR >150mL. The study was approved by the Local Research Ethical Committee and was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients.

Results

99 patients with a mean age of 61.6+-14years and 87.9% female have been included in the efficacy analysis. At 3 months treatment, we have observed a >50% improvement in urgency and UUI symptoms in 65% and 56% of the patients after 100U (p=0.086) and 150U (p=0.261) BONTA treatment, respectively and a >75% improvement in 40% of the patients after both 150U (p=0.022) and 100U (p=0.058) table 1 BONTA treatment, respectively. Generally, improvement of urgency and UUI was fast, and was already observed after 8 days and significantly different from placebo at 1 month in case of 150U (Figure 2). Results at 1 month were comparable after 100U and 150U BONTA, however, only 150U was significantly different from placebo. Benefits in symptom reduction showed a slight trend to decrease after 5 to 6 months. Frequency decrease was significantly different up to 6 months in the 150U group. Symptom improvement after 50U BONT-A was nearly similar as placebo. IqoL shows a significant improvement at 1, 3, 5 and 6 months for 100 and 150U.

LOCF		Placebo	onabotulinumtoxinA		
			50U	100U	150U
	N	28	19	20	25
Reduction> 50%	Success rate	29%	37%	65%	56%
	P (compared to placebo)	-	0.395	0.086	0.261
	P	0.062			
Reduction > 75%	Success rate	18%	5%	40%	40%
	P (compared to placebo)	-	0.040	0.058	0.022
	P	0.009			

Table 1 Primary criteria: percentage of patients with more than 50% or 75% improvement in urgency and UUI episodes at month 3 calculated with the LOCF method.

Figure 3

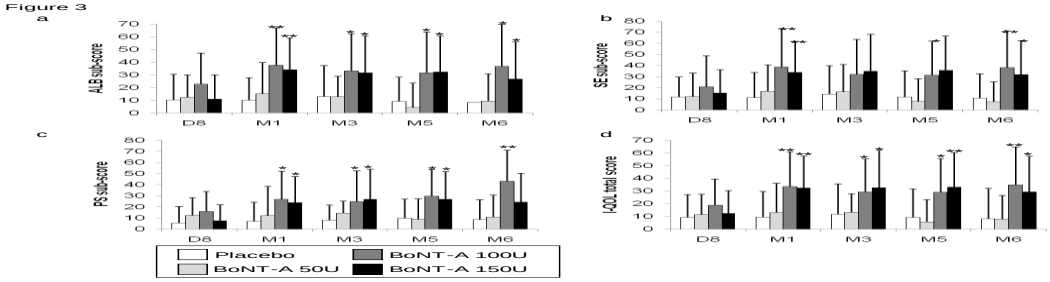

Figure 1 Mean differences in I-QOL questionnaire subscale scores (avoidance and limiting behaviour (ALB) (a), social embarrassment (SE) (b), psychosocial impacts (PS) (c)) and total score (d) compared to baseline according to the treatment group.

ALB: avoidance and limiting behaviour, SE: social embarrassment, PS: psychosocial impacts. *P* values are the comparison between placebo and BONT-A treatment *: 0.01≤*P* <0.05, **: 0.001 ≤*P* <0.05, ***: *P* <0.001.

In term of safety We have observed 4 patients at 3 months and 6 patients at 6 months with symptomatic UTI . PVR was increased in all treatment groups and was significantly different from placebo after 8 days of BONT-A injection, 3 months and 6 months. High PVR was low in all groups In the 150U group, we have observed 3 patients with à PVR >200mL at 8 days, only 1 after 6 months and four patients in that group had to use intermittent catheterization based on the decision of the investigator.

Interpretation of results

A high placebo effect was observed for symptoms variables. 50U does not show a significant effect. Low doses of onabotuliumtoxinA 100 and 150U significantly improved durably symptoms, and quality of life. Risk of chronic urinary retention is dose dependant and requires specific attention.

Concluding message

In this independent clinical study 100U and 150U shows a significant and durable improvement of symptoms and quality of life of patients suffering from refractory OAB with DO. Risk of urinary retention is dose dependant and requires specific follow up and information to patients.

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Specify source of funding or grant	**The study was sponsored by the Assistance Publique Hôpitaux de Paris and was funded by a grant from the Programme Hospitalier de Recherche Clinique 2003**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**The study was registered at ClinicalTrials.gov (registration number: NCT00231491).**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**The study was approved by the Local Research Ethical Committee (Ambroise Paré, Boulogne Billancourt,25 november 2004)**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**