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Long term follow-up reveals a low persistence rate of abobotulinumtoxinA injections for idiopathic overactive bladder.

Short title: AbobotulinumtoxinA in idiopathic overactive bladder

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Introduction

Overactive bladder (OAB) is defined as the presence of urinary urgency usually associated with frequency and nocturia, with or without urgency urinary incontinence[1]. Idiopathic overactive bladder (iOAB) is highly prevalent and greatly impacts health related quality of life (HRQOL) and work productivity[2–4]. When conservative measures and medical treatment have failed, intra-detrusor injections of botulinum toxin A (BoNT-A) can be proposed as a second line treatment[5].

Two different molecules are currently available in France for intra-detrusor injections: onabotulinumtoxinA and abobotulinumtoxinA marketed under the brand name Botox™ (Allergan Pharmaceuticals, Irvine, Ca, USA) and Dysport™ (Ipsen Biopharm Ltd., Wrexham, UK) respectively. **In France, onabotulinumtoxinA was authorized in 2012 for neurogenic OAB (nOAB) and in 2014 for iOAB associated with urinary incontinence[6]. Before that, both toxins were used off-labelled in tertiary reference centers[5].** AbobotulinumtoxinA has shown good short term results for iOAB management[7,8] with improvement in quality of life and symptoms score. **Nonetheless due to the lack of randomised controlled trials, abobotulinumtoxinA was not labelled and was therefore not proposed for new patients after 2012.**

AbobotulinumtoxinA has been recently brought to light by recent studies that suggested an efficacy of abobotulinumtoxinA in case of failure of onabotulinumtoxinA in

nOAB[9,10]. Recent reports show that after 5 years, two thirds of patients treated with onabotulinumtoxinA injections for iOAB stop their treatment because of a lack of efficacy (20%) or due to side effects (43%)[11]. **In this era of renewed interest for abobotulinumtoxinA it occurs that** long term data after repeated abobotulinumtoxinA injections remains scarce.

Our aim was to assess the long-term compliance with repeated abobotulinumtoxinA injections in patients with iOAB with or without detrusor overactivity (DO). We also report reasons for discontinuation and long-term efficacy.

Patients and Methods

Study design. **All patients who had failed conservative measures (including at least two oral antimuscarinics)** and were treated with abobotulinumtoxinA for iOAB in a tertiary reference centre between 2005 and 2012 were included in a retrospective analysis. Patients were identified through a chart review, using the national coding system for surgical acts. Patients with interstitial cystitis, bladder pain syndrome, chronic urinary retention or nOAB were excluded.

After failure of conservative measures, patients were proposed for BoNT-A injection **or sacral neuromodulation (SNM), according to patient's preference**, because of failure or adverse events of conservative measures. Before BoNT-A treatment, an urodynamic study was performed in most cases. Patients were systematically trained to perform clean intermittent self-catheterisation (CISC) prior to surgery. All patients were given oral and written information about BoNT-A injections including expected efficacy and side effects. **They were asked to stop their antimuscarinic medication prior to the injection.** The work was conducted in accordance with the principles of the Declaration of Helsinki and was approved by local ethics committee (protocol EH2020-08).

Injection technique. Injections were performed by the same surgeon, under local anaesthesia or general anaesthesia depending on patient preference in an outpatient procedure. AbobotulinumtoxinA was previously reconstituted with 0.9% normal saline to a dosage of 25 U, 50 U or 15 U per millilitres. First injections were performed with 500 U according to dosage used in first publications[12,13]. After publication of data suggesting 100 U as the standard dose of onabotulinumtoxinA and the conversion ratio of 1:3 between onabotulinumtoxinA and abobotulinumtoxinA of 3:1 in 2008[14], 250 U dosage was used for first injection. If patients did not want to perform CISC, an injection of 125 U was proposed.

The toxin was then injected supra-trigonally into the detrusor muscle in 20 injection points of 1mL each. After 2012, only labelled onabotulinumtoxinA was used for first injection in our centre.

Outcomes evaluation. Pre-operative data were collected in electronic records and included medical history, 3 day bladder diary, and urodynamic results. Data about intervention were retrieved from electronic chart including date, type of anaesthesia and dose of toxin.

After first injection or after switch to a higher dosage of BoNT-A, all patients were scheduled for a post-operative visit at Day 10 for evaluation of urinary flow rate, and post-void residual estimation. **If post-void residual volume was higher than 200 ml, patients were asked to perform CISC.** Efficacy was estimated at 6 weeks based on a 3 day bladder diary. In case of failure a repeat injections of the same toxin at a higher dosage (**500 U after 250 U and 750 U after 500 U**) was proposed at least three months after the first injection. **After 2012 and 2014, patients were proposed to go on with the same toxin or to switch to onabotulinumtoxinA.** Patients were then seen annually. **They also had the opportunity to contact a nurse for earlier evaluation in case of recurrence of OAB symptoms in order to perform another injection.**

The primary endpoint was the estimated discontinuation-free rate at 5 years of management with intra-detrusor abotulinumtoxinA. Other outcomes of interest were: rate of failure, reasons for discontinuation and subsequent treatment elected in those who did not persist with BoNT-A. Success of BoNT-A was defined as 50% improvement in urge UI, urgency or frequency as assessed at the 6-week evaluation. Primary failure was defined as lack of efficacy of any injection from the first one. Secondary failure was defined as lack of efficacy of at least two consecutive injections after successful initial injection. Causes of discontinuation were carefully assessed and recorded.

Statistical analysis. **Time to discontinuation and failure were calculated from the moment of the first botulinum injection until the last injection plus 6 months. Discontinuation-free and failure-free survivals were estimated using Kaplan-Meier analyses.** Statistical analysis were performed using McNemar's test and χ^2 test for all qualitative variables and Wilcoxon test for paired values of quantitative data. A p-value <0.05 was considered significant. Statistical analysis were performed using GraphPad Prism5 software.

Results

Patient characteristics (table 1)

Fifty nine patients (50 women and 9 men) were included. Mean age was 61 years [17.2-85.4]. Fifty patients (84.7%) had urinary incontinence. Twenty seven patients (45.7%) had detrusor overactivity on urodynamic study and median maximum cystomanometric capacity was 300 ml [30-740]. Forty three patients (72.8%) received 250 U of abobotulinumtoxinA as first injection. Twelve patients (20.3%) received 500 U and 4 (6.7%) who were worried about performing CISC received 150 U of BoNT-A.

Success of first injection

Overall, 35 patients (59.3%) were successfully treated with first injection, **including 16 who had prior DO (16/27, 59.2%)**. The 4 patients who received 150 U as first injection did not have any improvement in urinary symptoms at 6 weeks. One refused any other injection and was managed with antimuscarinic medication alone. Three underwent another injection at a higher dosage (250 U).

Of 43 patients injected with 250 U, 23 (53.4%) received a second injection. Thirteen (30.3%) were injected with the same dosage, 7 (16.2%) received higher dosage and 3 (6.9%) were switched to onabotulinumtoxinA.

Of 12 patients who were injected with 500 U, 3 (25%) received a second injection including one (8.3%) at a higher dosage (750 U).

Eighteen patients (30.5%) required CISC after first or repeated injection at a higher dosage.

Four out of 20 patients who received 500 U (20%) and 1 out of 2 patients (50%) who received 750 U required persistent CISC.

Discontinuation and failures of BT therapy

Median follow-up was 83.6 months [0.3-182.6]. Median number of injections per patient was 2 [1-15] with a median reinjection interval of 10.7 [3-86.4] months. Most patients stopped injections after the first (n=30, 50.8%) or second injection (n= 12, 20.3%).

The estimated 5-years discontinuation-free survival rate was 23.4% [**13.6-34.8**] with a median survival of 9.1 months (figure 1a). At last follow-up, 52 patients (88.1%) had discontinued BoNT-A injections including **20 patients (20/27, 74.1%) who had prior DO.**

The estimated 5-years failure-free survival rate was 64.8% [50.9-75.7] (figure 1b).

Failure free median survival was not achieved.

Causes of discontinuation

Fourteen patients (**14/59, 23.7%**) including **3 who had prior DO**, experienced persistent improvement of symptoms after a median number of injections of 2 [1-5] and did not require

any reinjections. Of them, 8 received 250 U, 5 had a higher dosage (500 U) and one was switched to onabotulinumtoxinA 100 U after first injection.

Main cause of discontinuation was primary failure which occurred in 21 patients (**21/59**, 35.5%) including **8 who had prior DO**. All patients with primary failure did not have post-void residual volume. Secondary failure occurred in 1 patient with prior DO (**1/59**, 1.6%) after 5 injections and 82.5 months after first injection.

Twelve patients (**12/59**, 20.3%) stopped the injections because of tolerability issues including **6 with prior DO**. Eight patients did not tolerate CISC, 2 had multiple urinary tract infections despite adequate prophylactic antibiotics and CISC, 1 experienced nightmares and headaches after first injection attributed to the toxin by the patient and 1 under anticoagulant therapy had persistent haematuria after each injection. Four patients (**4/59**, 6.7%) including **2 with prior DO**, found reinjections too restrictive and decided to stop.

Subsequent treatment

Six patients (**6/59**, 10.1%) refused to have another treatment after BoNT-A discontinuation. Twenty three patients (**23/59**, 38.9%) underwent subsequent treatment. Six patients (10.1%) switched back to anticholinergics at their request and two (3.3%) were treated with mirabegron. Two patients (3.3%) with primary inefficiency had a successful switch of abobotulinumtoxinA to onabotulinumtoxinA. Four (6.7%), with prior DO, underwent cystoplasty which relieved all OAB symptoms. Seven patients (11.8%) were treated with SNM. Of them, 3 were satisfied with no urgency, 1 underwent cystoplasty and 3 experienced persistent leakage. Of those three who remains unsatisfied after SNM, cystoplasty or cystectomy was proposed and refused by the patients. Four (6.7%) were treated with transcutaneous tibial nerve stimulation without efficiency. Two underwent SNM and 2

refused any other treatment. One patient (1.6%) with mixed UI underwent mid-urethral sling implantation. Subsequent treatment was not documented for 16 patients (16/59, 38.1%).

Factors associated with discontinuation

Mean age of patients who discontinued treatment was significantly higher than those who were still under injections at last follow-up (63.3 vs 53.2 years, $p=0.016$, table 2).

There was no difference of discontinuation between different dosages used at first injection ($p= 0.05$).

Male gender was significantly associated with discontinuation. Median duration of treatment for men and women were 6 and 17.6 months respectively ($p=0.02$).

DISCUSSION

To our knowledge, our study report the longest follow-up to date about the use of abobotulinumtoxinA in patients with idiopathic OAB.

Initial success of first injection was high with an improvement of more than 50% of symptoms on 3 day bladder diary in 59.3% of cases. This is in accordance with Craciun and al who recently reported improvement in OAB symptom score in 55% of cases[8].

However the estimated 5-years discontinuation-free survival rate was 23.4%. Those results are comparable to long term results after injection of onabotulinumtoxinA. Indeed, Mohee et al reported a 66.3% discontinuation rate at 3 years in 137 patients treated with onabotulinumtoxinA (200 U) for OAB[15]. These data were in accordance with those recently published by Marcelissen[11] et al who found a 70% discontinuation rate after a mean follow-up of 97 months in a cohort of patients treated with onabotulinumtoxin. Nitti et al have reported long term discontinuation of onabotulinumtoxinA from two randomised controlled

studies[16]. At 3.5 years, 52% of patients were still under injections. However, patients who did not succeed the initial trial[17] were not included in this long term analysis which, therefore, does not reflect clinical practice.

Given the well-known negative impact of OAB on patient's HRQOL[18], treatment discontinuation is often justified by a lack of efficacy, or significant adverse events. Indeed, in our study, main cause of discontinuation was primary lack of efficacy which explained 50% of failures (n= 21). Although secondary failure may occur, it seemed to be limited to very few cases in our study (n= 1). Those results are lower than those reported by Mohee et al who found a 11.7% (n= 14) rate of secondary inefficiency with onabotulinumtoxinA[15] at 3 years.

In our study 20.3% of patients discontinued treatment because of tolerability issues including 8 who did not tolerate CISC. Marcelissen et al found higher rates of discontinuation due to tolerability issues (43%)[11], but higher rates of CISC were seen after first injection (23%). Mohee et al, in a mixed population of idiopathic and neurogenic OAB also found higher rate of discontinuation therapy related to tolerability issues (34.3%)[15]. This can be explained by the higher dosage of BoNT-A used in these studies. Furthermore, four patients (9.5%) found reinjections too restrictive. Some of these patients decided to go back to oral medication even if they were not fully satisfied with it. Although treatment algorithm for third line therapy focus on either to choose between SNM, posterior tibial nerve stimulation or BoNT-A[19,20], failure of third line therapy does not necessarily implied going to therapeutic escalation. It is also an alternative to choose a treatment with less efficacy but better tolerance. This shows the importance of patient's choice and the role of the practitioner as a counsellor in order for the patient to find his own balance.

Most patients (79.4% n=31) discontinued treatment after first or second injection. This is consistent with Marcelissen et al results, who showed that among patients who discontinued treatment, 67% decided to stop after first injection. After two injections, we observed a plateauing effect. These results are also in line with Veeratterapillay who reported few discontinuation after efficacy of first BoNT-A injection[21]. **Interestingly, this high discontinuation rate is also seen in neurological population[22] where more than 50% of patients discontinued treatment at 10 years. It seems that botulinumtoxinA is not a life time treatment but is used to postpone further invasive surgery in neurological population.**

Interestingly, discontinuation of botulinum toxin was not always associated with failure or tolerability issues. In our study, discontinuation was due to persistent long term improvement of symptoms in 23.7% of cases. This is higher than Khan et al[23] who reported a rate of 10% of patients who considered themselves cured after injection of 200 U of onabotulinumtoxinA and 14 months of follow-up. More recently, Craciun et al[8] showed a significantly prolonged interval between injections of abobotulinumtoxinA (21.2 months) suggesting that some patients may have sustained long term efficacy. As previously debated[11], first botulinum injection could be perceived as a test injection in order to select patients responder or patients fit for reinjection. **We do not advocate for abobotulinumtoxinA to be seen as an alternative for patients who failed antimuscarinic as there is already onabotulinumtoxinA that showed good short and long term results. However, although onabotulinumtoxinA is the only toxin recommended in France, abobotulinumtoxinA could be seen as an alternative in patients initially responders to onabotulinumtoxinA who experienced secondary failure or tolerability issues. This would be in accordance with studies in neurological population that showed a benefit in switching between onabotulinumtoxinA and abobotulinumtoxinA in those cases[9].**

We acknowledge several limitations. The use of abobotulinumtoxinA is controversial as onabotulinumtoxinA is the only toxin recommended **in France by the HAS** since 2014[6]. **However all injections were performed before 2014 when no botulinumtoxinA was labelled.** Furthermore, abobotulinumtoxinA for OAB has shown good results in short term studies^{16, 17}. Heterogeneity of gender and dosage made difficult to assess the efficacy of the toxin. Post injections urodynamic data were insufficient to perform valuable analysis, notably because these tests are not routine practice in case of successful outcomes. Due to lack of phase III study, most efficient dosage of abobotulinumtoxinA is not known. Therefore, dosage is chosen mostly on conversion ratios (1:3) with onabotulinumtoxinA[14]. Based on phase III studies[17,24], the use of 100 U of onabotulinumtoxinA for first injection was approved by FDA in 2014. Therefore, we decide to choose 250 U of abotulinumtoxinA as first injection. In France, 50 U is the dosage recommended in first intention[6] explaining why we choose 125 U for few initial cases.

However, our study gives a clinical practice overview of abobotulinumtoxinA adherence in the long term.

CONCLUSION

Overall 59.3% of patients were successfully treated with first abobotulinumtoxinA injection. Although the estimated 5-years discontinuation-free survival rate is low, abobotulinumtoxinA could be considered as an alternative off-labelled in patients not responders to onabotulinumtoxinA after failure of other conservative measures.

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Conflict of interest

Disclosure of potential conflicts of interest: All authors have nothing to disclose for this submitted work

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study was approved by the ethic committee of Rouen University Hospital (Ethics board approval number: E2020-08).

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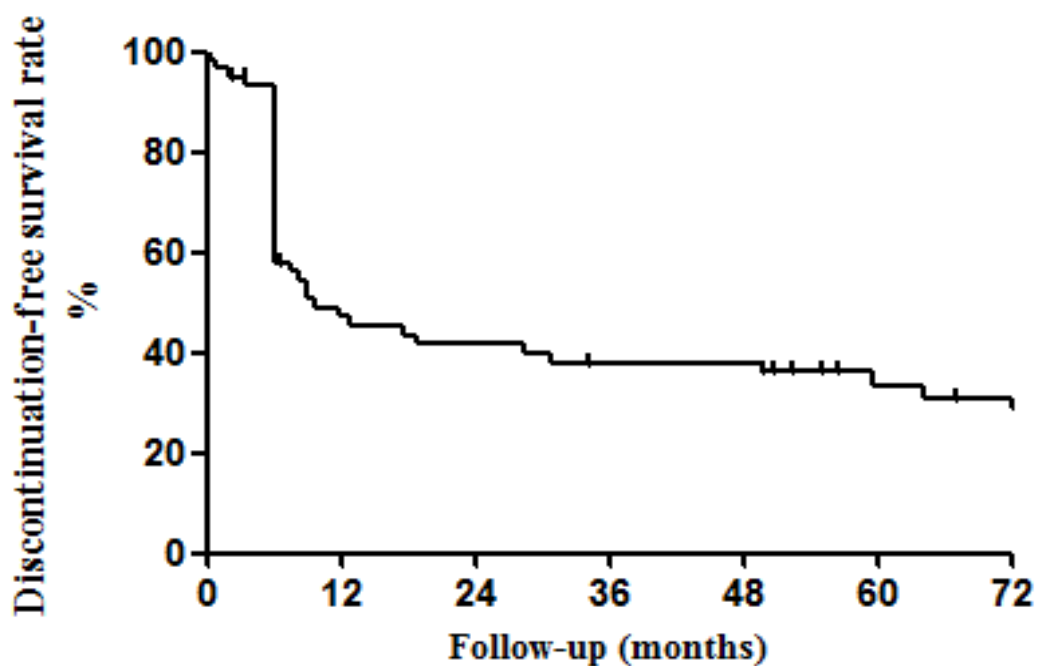
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Figure 1. Discontinuation free survival

Table 1. Baseline patients' characteristics

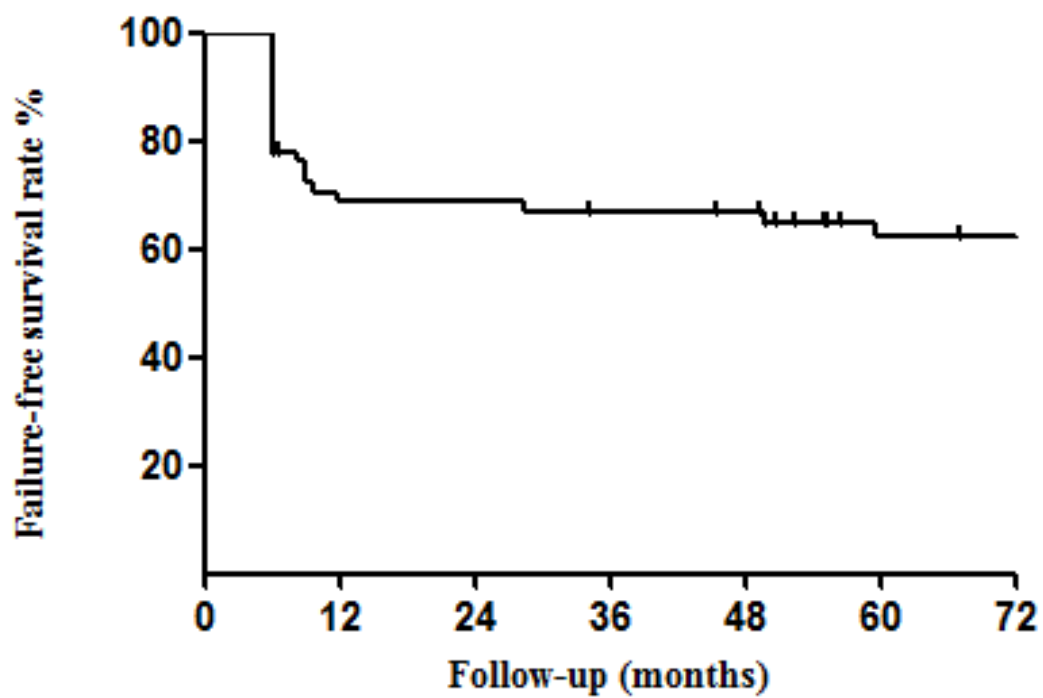
Table 2. Predictive factors for failure

Figure 1a. Discontinuation-free survival



Number at risk	53	52	50	48	42	38
Discontinuation-free survival (%)	45.7	37.3	32.2	30.5	25.2	19.8

Figure 1b. Failure-free survival



Number at risk	53	52	50	48	42	38
Failure-free survival (%)	68.7	68.7	66.8	66.8	62.3	62.3

Table 1. Baseline patients' characteristics

	N= 59 (%)
Men	9 (15.2)
Women	50 (84.8)
Age, mean (years, SD)	60.4 ± 14.3
Dosage of first injection of AbobotulinumtoxinA	
150 U	5 (8.5)
250 U	41 (69.5)
500 U	13 (22)
Urodynamic parameters	
Mean maximum cystometric capacity (ml)	329.3 ± 173
Mean Compliance (ml/cmH20)	55.8 ± 40.1
Mean Volume of first desire to void (ml)	163.3 ± 107
Mean maximum detrusor pressure (cm H20)	54.7 ± 28.9
Detrusor overactivity	
No	11 (18.6)
Yes	27 (45.7)
Unknown	20 (33.8)
Median Follow-up, months	78 [0.3-156.6]

U: Units, SD= Standard deviation

Table 2. Predictive factors for failure

	Cohort	Patients who discontinued treatment because of failure or tolerability issues	Patients still treated or with persistent long term improvement	p
N (%)	59	38 (64.4)	21 (35.6%)	
Gender				
Women	50	29	21	0.02
Men	9	9	0	
Age, range	60.4	64.9 [30.6-85.4]	58.7 [17.2-79]	0.03
MCC, ml	345.7	360	300	0.892
Dosage at first injection				
250 U	43	13	18	0.05
500 U	12	9	3	

MCC : Maximum cystometric capacity