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LONG TERM REAL LIFE EFFICACY OF ONABOTULINUMTOXINA FOR THE TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY IN A POPULATION USING INTERMITTENT SELF-CATHETERIZATION.

Hypothesis / aims of study
Intradetrusor injection of OnabotulinumtoxinA is recommended as a third-line therapy for patients with neurogenic detrusor overactivity (NDO) (1). However, there is few evidence of long term efficacy in a homogeneous population using clean intermittent self-catheterization (CIC). Moreover, there is no studies assessing reasons of abandonment or failure of this therapy. Thus the purpose of this study was to assess long term outcomes of NDO management by Intradetrusor injection of OnabotulinumtoxinA associated with CIC, in order to analyze long term efficacy and failure or abandonment causes

Study design, materials and methods
We performed a monocentric retrospective evaluation based on review of medical records of patients with NDO admitted in the department of Physical Medicine and Rehabilitation from January 2001 to September 2013 and managed with association of intradetrusor injection of OnabotulinumtoxinA and CIC. Inclusion criteriae were patients older than eighteen years old presenting NDO secondary to spinal cord injury (SCI) (traumatic, multiple sclerosis (MS) and myelomeningocele), who failed to be controlled by at least two anticholinergics for more than 3 months, followed up at least 3 years. Patients with a bladder surgery were excluded from the study.
Clinical, urodynamic and radiologic data were analyzed, before the first injection, six weeks after the first injection and six weeks after the last injection. Primary endpoint was the rate of failure and abandonment after 3, 5 and 7 years of management with intradetrusor injection of OnabotulinumtoxinA and CIC. Failure was defined either with urodynamic criteria (persistence of high maximal detrusorial pressure or low compliance (< 20 ml/cmH2O)) or clinical criteria defined by the patient's request to change treatment because of persistent urinary incontinence episode (UI). Secondary endpoint was failure risk factors. Thus, we differentiated primary failure (No efficacy from the first injection) and secondary failure (inefficacy after a period of efficacy). All causes of abandonment were recorded. Statistical analysis were performed using R *Statistical* (http:/www.R- Project.org) Software.

Results
292 patients were included. Patients had a mean age of 40 years ±13,6, and 58.2% were male. Aetiologies of NDO were traumatic SCI in 261 patients (84.6%), MS in 31 patients (10.6%) and myelomeningocele in 10 patients (3.4%). The mean duration of NDO was 10.8 years.
Number of patients still treated with intradetrusor injection of OnabotulinumtoxinA were 219 (80.6%; IC 95% [76.3%-85.4%]) after 3 years, 128 (71.1%; IC 95% [65,7%, 76.9%]) after 5 years and 58 (60.8%, IC 95% [54.0%, 68.4%]) after 7 years (Figure 1).
Failure ratio was 12.6 % (IC 95% [8.6 % - 16.5%]) after 3 years, 22.2 % (IC 95% [16.6 % - 27.3%]) after 5 years and 28.9% (IC 95% [21.9%; 35.3%]) after 7 years of follow-up. The primary failure ratio was 5,1% (n=15). The failure survival curve is presented in figure 2.
Abandonment ratio after 7 years of follow-up was 11,3% (n=33). Reasons of abandonment are detailed in table 1.
When intradetrusor injection of OnabotulinumtoxinA were stopped, alternative therapeutics were bladder augmentation surgery in 56 patients (19.2%), cystoplasty associated with Mitrofanoff procedure in 5 patients (1.7%) and Bricker intervention in 6 patients (2.1%).
After univariate analysis, we noticed clinical, urodynamic and radiologic major risk factors of failure if present before starting intradetrusor injection of onabotulinumtoxinA: a mixt clinical and urodynamic indications with UI, more than 3 febrile UTI per year, low compliance and high maximal detrusor pressure; renal-bladder ultrasounds abnormalities (hypertrophy of the bladder wall and hyronephrosis). Seniority of NDO was not a failure risk factor

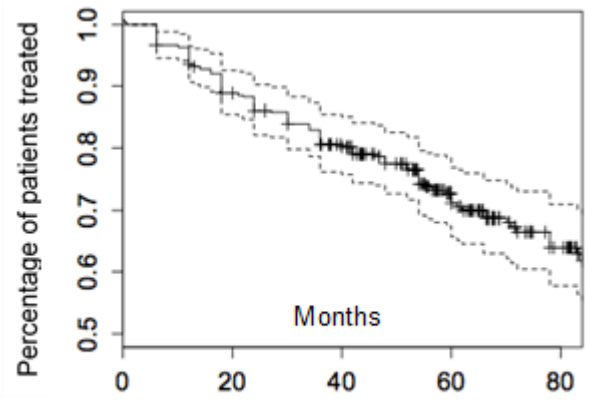

Fig 1 : Treatment stopped survival curve

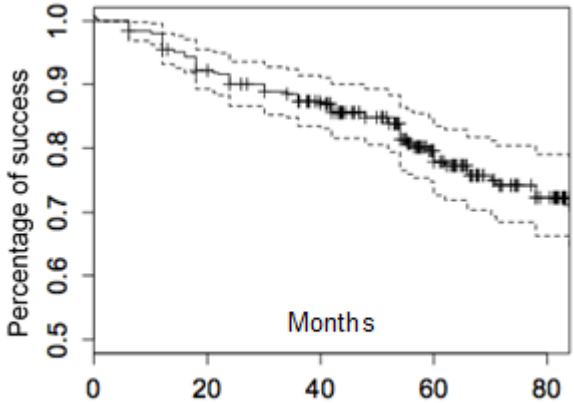

Fig 2 : Failure survival curve

Causes of abandonment	N (%)
Difficulties related to CIC	11 (3,8)
Personal convenience	8 (2,7)
Pseudobotulisme	7 (2,4)
Pregnancy	3 (1,03)
Pain	3 (1,03)
Prostatic cancer	1 (0,3)
TOTAL	33 (11,3)

Table 1 : Causes of abandonment

Interpretation of results

To our knowledge, it is the first study with a long term follow-up (7 years) of a large and homogenous population of patients (292 patients) suffering with NDO treated with intradetrusor injection of onabotulinumtoxinA (a mean number of 9.7 injections) associated with CIC as mandatory inclusion criteria.

After seven years of follow-up, only 60.8% of patient remain treated. Among patients who stopped treatment, we noticed 28.9% of failures, which could be either primary since the beginning or secondary failures after a time-elapsed of efficacy; and 11, 3% of abandonments.

Causes of failures remain difficult to determine. However, severe NDO before the first injection seems to be a major failure risk factor. Moreover failure was independent from the neurological disease and from the time elapsed since the beginning of NDO. Thus, in order to improve management of these patients, we may discuss about the best moment to introduce intradetrusor injection of OnabotulinumtoxinA. To prevent evolution of NDO in this population, we suggest a prior management by OnabotulinumtoxinA A for patients becoming refractory to anticholinergic, even if they are still able to perform voluntary micturition. However, further studies remain mandatory to determine if a prior treatment in patients with less severe NDO could increase long term efficacy allowing to limit potential failures and secondary irreversible surgical procedure.

The mean reason of abandonment was difficulties related to CIC. These difficulties may be exacerbated either by the evolution of neurological impairments (MS patients) or by the loss of patients' autonomy secondary to their old age (limitation to perform transfers).

Concluding message

This study confirms the good long term efficacy and tolerance of intradetrusor injection of onabotulinumtoxinA associated to CIC in patients with NDO. Long term failure and abandonment ratio remain weak but significant and need to be managed. Causes of failure remain difficult to identify, however a severe NDO at the beginning of the management seems to be a failure risk factor. Moreover, we noticed the long term abandonment importance, notably owing to CIC difficulties.

References

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Disclosures

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