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ORIGINAL ARTICLE

Five years follow-up study and failures analysis of Botulinum toxin repeated injections to treat neurogenic detrusor overactivity☆,☆☆

Injections intradétrusoriennes de toxine botulique A dans le traitement de l'incontinence urinaire par hyperactivité neurogène du détrusor : suivi d'une cohorte à cinq ans et analyse des échecs

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Botulinum toxin;
Overactive bladder;
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Treatment failure

Summary
Introduction. — The aim of this work was to follow prospectively a cohort of patients suffering from neurogenic overactive bladder, treated by botulinum toxin A, study the efficiency of this treatment, analyse the primary failures, secondary and surrender.
Patients and methods. — Thirty-one patients suffering from neurogenic OAB received a detrusor injection of 300 units of Botox™ (ALLERGAN, Irvine, CA) and were followed prospectively (median 5 years). They were evaluated by voiding diary, Qualiveen™ questionnary and urodynamics before treatment, 2 months after the first injection and the last re-injection.
Results. — Five years after the beginning of the treatment, 17 patients of 31 (54.8%) were still injected, it means 60.7% of the primary responders. Eleven patients had left up the treatment, after at least one effective injection. We identified three reasons of surrender: echapment of treatment for two patients of 11 (7.1%); cessation of self catheterize for six patients of

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11 (54.6%) and the surrender of the treatment without clinical or urodynamical failure, for three patients of 11 (27.3%). Although the cessation of self catheterize was more frequent for patients suffering from multiple sclerosis, no predictive factor of surrender was statically significant.
Conclusion. — In this series, bladder BTA injections was efficient at middle term to treat neurogenic OAB. The echapment was a rare event (7%). The major cause of surrender was the increase difficulty to self catheterize, due to progression of disability, more frequent for patients suffering of multiple sclerosis.
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MOTS CLÉS
Toxine botulique ;
Hyperactivité vésicale ;
Incontinence urinaire ;
Vessie neurologique ;
Échec de traitement

Résumé
Introduction. — L'objectif de ce travail était de suivre prospectivement, une cohorte de patients traités par injections de toxine botulique A (TBA) pour hyperactivité neurogène du détrusor (HND), d'étudier l'efficacité du traitement au fil des réinjections et de caractériser les échecs primaires, les échappements et les abandons.
Matériel et méthode. — Trente et un patients consécutifs souffrant d'HND ont reçu une première injection intradétrusorienne de 300 unités Botox™ (Allergan, Irvine CA) et ont été suivis prospectivement (médiane cinq ans). Ils étaient évalués par calendrier mictionnel, questionnaire Qualiveen™ et urodynamique avant traitement, deux mois après première injection et dernière ré-injection.
Résultats. — Cinq ans après début du traitement, 17 patients sur 31 (54,8 %) étaient toujours réinjectés, soit 60,7 % des répondeurs primaires. Onze patients avaient abandonné le traitement, après avoir eu au moins une injection efficace. Nous avons identifié trois causes d'abandon : l'échappement au traitement chez deux patients sur 11 (7,1 %) ; l'arrêt des autosondages chez six patients sur 11 (54,6 %) et l'abandon du traitement sans échec clinique ni urodynamique chez trois patients sur 11 (27,3 %). Bien que l'on observe abandon des autosondages plus fréquent chez les patients souffrant de SEP, aucun facteur prédictif d'abandon n'a pu être caractérisé statistiquement.
Conclusion. — La TBA intradétrusorienne est efficace à moyen terme (cinq ans) pour traiter l'HND. L'échappement est un phénomène rare (7 %). La principale cause d'abandon du traitement est l'augmentation de la difficulté à réaliser les autosondages propres intermittents liée à l'évolution du handicap qui pourrait être plus fréquente chez les patients atteints de SEP.
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Abbreviations

BtA	botulinum toxin type A
NDO	neurogenic detrusor overactivity
ISC	intermittent self-catherization
MDP	maximum detrusor pressure
MCC	maximum cystomanometric capacity
RV	reflex volume
MS	multiple sclerosis
CBEU	cytobacteriological examination of urine
Ab-aBtA	anti-BtA antibodies

Introduction

The efficacy of intradetrusor injections of botulinum toxin type A (BtA) has been shown in the second-line treatment of incontinence by neurogenic detrusor overactivity (NDO) after failure of anticholinergic treatment in patients performing intermittent self-catherization (ISC) [1]. Recommended by the principal learned societies of urology and physical medicine [2—4], BtA injections (Botox™, Allergan, Irvine, CA) obtained marketing authorization for this indication for patients with medullar pathology or multiple sclerosis in September 2011.

The reduction in urinary and urge incontinence and urinary infections obtained by this treatment has provided a marked improvement in the quality of life for over 80% of these patients. The two key urodynamic criteria, maximum detrusor pressure (MDP) and maximum cystomanometric capacity (MCC) were improved for a mean duration of 9 months, providing effective protection for the upper urinary tract. Up to 10 reinjections have been documented as effective [5].

Up to the present, few studies have focused on BtA treatment failure, primary or secondary after an initial period of effectiveness, i.e. resistance to the treatment.

The aim of this study was to prospectively follow up a cohort of patients treated by BtA injection for 5 years in order to evaluate the efficacy of repeated injections in responder patients and characterize the population of patients who were non-responders, resistant to treatment or lost to follow-up during this period.

Patients and methods

Between April 2004 and December 2005, 31 consecutive patients, including 30 toxin-naïve (vesical or extravesical), received an intradetrusor injection of 300 units

Botox® (Allergan, Irvine, CA) for urinary of incontinence owing to NDO refractory to anticholinergics (insufficient or poorly tolerated) and due to a chronic medullary lesion. Anticholinergic failure was defined by the persistence of urinary leakage and/or pressure NDO > 40 cm H_2O despite treatment at the maximum dose tolerated by the patient. Only one patient had had his/her first injection in another center. ISC was a prerequisite to this treatment. Patients who had not done ISC before treatment were trained to do it before injection. Injection was performed under local anesthesia after instillation of xylocaine and bicarbonate under endoscopic control. All of the patients who were on anticholinergics before the injection continued the treatment until the first follow-up consultation. Good responders recommended self-adjustment according to the reappearance of leaks or urge incontinence. These patients were followed up prospectively for 5 years.

Evaluation criteria

We evaluated each patient before the first injection of BtA, two months after the first injection, then two months after the last injection by interview, Qualiveen™ questionnaire (quality of life linked to urinary status in patients with medullar pathology or multiple sclerosis (MS) [6], a 3-day voiding schedule and urodynamic examination performed according to ICS guidelines.

The following clinical criteria were collected: mean number of leakage episodes per 24 hours and overall Qualiveen™ score (from 0 = normal quality of life to 4 = very poor quality of life, minimum significant difference ± 0.5 [7]. Urodynamic criteria were MCC, MDP and reflex volume (RV).

According to the clinical and urodynamic responses following the first injection, we defined three types of patients: good responders, partial responders and non-responders (or primary failure).

Clinical response was defined by an absence of leakage between ISC.

Urodynamic response was defined by the association of two criteria: an increase in MCC of more than 30% and a reduction in MDP inferior to 40 cm H_20.

A patient was qualified as a good responder when he/she had a clinical and urodynamic response, a partial responder when the clinical and/or urodynamic response was partial (reduction in leakage or variations in subthreshold urodynamic criteria), and a non-responder when there was neither clinical nor urodynamic response.

A non-responder could be primary if he/she had never had a response to treatment or secondary after an initial response period to treatment. Secondary non-response defined resistance. Non-responder status (primary or secondary) was confirmed by a second injection with neither clinical nor urodynamic response.

In patients who responded (good and partial) to the first injection, we noted the number of reinjections per patient and the time period between each injection.

For non-responders, we specified the alternative therapy prescribed.

Statistical analysis

The various comparisons of quantitative variables were performed by paired non-parametric tests (Wilcoxon paired test) and the survival curves were evaluated by the Kaplan-Meier technique and compared with the log-rank test. Statistical analyses were performed on SPSS software.

Results

Thirty-one of the patients with NDO received their first injection of BtA between April 2004 and December 2005: 20 patients (64.5%) had medullar pathology, 10 (32.3%) had MS and one (3.2%) had a history of spina bifida.

The mean age of the cohort was 44.8 years and the gender ratio was 15 men/16 women.

The mean period for medullar pathology was 8 years (S.D.: 6.5; range: 6 months—24 years) and the mean period from MS diagnosis was 14.4 years (S.D.: 11.0; range: 2.5—39.7 years).

The mean period of follow-up for the cohort was 5.6 years (S.D.: 0.46; range: 4.8—6.1 years) and no patient was lost to follow-up.

Before the beginning of treatment, the mean number of leaks per day was 4.75 (S.D.: 2.87; range: 0—14), 3.5% of the patients were continent and the mean Qualiveen score was 2.469 (S.D.: 0.70; range: 1.4—3.9).

On a urodynamic level, the mean MCC was 265.33 mL (S.D.: 118.2 mL; range: 90—500 mL), the MDP was 65.29 cm H_2O (S.D.: 24.64 cm H_2O; range: 23—130 cm H_2O) and the mean value of RV was 199.59 mL (S.D.: 95.81 mL; range: 57—408 mL).

Two months after the first injection, the mean number of daily leaks was 0.75 (S.D.: 1.2; range: 0—4; $P < 0.0005$), 71.4% of the patients were continent and the Qualiveen score went from 2.467 to 1.55 (S.D.: 0.86; range: 0.1—3.9; $P < 0.0005$).

On a urodynamic level, the mean MCC was 479.9 mL (S.D.: 119.48; range: 290—800 mL; $P < 0.0005$), the MDP was inferior to 40 cm H_2O in 22 out of 31 patients (70.9%) and the mean postoperative value was 26.6 cm H_2O (S.D.: 20.34 cm H_2O; range: 5—70 cm H_2O; $P < 0.0005$). The mean RV was 468.5 mL (S.D.: 129.9 mL; range: 250—800 mL; $P < 0.0005$).

According to the above definitions, 28 out of 31 patients (90.3%) were considered as primary responders including 27 good responders and one partial responder. Three out of 31 patients (9.7%) were primary non-responders.

Five years after the beginning of treatment, 17 out of 31 patients (54.8%) were regularly being reinjected and still considered as responders (60.7% of the primary responders) (17/28). Patients were reinjected when they presented clinical recurrence (leakage between ISC). In all of the cases, recurrence was confirmed by performance of a urodynamic work-up. A Kaplan-Meyer curve (Fig. 1) shows the evolution of the 31 patients. A ''disappearance'' on the curve corresponds to an abandonment of treatment. Fig. 2 shows the responses to treatment of our cohort.

The mean number of injections per patient was 6.06 (S.D.: 3.1; range: 2—12). The mean period between injections was 8.3 months (range: 6—24 months).

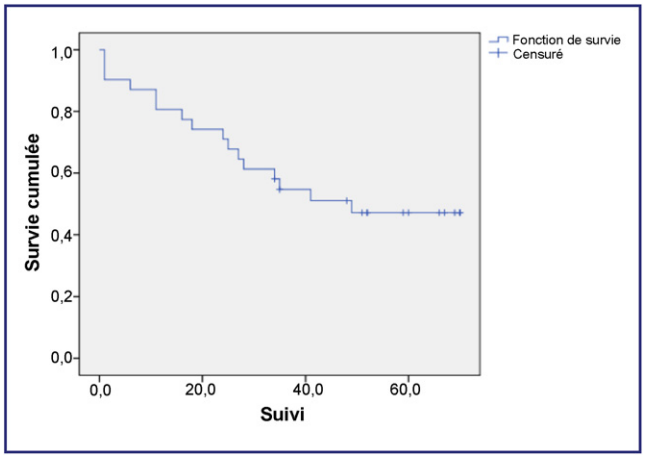

Figure 1. Cohorte survey curve.

For the 17 patients continuing injections, two months after the last treatment, the mean number of daily leaks was 0.31 (S.D.: 0.78; range: 0—3; $P < 0.0005$), 85.2% were continent and the Qualiveen score was 0.593 (S.D.: 0.33; range 0.2—1.2).

On a urodynamic level, the mean MCC was 465 mL (S.D.: 85.14 mL; range: 350—600 mL; $P < 0.0005$), mean MDP was 21.70 cm H_2O (S.D.: 17.33 cm H_2O; range: 3—60 cm H_2O: $P < 0.0005$) and the mean RV was 475.4 mL (S.D.: 92.34 mL; range: 350—600 mL; $P < 0.0005$).

All of the clinical and manometric results are comparatively summed up in Figs. 3 and 4 and Figs. S1—S3.

At 5 years, 11 out of 28 primary responders (39.3%) had abandoned BtA treatment. We identified three causes for abandonment:

- secondary failure of treatment or resistance (as defined in the Methods section) after at least one effective injection, according to the criteria defined for good or partial

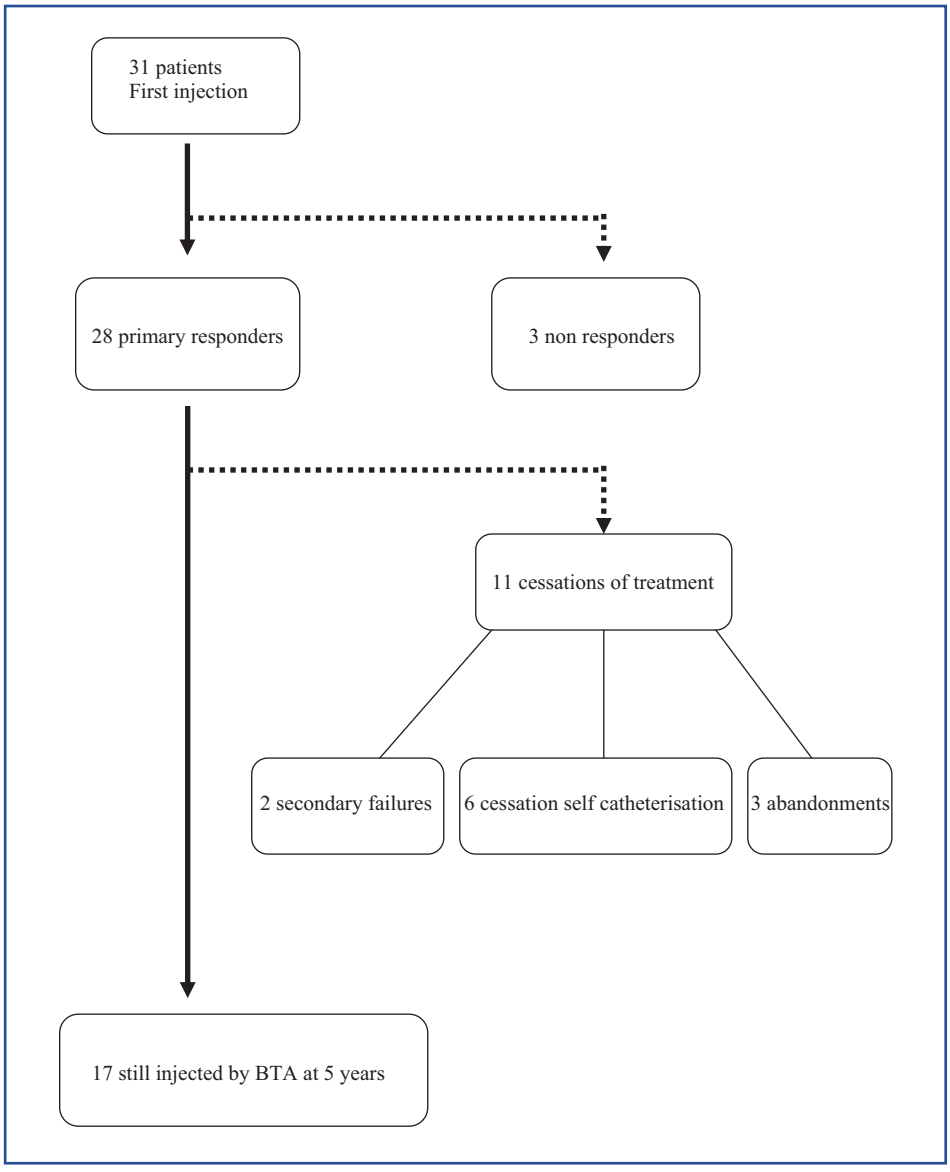

Figure 2. Treatment response of the cohort.

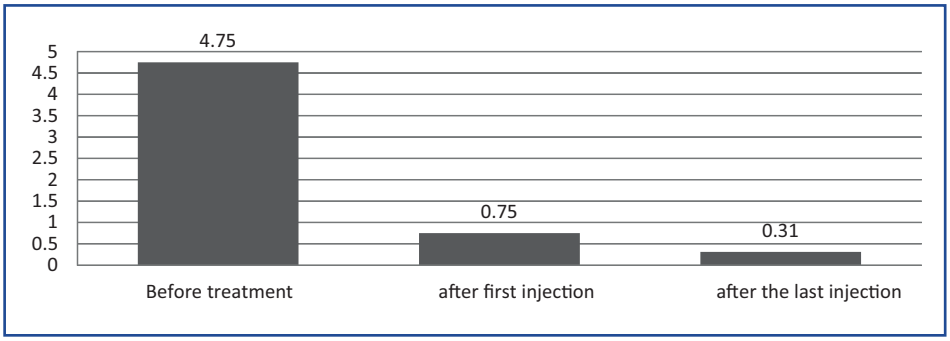

Figure 3. Nombre moyen de fuites.

responders. Two patients out of 11 (18.1%) had resistance after four effective injections for one and two effective injections for the other. This represented 7.1% of the primary responders and 6.4% of the cohort. One patient had an enlargement enterocystoplasty and the other stabilized with anticholinergic treatment following the placement of a Lioresal pump for spasticity;

- discontinuing ISC because a patient was unable to perform them led to a stop in BtA treatment. Six out of 11 patients (54.6%) could no longer ensure their ISC, contraindicating BtA treatment. Two of these patients had medullar trauma: a C6—C7 quadriplegic with increasing ISC difficulties (catherization time superior to 35 minutes) and a D9 paraplegic with pelvic tilt preventing catheterization. Both patients had continence cystotomy as an alternative. The four other patients had MS, two with a modification in their cognitive functions and the two others with upper-limb motor difficulties. ISC became impossible in all four of these cases. Three of them had Bricker urinary diversions and one patient who refused this treatment currently has an indwelling catheter;
- three out of 11 patients (27.3%) stopped treatment without clinical or urodynamic failure. One patient whose anticholinergic treatment became sufficient again after three effective injections and two patients whose refusal to perform ISC led to abandonment of their urinary therapeutic project.

We could not identify any predictive factors for primary non-response, resistance or abandonment of treatment.

Discussion

After the first intradetrusor injection of BtA to treat NDO, we observed a 90.3% rate of primary responders and an amplitude of effect comparable to those reported in the mainstream literature [1,5,8]. Yet, at 5 years, only 17 out of the 28 primary responders (61%) were continuing BtA treatment for their vesico-sphincter dysfunction. In these 17 patients, the amplitude of effect (clinical and urodynamic) observed after the first injection was maintained during reinjections (six on average) as reported by Reitz et al. and Khan et al. in the two largest studies devoted to the effects of reinjections [9,10]. In our cohort, resistance was a rare phenomenon (2/28 or 7%) and the least frequent cause for abandoning BtA treatment. The causes for abandonment of treatment were dominated by the difficulty to perform ISC which progressively occurred within the framework of the evolution of a handicap.

Three studies have analyzed primary and secondary failures of BtA injections for the treatment of NDO: Grosse et al. [11], Chenet et al. [12], and Del Popolo et al. [13] reported 7 to 10% primary failures and 5 to 7% secondary failures, which corresponds to our observations.

The causes of primary treatment failure of intradetrusor injections of botulinum toxin are poorly understood. The existence of vesical compliance dysfunction was considered following description of the technique by Brigitte Schurch as a cause of poor response and has led numerous teams to exclude patients with low vesical compliance from their studies. The results of two principal series dedicated

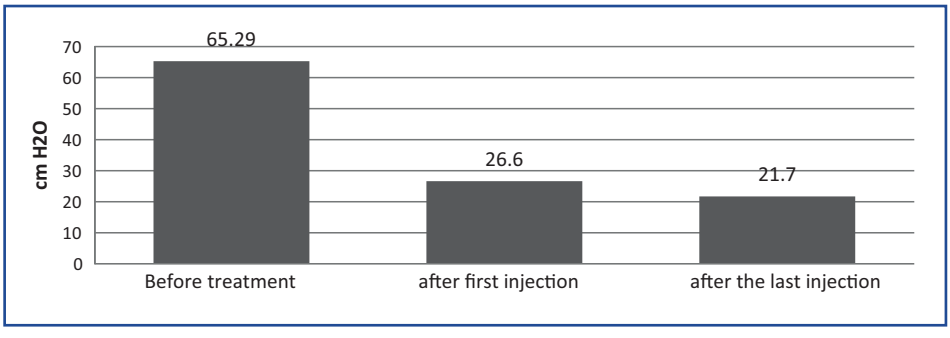

Figure 4. Maximal detrusor pressure.

to patients with low compliance differ on the subject: for Klaphajone, seven patients over 10 with medullar injuries and low compliance improved with an injection of 300 units Botox [14] whereas for Horst, only one child out of 11 had transitory improvement after toxin injection [15]. This difference could be due to variations in the definition of compliance dysfunction or as Chartier Kastler et al. suggested, to different forms of compliance dysfunction involving or not irreversible structural changes in the vesical wall [16]. No patient in our cohort had compliance dysfunction (compliance < 20 cm H_2O/mL).

There are two causes of secondary failure or resistance under discussion. The appearance of antitoxin neutralizing antibodies or modifications induced by repeated injections in the wall leading to fibrosis and secondary compliance dysfunction rendering toxin treatment ineffective.

The possibility of the development of anti-BtA antibodies (Ab-aBtA) has been proposed following observations of secondary resistance after repeated injections in the stria muscle [17—20].

However, the cause-and-effect link between the presence of Ab-aBtA and non-response is still being debated because several teams have noted a dissociation between the presence of Ab-aBtA in 40% of responder patients and the absence of Ab-aBtA in 50% of the non-responder patients. In a meta-analysis of 2240 patients treated from one to 15 times with Botox® BtA for five different indications, Nauman et al. [21] reported 11 cases (0.49%) with the appearance of Ab-aBtA and only three out of the 11 patients became non-responders. No case involved vesical injections which represented only 1% of the indications (22/2240).

It is difficult to compare these results with those observed in urology. Indeed, the injected tissue is different, injections in vesical smooth muscle have longer action than those in stria muscle (6—9 months versus 2—4 months [22]) and the exact mechanisms of these differences in duration of action remain unknown. Seven studies have researched Ab-aBtA to explain secondary treatment failure by BtA in urology. Schulte-Baukloh et al. [23] studied a population of patients with NDO. Three treatment failures were noted and corresponded to three out of the four patients with high Ab levels. On the other hand, one patient with a significant Ab level was totally satisfied with the treatment. In 17 children with spina bifida, the same team (2011) observed the presence of antitoxin Ab in 35% (6/17) leading to 12% inefficacy (2/17) [24]. Kajbafzadeh et al. [25] studied a population of 44 children with NDO: 43 were considered as improved or cured despite the presence of Ab-aBtA in 18% of them. Finally, Hegele et al. [26] only noted five out of 31 patients (16%) with antitoxin antibodies, two of whom had an effective second injection. Therefore, these elements do not make it possible to conclude on a secondary resistance to BtA treatment owing to the presence of Ab-aBtA in non-responders with NDO. Antitoxin antibodies were not researched in our cohort. The other hypothesis to explain resistance was the appearance of histological modification after repeated injections of BtA (parietal fibrosis). Three studies have come to the same conclusion: there is no significant difference in inflammation, fibrosis or edema in patients with NDO before or after one or several intradetrusor injections of BtA [27—29] whether the patients are responders or not.

Our study is the second after the Mohee study to look at abandonment of treatment by intradetrusor BtA and its causes. At 5 years, we noted a high rate of abandonment of treatment (39%) although it was inferior to the 45% reported by Mohee et al. [30]. Like the Leeds team, we observed that the majority of the cases of treatment abandonment were linked to a problem of therapeutic tolerance, in particular, the problem of performing ISC (6/11) or the refusal to do them (2/11) during the cycles of reinjection.

We noted that four out of the six cases of abandonment owing to ISC difficulties involved patients with MS rather than patients with medullar injuries. However, this difference was not significant ($P = 0.15$; Chi^2 test and Yates correction). Thus, the MS etiology of NDO could be a medium-term risk factor for abandonment given the evolvement of the handicap in this pathology and despite a demonstrated efficacy in this population [9]. Larger cohorts will be necessary to confirm this.

Contrary to Mohee et al., we did not observe abandonment linked to recurrence of urinary infections (a posteriori analysis of the causes of abandonment). However, our study did not include prospective systematic collection of CBEU between injections. Moreover, it should be noted that the British study included a large proportion of non-neurologic patients who are difficult to compare with our population vis-a-vis urinary bacteriology.

Conclusion

Repeated intradetrusor injections of botulinum toxin type A are effective in the medium term (5 years) for treatment of urinary incontinence secondary to neurogenic detrusor overactivity. The principal cause of treatment abandonment is the increasing difficulty to perform intermittent self-catherizations owing to the evolution of a handicap particularly in MS patients. Primary failures and resistance are rare events. A national multicenter inventory (registry) is needed in order to understand their precise characterization.

Disclosure of interest

Gilles Karsenty is or has been investigator consultant or speacker for Allergan, IPSEN, Astra Tech and Coloplast

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.purol.2012.10.006.

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