

Botulinum toxin in spinal cord injury patients with neurogenic detrusor overactivity

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Evidence for the efficacy and safety of intravesical onabotulinum toxin A (onabotA) injections has led to them being licensed in many countries, including Korea, for the treatment of patients with urinary incontinence due to neurogenic detrusor overactivity (NDO) resulting from spinal cord injury or multiple sclerosis who are refractory or intolerant to anticholinergic medications. OnabotA injections have an inhibitory effect on acetylcholine release for up to 10 months, with a recommended dose of 200 U. OnabotA treatment has a beneficial effect not only on urinary symptoms, but also on quality of life. Several clinical studies have shown onabotA to have better effects than placebo in achieving continence, reducing incontinence episodes, improving urodynamic parameters, and improving health-related quality of life. Urinary tract in-

fections and postvoid residual volume are the most prevalent side effects. In patients with residual volume, clean intermittent catheterization may be necessary. In patients with spinal cord injury or multiple sclerosis, it is recommended to evaluate physical and cognitive function before intravesical onabotA injection to ensure that the patient and caregiver are able to perform catheterization if necessary. Further controlled trials should assess the optimal dose, injection technique, long-term safety of repeated injections, and optimal timing of onabotA treatment in the treatment of NDO.

Keywords: Botulinum neurotoxin A, Neurogenic bladder, Spinal cord injuries, Multiple sclerosis


INTRODUCTION

In patients with neurological disorders, bladder dysfunction associated with detrusor overactivity (DO) impairs quality of life (QoL) and often poses a threat to the upper urinary tract. Therefore, it represents a major health problem in this population. According to the standardized terminology of lower urinary tract function published by the International Continence Society, DO is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked (Abrams et al., 2003).

Individuals with overactive bladder (OAB) often complain of one or more of the following problems: urgency (with or without urgency incontinence), urinary frequency, and nocturia. This may occur due to neurogenic or idiopathic causes. Urodynamic studies can confirm that an individual's symptoms are due to DO. The term neurogenic detrusor overactivity (NDO) is used to describe a

urodynamic finding characterized by involuntary detrusor (bladder) contractions during the filling phase, which may be spontaneous or provoked by a relevant neurological condition (e.g., spinal cord injury [SCI] or multiple sclerosis [MS]) (Abrams et al., 2002; Abrams et al., 2010).

It is important that individuals with NDO maintain low bladder pressure during bladder storage and voiding with few to no involuntary bladder contractions. Failure to maintain low bladder pressure may lead to upper tract complications due to stasis and poor drainage of the upper tract. High detrusor pressure may also exacerbate vesicoureteral reflux. NDO may also cause lower urinary tract complications, such as recurrent urinary tract infections (UTIs), bladder stones, fibrosis, trabeculation and a loss of bladder wall compliance, and autonomic dysreflexia (AD). In addition, urinary incontinence resulting from NDO has been found to have a significant negative impact on sexuality, cause embarrassment, and lead to impaired QoL. In one study, 35.3% of individuals

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with SCI reported that bladder/bowel issues prevented them from engaging in sexual activity on at least some occasions (Anderson et al., 2007; Coyne et al., 2008).

The mainstay of treatment for NDO when pharmacological therapy is indicated is anticholinergic (antimuscarinic) medications. An important function of anticholinergic medications is to suppress involuntary bladder contractions. Clinically, this helps to facilitate drainage from the upper tract by lowering the pressure within the bladder wall (Linsenmeyer, 2013). From the patient's perspective, the ability of anticholinergic medications to inhibit involuntary contractions results in improved bladder capacity, and helps to prevent urinary frequency, urgency, and urinary incontinence. A meta-analysis in patients with SCI showed a statistically significant improvement in symptoms and moderate improvement in QoL compared to placebo (Nabi et al., 2006).

Despite their effectiveness, a major drawback of anticholinergic medications is their side effects. Among patients taking oxybutynin, dry mouth develops in at least 50%, constipation in approximately 15%, drowsiness in approximately 12%, and blurred vision in approximately 5%. Dry mouth and constipation are particular problems in patients with NDO who are trying to limit fluid intake due to an intermittent catheterization program or who already have issues with constipation resulting from neurogenic bowel dysfunction. Moreover, patients with NDO often need larger doses of anticholinergic medications than able-bodied individuals with idiopathic DO because the goal is not only to minimize frequency and urgency, but to encourage urinary retention in order to prevent incontinence between catheterizations. Large doses or combinations of several types of anticholinergic medications are frequently needed (Horstmann et al., 2006). Another problem with anticholinergic medications is that they need to be taken on a long-term, consistent basis. In an observational study from 2002 to 2007 evaluating the medical and pharmacy bills of individuals with a neurological disease and with ≥ 2 neurogenic bladder diagnoses, it was noted that consistent medication adherence was low, with 81% of neurogenic bladder patients having experienced interrupted OAB treatment as indicated by discontinuation rates. The reasons for the interruptions in anticholinergic medications were not established, but may have been related to side effects, cost, ineffectiveness, or forgetting to take the medications (Manack et al., 2011).

Other traditional bladder management options for patients on intermittent catheterization who have problems with NDO include indwelling catheters, which also usually require anticholinergic medications, a switch to reflex voiding with or without a

sphincterotomy, bladder augmentation, urinary diversion, or neurostimulation devices such as a sacral cord stimulator. These options are frequently not acceptable to many individuals with NDO because they involve surgery or wearing a urinary device. For these reasons, botulinum toxin has emerged as an effective alternative for patients with NDO who do not tolerate or have had poor results with anticholinergic medication (Linsenmeyer, 2013).

MATERIALS AND METHODS

Botulinum toxin (BTX), first isolated by van Ermengem in 1897, is a potent neurotoxin produced by the gram-positive anaerobic bacterium *Clostridium botulinum* (van Ermengem, 1897). From a structural viewpoint, the toxin is a 150-kD amino acid di-chain molecule consisting of a light (50 kD) and a heavy chain (100 kD), which are linked by a disulfide bond. The role of BTX at the neuromuscular junction has been well described and involves the inhibition of acetylcholine release, resulting in striated muscle relaxation (Montecucco and Schiavo, 1995). However, increasing evidence suggests that BTX may have a much greater range of neurological effects. BTX has been found to inhibit the release of a number of neurotransmitters, including acetylcholine and adenosine triphosphate, and neuropeptides such as substance P, as well as to downregulate the expression of purinergic and capsaicin receptors in afferent neurons within the bladder (Chapple and Patel, 2006). These data support the proposal that BTX works to treat DO and OAB by affecting both sensory and motor pathways.

BTX was first approved by the U.S. Food and Drug Administration (FDA) in 1989 for the treatment of strabismus. Since then, it has been used for a number of nonurological labeled medical indications including muscular dystonia, focal hyperhidrosis, upper limb spasticity, cosmetic surgery, and most recently, migraine headaches (Verheyden and Blitzer, 2002).

Of the 7 distinct but structurally similar serotypes of BTX, types A (BTX/A) and B have been used with clinically beneficial outcomes in various neurological disorders. The first urological application (off-label) was for the treatment of detrusor sphincter dyssynergia in 1988 (Dykstra et al., 1988). In 2000, BTX was described as an effective and viable option for treating patients with SCI with urinary incontinence who performed intermittent catheterization (Schurch et al., 2000). Since then, the popularity of BTX has increased, as it is considered to be an excellent alternative for those with NDO who do not tolerate anticholinergic medications due to its effectiveness, safety, easy use and learning curve, and reproducible results in repeated use. The most com-

monly used preparations of BTX/A for NDO are Botox (onabotulinum toxin A) and Dysport (abobotulinum toxin A). In late August 2011, Botox received U.S. FDA approval for injection for the treatment of urinary incontinence due to DO associated with a neurological condition (e.g., SCI or MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication, based on the clinical results of phase III studies (Cruz et al., 2011).

In Korea, BTX/A injection treatment for NDO and OAB has been covered by the National Health Insurance Service since October 2015, with treatment indicated for NDO or OAB patients in whom treatment with anticholinergics has failed.

RESULTS

Results of clinical and urodynamic studies

All published series and reviews have supported the use of BTX/A for the treatment of NDO. In 2000, the first paper was published that evaluated and showed the success of intradetrusor injections of BTX/A, specifically Botox, in individuals with NDO. This study reported findings from 21 SCI patients who had NDO and urinary incontinence despite anticholinergic medications. A significant increase was found in the mean maximum cystometric capacity (MCC) and a mean decrease of the maximum detrusor pressure (MDP) after BTX treatment. Seventeen of the 19 patients were no longer incontinent. Moreover, the investigators noted that the clinical effects and urodynamic improvements lasted much longer than the expected 3-month time course for BTX/A. These effects were still present at 9 months in the 11 patients who were still being followed at that point (Schurch et al., 2000).

Reitz et al. (2004) published the largest retrospective multicenter European study consisting of 200 individuals with severe NDO who performed intermittent catheterization and were treated with Botox. Three months after intradetrusor injections of 300 U of Botox, 73% of the patients reported full continence between catheterizations and the others reported some improvement. The MCC and mean volume at the first detrusor contraction increased by more than 50%, and the MDP decreased by more than 50%. This study documented a reduced need for anticholinergic medications after the injection. The investigators not only showed the effectiveness of intradetrusor Botox injections, but also showed that they could be used as an alternative to anticholinergic medications. It was also noted that 27% of the patients discontinued their anticholinergic medications completely and the remainder significantly decreased their dosage. The beneficial clinical effects

persisted for more than 6 months (Reitz et al., 2004).

In addition to performing the first prospective open-label study of BTX/A, Schurch et al. (2005) also performed the first randomized placebo-controlled study of BTX/A in individuals with NDO and urinary incontinence. A total of 59 patients were evaluated, 53 with SCI and 6 with MS. Thirty-eight individuals receiving Botox were divided into two groups: one group had 200 U injected into the detrusor and the other group underwent injections of 300 U. The placebo group had normal saline injected into the detrusor. Significant posttreatment reductions were found in incontinence episodes (approximately 50%) from baseline in both BTX/A groups, but not in the placebo group ($P \leq 0.05$). These improvements were seen at the first evaluation at 2 weeks and continued throughout the 6-month period. Moreover, at 6 months, a significant improvement in QoL was observed in those receiving Botox compared to placebo (Schurch et al., 2005).

Another study was unique in that it focused on individuals with NDO due to MS (Kalsi et al., 2007). The researchers prospectively evaluated the impact of 300 U of Botox on bladder function and QoL in 43 patients with MS with significant NDO despite anticholinergic medications. After the injections, significant clinical and urodynamic improvements were noted ($P < 0.0001$). At 4 weeks after the Botox injections, the researchers observed a 45% decrease in urinary frequency, a 77% decrease in incontinence episodes, a 78% decrease in micturition episodes associated with urgency, and a 47% decrease in nocturia. Urodynamic studies showed an increased bladder capacity (303% of baseline) at 4 weeks, and a 33.5% decrease in the MDP during involuntary contraction. The mean duration of the effect was 9.4 months (Kalsi et al., 2007).

Deffontaines-Rufin et al. (2011) described the results of administering BTX/A to patients with NDO secondary to MS. Their study gave further insights into the use of BTX in this patient population. Seventy-seven percent of the treated patients exhibited clinical improvement or full success with a reduction of their urgency and incontinence. Significant urodynamic improvements after treatment were shown according to a range of parameters, including volume at first involuntary bladder contraction, MCC, and MDP. Forty-six percent of the patients were considered to have experienced complete success, and 31% of the patients exhibited a partial improvement. However, BTX/A failed to lead to improvements in 23% of the patients suffering from MS. The investigators found that the duration of MS was a predictive factor of treatment failure ($P = 0.015$) (Deffontaines-Rufin et al., 2011). As the neurological condition progresses, so does the severity of

the urinary symptoms. Therefore, these authors concluded that injection therapy should be considered as soon as anticholinergic medications fail to control NDO in patients with MS rather than waiting until potentially irreversible histological and neurological damage has occurred (Deffontaines-Rufin et al., 2011).

Kuo (2006) carried out a prospective study of the impact of BTX on NDO not only in those with SCI, but also in those with chronic cerebrovascular accidents (CVAs). Several lessons regarding the use of BTX in CVA patients were learned in this study. A lower dose of Botox, specifically 200 U rather than 300 U, was used in order to minimize the need for clean intermittent catheterization (CIC) as a result of urinary retention caused by Botox. This was important since intermittent catheterization can be more difficult for elderly patients with chronic CVAs (Kuo, 2006). Twenty-four subjects were enrolled; 12 had a CVA and 12 had SCI. After treatment, the volume of the first involuntary detrusor contraction and bladder capacity increased twofold and the postvoid residual volume increased fourfold for both patient groups after 1 month, with a slight decrease at 3 months. At 4 weeks, a significant improvement in complete continence and an improvement in incontinence were achieved in the SCI group. Five patients achieved urinary continence after treatment, 6 showed improvement, and 1 experienced treatment failure. At 3 months, a successful result was noted in 11 patients (91%) in the SCI group. However, at 4 weeks, only 1 patient with a CVA had regained urinary continence, 3 showed improvement, and 6 experienced failure. At 3 months, only 50% of subjects in the CVA group experienced a successful outcome. The investigators proposed several causes for these findings. Urinary incontinence in persons with CVA is due to DO with a weak sphincter. Therefore, when the bladder reaches its maximum capacity, even if it is larger, and a contraction occurs, a person with a CVA is more likely to have incontinence. Cognitive issues may also affect the sensation of bladder fullness, lead to mobility issues, and result in greater technical difficulties in performing intermittent catheterization (Kuo, 2006).

Cruz et al. (2011) reported their results of a pivotal phase III randomized, double-blind, placebo-controlled trial on the efficacy and safety of Botox in SCI and MS patients with urinary incontinence due to NDO. Patients received 30 intradetrusor injections of 200 or 300 U of onabotulinum toxin A or placebo. Improvements with the drug compared to placebo were present at 2 weeks, with further improvements at 6 weeks. The mean decrease in urinary incontinence episodes per week was significantly greater with 200 and 300 U compared to placebo (-21.8, -19.4, and -13.2, respectively) ($P < 0.01$). The mean improvements in MCC,

MDP, and QoL at 6 weeks were significant in comparison with placebo ($P < 0.001$). The median time before a patient requested retreatment was 42 weeks (Cruz et al., 2011). No differences were noted in efficacy or duration between the two doses of the drug. However, participants who received the 300-U dose had more side effects (Cruz et al., 2011).

The results of a number of clinical studies using BTX/A in adults with NDO showed significant decreases in urinary incontinence (19%–89%) and significant improvements in urodynamic parameters such as bladder capacity, and MDP. The mean duration of action was 6–9 months. Specific considerations apply to the use of BTX in those with NDO due to SCI, MS, and CVAs.

Results of repeated injection treatments and long-term efficacy

Several investigators have studied the repeated, long-term use of BTX. Reitz et al. (2007) evaluated 20 consecutive patients with NDO who had received at least 5 intradetrusor injections of 300 U of onabotulinum toxin A. Each session consisted of endoscopic injections into the detrusor muscle at 30 sites (10 U/per site, sparing the trigone). They were followed both clinically and with urodynamic evaluations for at least 4 of the 5 injections. The results of 100 injections were analyzed. Clinical continence and urodynamic parameters improved significantly after the first injection and then remained constant after repeated injections. Clinically, no toxin-related side effects were observed (Reitz et al., 2007).

Karsenty et al. (2006) analyzed clinical parameters and urodynamic parameters after repeated injections in 17 patients with NDO. The time points for evaluation were before the first injection, after the first injection, and after the last injection. The mean number of injections per patient was 5.4 (range, 3–9). The mean number of incontinence episodes per day decreased from 2.6 at baseline to 0 after the first injection, and remained at 0 after the last injection. The maximum cystometric bladder capacity and residual volume increased significantly after the first and last injection compared to baseline. The maximal detrusor pressure decreased significantly after the first and last injection compared to baseline. They found significant and consistent improvements in both clinical and urodynamic parameters that persisted after 4.5 injections (Karsenty et al., 2006).

Kuo and Liu (2011) evaluated the impact of repeated Botox injections into the bladder in SCI patients on urinary incontinence, renal function, MCC, and mean detrusor pressure. Individuals were injected every 6 months with 200 U of Botox for 2 years. They found that repeated injections reduced incontinence, in-

creased bladder capacity (with an almost twofold increase in size, from 207 ± 111 to 412 ± 33 mL), and reduced intravesical pressure. Over a 2-year treatment period, no change in serum creatinine was observed; however, overall, the mean glomerular filtration rate (GFR) decreased significantly, as measured by renal scans over the 2 years (from 93.4 ± 20.4 to 83.5 ± 24 mL/min, $P = 0.028$) (Kuo and Liu, 2011). However, this significant reduction in GFR occurred in patients who had a poorer response to Botox, with bladder compliance that increased by < 10 cm H₂O ($P = 0.002$), and in patients with a detrusor pressure that decreased by less than 10 cm H₂O after treatment ($P = 0.036$). However, they did not find any improvement in renal function. Several explanations exist for the lack of observed improvement in renal function. The authors noted the small group of patients ($n = 38$), with a 7-year mean duration of injury and a relatively short follow-up period (2 years). Since the study did not include a placebo group, it is difficult to know whether the injection group would have maintained renal function significantly better than the control group. It is also possible that prior renal damage manifested itself, and the rate of decline in function would have actually have decreased in the Botox-treated group compared to the placebo group. It is also possible that longer follow-up would have showed an improvement in renal function (Kuo and Liu, 2011; Linsenmeyer, 2013).

DISCUSSION

A number of potential clinical benefits have been observed following the injection of BTX/A. The following section presents a discussion of some of the more common benefits that have been reported in the literature regarding the use of BTX/A for NDO.

Improvements in urinary incontinence

As discussed above, the major clinical benefit of BTX is that it decreases the incidence of urinary incontinence in those with NDO who do not tolerate anticholinergic medications. This improvement occurs because BTX increases the maximum cystometric (bladder) capacity and decreases the MDP. These outcomes are accomplished by suppressing uninhibited bladder contractions. Studies also suggest that these outcomes may result from a decrease in the afferent input from bladder wall distention, which may prevent and eventually reduce bladder wall fibrosis.

Reduction in AD

Although no randomized or placebo-controlled studies have assessed the impact of BTX on AD, the existence of a beneficial ef-

fect can be presumed. Linsenmeyer et al. (1996) documented that AD occurs not only during bladder distention but also with the onset of uninhibited bladder contraction in those with SCIs at T6 and above. Schurch et al. (2000) reported that 3 patients with tetraplegia and severe AD experienced resolution of AD after 300 U of Botox was injected into the bladder wall.

Decrease in the use of anticholinergic medications

It has been noted that BTX/A allows individuals to decrease or even stop their anticholinergic medications. This effect has been found to be persistent (Grosse et al., 2005).

Decrease in UTI

It has been reported that BTX/A injections have helped to reduce the incidence of UTIs, specifically pyelonephritis, orchitis, and prostatitis (Gamé et al., 2008; Giannantoni et al., 2009). Gamé et al. (2008) tracked UTIs (cystitis, pyelonephritis, orchitis, and prostatitis) in 30 individuals with NDO for 6 months before a BTX injection (Botox 300 U) and for 6 months after the injection. Before the BTX injection, the mean number of symptomatic urinary infections over 6 months was 1.75 ± 1.87 . After the injection, the mean was 0.2 ± 0.41 ($P = 0.003$). It was also noted that the 3 individuals who did present with UTIs showed less improvement in their urodynamic parameters (volume of the first uninhibited contraction, maximum bladder pressure, and MCC) after injection than those who did not have UTIs (Gamé et al., 2008). One reason for a decrease in pyelonephritis may be a decrease in the MDP, which reduces the vesicoureteral reflux of urine back up into the kidneys (Giannantoni et al., 2009). Another reason for a decrease in UTIs may be improved blood flow and increased tissue oxygen levels after BTX injections due to a decrease in the MDP and increase in the MCC. Since a variety of studies have shown a decrease in the MDP after BTX/A detrusor injections, decreases in UTIs and, possibly, fibrosis of the bladder wall may be due to the reduction of relative ischemia of the bladder wall by lowering the mean detrusor pressure (Linsenmeyer, 2013).

Upper tract improvement

With significant improvements in the MCC and decreases in the MDP after BTX injections, improvements in upper tract drainage may be expected. Giannantoni et al. (2009) evaluated and discussed upper tract changes in their study. They prospectively evaluated 17 SCI patients receiving repeated Botox injections over a 6-year period. Six of their 17 patients initially had bilateral renal pelvis dilatation and five had unilateral dilatation. An

additional three had unilateral dilatation due to grade 3 vesicoureteral reflux. After 6 years, in addition to sustained improvement in clinical, urodynamic, and QoL changes, significant upper tract changes were noted. Vesicoureteral reflux and renal pelvis dilatation resolved in all patients (Giannantoni et al., 2009). Further long-term studies are needed to evaluate the impact of BTX on renal function.

QoL and patient satisfaction

Studies have shown that BTX/A injections improve QoL in patients with NDO regardless of whether NDO is due to SCI or MS. In 43 patients with NDO due to MS who were refractory to anticholinergic medications, Botox significantly reduced urgency, frequency, urinary incontinence, and nocturia (Kalsi et al., 2007). Despite 98% of the patients having to perform intermittent catheterization, sustained improvements were exhibited in QoL scores in all categories. A highly significant decrease was found in the combined Urogenital Distress Inventory-6 and Incontinence Impact Questionnaire-7 score. The mean duration of the clinical effects was 8 months (Kalsi et al., 2007).

Giannantoni et al. (2009) prospectively evaluated clinical, urodynamic, and QoL issues in 17 individuals over 6 years. Patients received repeated injections of 300 U of Botox over this time. The mean interval between injections was 11 months. In addition to significant clinical and urodynamic improvements, this study showed that sustained QoL improvements could be achieved by repeated detrusor BTX/A injections over a 6-year period (Giannantoni et al., 2009).

In summary, a number of studies have confirmed that after the injection of BTX, significant improvements occurred in the QoL in individuals with SCI or MS who have NDO. This took place despite nearly all study patients having to perform CIC, suggesting that CIC had a less significant effect on patients' QoL than relief from their troublesome bladder symptoms (Linsenmeyer, 2013).

Adverse effects and complications

Several potential adverse effects (AEs) or complications may take place following the injection of BTX/A. The most common adverse reactions (occurring in $\geq 5\%$ of patients, with effects greater than placebo) listed in the prescribing information for Botox, revised in August 2011 for DO, are UTIs and urinary retention (Ehren et al., 2007).

Schurch et al. (2005) noted in their prospective, randomized, single-treatment, placebo-controlled, 6-month study that UTIs were the most common AE. This occurred in all three of the

groups in this study: 3 of 21 patients (14.3%) in the placebo group, 6 of 19 patients (31.6%) in the 200 U of onabotulinum toxin A group, and 4 of 19 patients (21.1%) in the 300 U of onabotulinum toxin A group. However, no statistically significant differences were found among the three groups ($P = 0.455$) (Schurch et al., 2005).

In the study by Cruz et al. (2011), the most common AE during the first 12 weeks was also UTIs. In the SCI population, the incidence was the same among all treatment groups, including placebo. The overall UTI incidence for patients with SCI for the placebo group and the 200 and 300 U of onabotulinum toxin A groups was 50%, 52.6%, and 56.4%, respectively (Cruz et al., 2011).

It should be noted that a clear distinction was not made between symptomatic UTIs and colonization. A UTI diagnosis was based on a laboratory finding of a positive urine culture. However, for an individual with neurogenic bladder dysfunction to be considered to have a UTI, three criteria have to be met: bacteria in the urine, elevated levels of white blood cells in the urine, and the new onset of symptoms (National Institute on Disability and Rehabilitation Research Consensus Statement, 1992).

Kalsi et al. (2007) discussed symptomatic UTIs after Botox injections in 43 patients with MS. They reported that seven patients (16%) developed UTIs (single or recurrent) after the injection. However, three of these patients had a history of UTIs prior to the injection. Therefore, 4 of the 43 patients (9%) developed a UTI as a consequence of the intervention. The reason for this is not known. However, a large number of patients had to start CIC after the injection. It is possible that with the resolution of symptoms, patients decreased the frequency of catheterization or allowed their bladders to become overdistended (Kalsi et al., 2007).

The second most common AE in the study by Cruz et al. (2011) was elevation in postvoid residual urine (PVR) after onabotulinum toxin A injections. In patients not performing CIC at baseline, PVR values significantly increased following onabotulinum toxin A injections in a dose-related manner over the 12-week follow-up period. The percentage of patients with a PVR > 200 mL was highest in the 300 U group (Cruz et al., 2011).

The percentages of patients with a PVR ≥ 200 mL in the placebo, 200 U, and 300 U groups were 2.7%, 28.6%, and 53.7%, respectively. Urinary retention primarily occurred in patients with MS, and again was most common in the 300 U group. Overall, the incidence of initiating intermittent catheterization in the placebo, 200 U, and 300 U groups was 12.2%, 29.5%, and 42%, respectively (Cruz et al., 2011).

It is possible that the combination of intermittent catheteriza-

tion and stopping or decreasing anticholinergic medications improved the QoL of a number of individuals with NDO who experienced a large number of incontinent episodes and side effects from their anticholinergic medications.

The phase III data demonstrated that the risk of UTI was 24% (compared to 17% for placebo) in patients with NDO treated with 200 U of onabotulinum toxin A and 18% (compared to 6% for placebo) in patients with OAB treated with 100 U of onabotulinum toxin A. An increased risk of UTI and retention does appear to be present in older patients with OAB (Ginsberg et al., 2012).

The gold-standard treatment for NDO is anticholinergic medication and, if necessary, intermittent self-catheterization. However, anticholinergics are often inefficient, even at a double or triple dose or in combination therapy; furthermore, the many side effects of these oral medications lead to high withdrawal rates. Onabotulinum toxin A seems to be a promising alternative for patients who are refractory to or do not tolerate the first-line therapy. It is a minimally invasive treatment with an established efficacy and safety profile.

BTX intradetrusor injections are well tolerated and provide clinically beneficial improvements in adults with NDO and incontinence refractory to anticholinergic medications. These improvements are seen up to 9 months after injection. Onabotulinum toxin A may provide superior clinical and urodynamic benefits for populations with NDO. Onabotulinum toxin A also has been found to significantly improve urodynamic outcomes in patients with NDO due to MS and SCI. Future research may evaluate the efficacy of first-line onabotulinum toxin A compared with anticholinergic medications, particularly in patients with NDO and incontinence that develops rapidly (e.g., after an SCI). In addition, the use of onabotulinum toxin A in patients with high cervical lesions above T1 should be the focus of a specific study, due to the risk of developing muscular weakness in the respiratory muscles. In OAB, future research may evaluate the predictors of success of onabotulinum toxin A, the role of onabotulinum toxin A in the treatment algorithm (e.g., as a first-line therapy in some individuals), and its use in the OAB dry population.

Further controlled trials should assess the optimal dosage, injection technique, long-term safety of repeated injections, most favorable timing, indications for reinjections, and the adjuvant administration of anticholinergics and their impact on the efficacy and duration of onabotulinum toxin A treatment. Future studies also should focus on other neurogenic indications, such as supra-cervical spinal lesions, Parkinson disease, and strokes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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