Botulinum neurotoxin–A treatment of lower urinary tract symptoms in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is the most common neuroinflammatory disease of the central nervous system and a leading cause of disability in young adults. Symptoms related to vesicourethral dysfunction are very prevalent, but not specific to underlying urodynamic abnormalities. Detrusor overactivity and detrusor external sphincter dysynergia are the most frequent findings and are usually linked. Botulinum neurotoxin-A injection represents a significant advance in the management of voiding dysfunction among MS patients failing first-line therapy. It significantly improves patients' urodynamic parameters and quality of life, with efficacy sustained by repeated injections and minimal risk of adverse events.

Introduction

Multiple sclerosis (MS) is the most common neuroinflammatory disease of the central nervous system (CNS). It typically occurs between the ages of 29 and 40, and its prevalence depends on geographic location; southern Canada and the United States are high-incidence areas (more than 100 per 100 000 population).[1] MS is the leading cause of disability in young adults. Its socioeconomic consequences and impact on patients' quality of life (QoL) are considerable.[2]

MS displays marked clinical heterogeneity and can progress through different modes. Diagnosis meets the revised McDonald criteria with magnetic resonance imaging (MRI) and timing intervals.[3] Bladder and urethral dysfunction develops within 6 to 10 years after disease onset and is reported in 50% to 96% of patients, coinciding with disease progression and symptom severity.[4-6] Urinary symptoms are not specific to underlying urodynamic abnormalities. In addition, the evolution of MS results in increasing disability and damage at multiple CNS levels, modifying symptoms and urodynamic findings over time with later treatment failure.

Botulinum neurotoxin-A (BONT-A), and specifically onabotulinumtoxinA, is currently approved by the US Food and Drug Administration and by many European countries for the management of voiding dysfunction in MS patients. Its injection results in the significant improvement of urodynamic and QoL parameters.

Pathophysiology of lower urinary tract symptoms in MS

The normal process of bladder storage and voiding involves complex networks with activation or inhibition of the pontine micturition centre (PMC). Pathways from the PMC project to different levels of the spinal cord, rather than to the bladder and external urethral sphincter (EUS), via multiple peripheral nerves and elicit different reflexes.[7-9] Lesions affecting the connection of the PMC and spinal centres culminate in a lack of EUS inhibition at the time of micturition (detrusor external sphincter dysynergia [DESD]), and in the emergence of segmental reflexes responsible for uncontrolled detrusor contractions in response to bladder distension (detrusor overactivity [DO]). Detrusor areflexia and reduction of bladder sensation may occur as well.[10] Different combinations of detrusor and EUS-related symptoms can be seen.

These conditions tend to worsen as the disease progresses, either in relapsing/remitting or progressive mode, primarily in relation to increased spinal cord involvement.[11,12] Worsening paraparesis and spasticity (evaluated by the Expanded Disability Status Scale [EDSS]), reduction of general mobility, recurrent urinary tract infections (UTI) and cognitive impairment are responsible for worsening symptoms as well.[13,14]

Some authors postulate correlations between urological complaints, urodynamic studies (UDS) and spinal cord abnormalities on MRI,[15,16] but others have not established significant connections between CNS levels and voiding

dysfunction[17,18] in imaging and autopsy studies. Few have reported associations of urinary symptoms with brain MRI parameters.[19]

Evaluation and management of LUT symptoms in MS patients

Lower urinary tract symptoms (LUTS) are polymorphic and subject to changes, depending on the clinical evolution of MS (Table 1). Motor handicap severity is regularly correlated with the incidence of voiding dysfunction.[11,12]

The most prevalent symptoms are frequency, urgency and urinary urge incontinence (UUI) (32%-99%, 32%-85% and 19%-80%, respectively). Obstructive symptoms are found, but to a lesser degree. The clinical presentation of vesicourethral dysfunction (VUD) offers little information on the type and severity of detrusor-sphincter disorders, and is highly influenced by MS duration, as well as neurological deficiencies and disabilities (estimated through the EDSS).[25] Also, men are more prone to developing obstructive symptoms, whereas women experience incontinence and irritative symptoms.

UDS are essential to evaluate MS patients for appropriate first-line management and in cases of therapeutic failure, new urinary symptoms or when surgical or intravesical treatment is planned. Of note, half of "asymptomatic" MS patients present UDS abnormalities and almost 30% of patients experiencing LUTS do not show UDS aberrations.[26] DO is the most frequent finding (34%-90%): first overactive contraction amplitude, maximum detrusor pressure and threshold bladder volume are reported to be higher among MS patients compared to neurogenic and idiopathic DO.[27] Detrusor underactivity (DU) (5%-37%) and poor bladder compliance (2%-10%) are also encountered.[25] These findings change unpredictably over time in more than 50% of patients, independently of clinical neurological stability.[28] DESD occurs in 6% to 82% of cases, in association with either DO or DU, and it usually persists once DO or DU has developed.[26]

Urological complications in MS include those in the lower urinary tract (UTI, bladder alteration) and upper urinary tract (renal calculi, hydronephrosis, vesicoureteral reflux and renal insufficiency). These complications seem to be less common in MS compared to spinal cord injury (SCI) patients, with no reason identified.[29] The duration of disease progression, method of urinary drainage and post-void residual (PVR) are the principal risk factors for urological complications. DESD, male gender and age over 50 years are also considered risk factors.[25]

Management (i.e., initial rehabilitation and behavioural techniques [fluid intake, bladder emptying]) should account for patients' mental status and disabilities. Reflex voiding is potentially dangerous and should be replaced by clean intermittent catheterization (CIC) in patients with DU or DESD and significant PVR. CIC is superior to both indwelling and suprapubic catheters in reducing UTI. Antimuscarinics, especially long-acting formulations, seem to be logical first-line treatments, as most symptoms are related to DO. However, the evidence for their administration is poor, and the progressive nature of the disease with shifting urodynamic consequences, along with increased rates of adverse events, limits their prescription.[30,31] Alpha-adrenergic antagonists may reduce outlet resistance, and other oral therapies (desmopressin and cannabinoids) may be indicated to improve urinary symptoms in specific situations.[29,32] Intravesical therapy of urgency and incontinence with vanilloid agents (resiniferatoxin, capsaicin) has delivered inconsistent outcomes.[33] Sacral nerve stimulation appears to be more effective than posterior tibial or dorsal penile/clitoral stimulation; however, the implantable stimulator precludes further MRI evaluation.[34] Surgical interventions (urethral sphincterotomy, urinary diversion/reconstruction) can be offered to select patients with careful preoperative counselling.

BONT-A in MS

Rationale of treatment, dosage, concentration and injection technique

BONT-A is synthesized by *Clostridium botulinum* strains. Its effect in treating VUD in MS is attributed to temporary and reversible paralysis of the injected detrusor or EUS by blocking the vesicular release of parasympathetic acetylcholine

Table 1. Prevalence of LUTS in MS in the literature

Authors	No. patients	Urgency	UUI	Frequency	Dysuria	Urinary retention
Awad et al.[11]	47	85.1%	72.3%	65%	36.1%	—
Mayo and Chetner[20]	89	71%	57%	57%	56%	—
Amarenco et al.[21]	225	72%	63%	42%	46%	24%
Koldewijn et al.[12]	211	38%	26%	38%	27%	—
Giannantoni et al.[22]	116	—	41.7%	99%	79.5%	—
Gallien et al.[23]	149	79.8%	69.1%	67.7%	73.8%	—
Hennessey et al.[24]	191	71%	58%	76%	48%	—

LUTS: lower urinary tract symptoms; MS: multiple sclerosis; UUI: urinary urge incontinence.

at the neuromuscular junction. It also seems to affect the afferent arm of reflex bladder contractions.[13,35,36]

BONT-A is marketed under different brand names: Botox (onabotulinumtoxinA, Allergan, Irvine, CA), Dysport (abobotulinumtoxinA, Ipsen, Slough, Berkshire, UK), Xeomin (incobotulinumtoxinA, Merz Pharmaceuticals UK Ltd., Herts, UK), Prosigne (Lanzhou Biologic Products, Lanzhou, China) and PurTox (Mentor Corporation, Madison, WI). A direct comparison between these preparations in urology is not currently possible. Prosigne administration has been described in 1 study,[37] but no studies have reported on Xeomin or PurTox for urological purposes. Recently, Xeomin (pure NTX-A) was shown to be inferior to Botox in cervical dystonia patients.[36]

As BONT-A therapy might be continued over many years, loss of therapeutic response has been reported in some patients.[38] The loss of efficacy is due to the development of detectable neutralizing antibodies in these patients.[39] Various factors might affect BONT-A immunogenicity. They include product-related factors, such as manufacturing process and antigenic protein load (accessory proteins have been shown to increase the immunological response to NTX-A[40-42]), as well as treatment-related factors, such as overall toxin dose and prior vaccination or exposure.

Detection of antibodies by laboratory tests might not necessarily predict the clinical success or failure of treatment.[38] Chinnapongse and colleagues[43] analyzed 4 prospective multicentre trials combining a total of 1134 subjects given BONT-B about every 3 months for cervical dystonia. The presence of antibodies to BONT-B, assessed by mouse-neutralizing antibody assay, did not have a meaningful clinical impact or correlate with treatment failure over total treatment durations of at least 6 years. No such studies have been conducted with BONT-A for urological indications.

The use of BONT-A in MS was extrapolated from initial studies on intradetrusor and intrasphincteric injection in SCI patients.[44,45] OnabotulinumtoxinA (Botox) is currently approved in the United States, Canada and some European countries (France, Spain, Belgium, Germany, Poland, the Netherlands, but not yet in the UK, Italy and Switzerland) as a 200-U dose for intravesical injection in patients with urinary incontinence (UI) due to neurogenic detrusor overactivity (NDO), including MS patients.[46] To date, BONT-A has not been approved to treat DESD.

BONT-A in DO

The procedure is often performed in outpatient settings, with a rigid or flexible cystoscope, after local anesthesia with intraurethral 2% lidocaine jelly, or 30 mL of intravesical 2% lidocaine for 10 minutes in poorly-tolerating subjects.

Multiple, disposable, flexible injection needles are available on the market. However, a 4-mm needle (BONEE, Coloplast, Sweden) seems to have simplified the procedure. Although most initial studies delivered OnabotulinumtoxinA at the 300-U dose level, 200 U has been shown to be as effective in relieving symptoms and restoring continence;[47-50] it is now the approved dosage. Recently, a small study reported significant improvement with 100 U.[51] AbobotulinumtoxinA is usually injected at a dose level of 500 U.[52,53] It is diluted in saline 10 or 20 U/mL, and 10 U are injected per detrusor site.[54-56] Injections are evenly distributed across the dome, posterior, right and left lateral walls of the bladder. Several reports have advocated the safety of trigone injection without vesicoureteral reflux.[57,58] Smith and Chancellor[59] suggested that 100 U of onabotulinumtoxinA, diluted in 10 mL of preservative-free saline, can be injected submucosally into 10 trigone sites as effectively as 30 injection plans. Others have indicated that trigonal injections may improve daily incontinence and lead to better continence rates than detrusor injections alone;[60-64] however, the urodynamic parameters in these studies were less affected.

BONT-A in DESD

EUS injections can be given alone or in combination with detrusor injections. OnabotulinumtoxinA (100 U) reconstituted in 4 mL of normal saline[65] or AbobotulinumtoxinA (150-250 U)[66,67] can be administered. For cystoscopy-guided injection, the needle is inserted to a depth of 1 cm at 2 to 4 sites (12, 3, 6 and/or 9 o'clock) in the sphincter.[67] Injection can also be delivered transperineally in men and transvaginally in women under electromyographic guidance at a single median site or as 2 paramedian injections. Recognition of EUS location is ensured through its activity during the bulbocavernous reflex. Both techniques can be performed under local anesthesia and are reported to be equally effective.

Efficacy

Few studies have specifically focused on MS patients, and most available data come from trials that included both MS and SCI patients (Table 2). Intradetrusor injection of BONT-A for DO management significantly reduces the number of urgency and UUI episodes and improves cystometric parameters (maximum cystometric capacity, maximum detrusor pressure during first involuntary detrusor contraction, maximum volume at first involuntary detrusor contraction) and health-related quality of life scores. BONT-A may also decrease urethral leakage in the setting of indwelling urinary catheters,[76] and has been shown to reduce UTI frequency.[71] MS duration seems to be a predictive factor of BONT-A treatment failure, as neurological and urinary conditions worsen with time and result in more severe DO than in the early stage of the disease.[68]

Gallien and colleagues[65] reported significantly increased voiding volume (+54%, $p = 0.02$) and reduction of pre-

Table 2. Efficacy of BONT-A in voiding dysfunction secondary to MS

Author	No. patients with MS (total no. patients)	BONT-A type	Dosage	Injection site	Urodynamic and/or QoL outcomes	Notes
Cruz et al.[47]	154 (275)	OnabotulinumtoxinA	200 or 300 U	Detrusor	UI: -24.2 (18.9) episodes/week V/V: +119.8 (117.5) mL MCC: +159.2 (156.9) mL $P_{detmaxIDC}$: -14.6 (36.0) cmH_2O $V_{PmaxIDC}$: +217.3 (213.5) mL DC: 104.4 (166.5) mL/cmH_2O Patients with no IDC at 6 weeks: 66.0%	Multicentre, international, randomized, double-blind, placebo-controlled phase 3 study
Ginsberg et al.[48]	227 (416)	OnabotulinumtoxinA	200 or 300 U	Detrusor	UI: -23 episodes/week MCC: +142 (179) mL $P_{detmaxIDC}$: -28.4 (31.9) cmH_2O I-QoL: 28.0 (28.0)	52-week, multicentre, international, randomized, double-blind, placebo-controlled trial Trigone-sparing injections
Deffontaines-Rufin et al.[68]	77 (77)	OnabotulinumtoxinA	300 U	Detrusor	MCC: +90 mL $V_{PmaxIDC}$: +140 mL $P_{detmaxIDC}$: -25 cmH_2O	
Khan et al.[69]	137 (137)	OnabotulinumtoxinA	300 U	Detrusor	Complete continence in 76% of patients Mean UDI-6: -37.3 Mean IIQ-7: -44.5	Mean follow-up 29 months (9-80)
Herschorn et al.[70]	19 (57)	OnabotulinumtoxinA	300 U	Detrusor	Mean daily UI episodes: -50% $V_{PmaxIDC}$: +50 mL Max detrusor pressure during filling: -20 cmH_2O MCC: +60 mL Complete continence: 10.7% of patients Improvement of I-QoL total scores	Results at 36 months in both groups (SCI and MS)
Game et al.[71]	15 (30)	OnabotulinumtoxinA	300 U	Detrusor	MCC: +150 mL $P_{detmaxIDC}$: -25 cmH_2O	Decrease in incidence of symptomatic urinary infections
Kalsi et al.[72]	43 (43)	OnabotulinumtoxinA	300 U	Detrusor	MCC: +300% Frequency: -45% Incontinence episodes: -77%	
Schurch et al.[73]	6 (59)	OnabotulinumtoxinA	200 or 300 U	Detrusor	UUI: -1.1 episodes/day	
Schulte-Baukloh et al.[62]	16 (16)	OnabotulinumtoxinA	300 U	Detrusor	MCC: +58%-77% Pad use: -38%-64%	
Ehren et al.[74]	6 (31)	AbobotulinumtoxinA	500 U	Detrusor	Mean MCC: +100 cc Mean $P_{detmaxIDC}$: -20 cmH_2O	No stratification of results by NDO etiology Intake of antimuscarinics significantly lower in BONT-A group
Gallien et al.[65]	86 (86)	OnabotulinumtoxinA	100 U	EUS	VV: +54% $P_{detmaxIDC}$: -21% MUCP: -21%	
Smith et al.[75]	48 (110)	OnabotulinumtoxinA	100 or 200 U 100 or 300 U	EUS (32 patients) Detrusor (16 patients)	Improvement of PVR, $P_{detmaxIDC}$, MCC	Included trigonal injections

QoL: quality of life; BONT-A: botulinum neurotoxin-A; MS: multiple sclerosis; DC: detrusor compliance; EUS: external urethral sphincter; IIQ-7: Incontinence Impact Questionnaire-short form; I-QoL: incontinence QoL; MCC: maximum cystometric capacity; MUCP: maximal urethal closure pressure; NDO: neurogenic detrusor overactivity; PdetmaxIDC: maximum detrusor pressure during first involuntary detrusor contraction; SD: standard deviation; UDI-6: Urogenital Distress Inventory questionnaire-short form; UI: urinary incontinence; UUI: urinary urge incontinence; VpmaxIDC: volume at first IDC; V/V: volume/void (volume per void is derived from total voided volume over a 24-hour period).

micturition and maximal detrusor pressures with EUS injection compared to placebo (-29% and -21%, respectively, $p = 0.02$), with similar tolerance. However, they noted improvement of PVR.

In general, BONT-A efficacy is limited in duration. Previous studies suggest that benefits begin to wane after 6 months[34] with intradetrusor injection. Ginsberg and colleagues[48] report a median time of 8.4 months to patient re-treatment request. When injected in the EUS, efficacy is maintained for 1 to 4 months.[67,68] Repeat BONT-A injections remain effective in most patients.[63,71]

Safety

Bladder or urethral BONT-A injection is generally administered under local anesthesia and is well-tolerated. The most common adverse effects are bladder pain, UTI (2%-35%), urinary retention (17%-20%) and mild hematuria (2%-20%).[47,48] Patients should be consulted about the risk of *de novo* CIC because of increased PVR (30%-40% of patients).[47] No severe systemic effects directly related to BONT-A injection have been reported to date, although a few patients experience benign, transient generalized weakness after treatment.[77]

Data on the risk of UTI after Botox injection are conflicting. Some authors report reduced risk,[65] while others report an increased risk of UTI.[77]

Current BONT-A treatment in MS

Intradetrusor BONT-A injection is now an approved treatment modality for UI secondary to NDO. It should be available to patients who failed first-line therapy (behavioural modifications and oral therapy), before considering more invasive alternatives (e.g., sacral neuromodulation).[29] Few studies have compared BONT-A to other intravesical vanilloids (capsaicin, resiniferatoxin) whose efficacy is supported by level 1b evidence.[78,79] One randomized investigation compared BONT-A to resiniferatoxin as second-line therapy of NDO patients.[80] BONT-A significantly decreased the frequency of daily incontinence episodes ($p < 0.05$), significantly increased first uninhibited detrusor contractions ($p < 0.01$) and maximum bladder capacity ($p < 0.01$), and significantly reduced maximum pressure of uninhibited detrusor contractions ($p < 0.01$) compared to resiniferatoxin at the 6-, 12- and 18-month follow-up. However, this study investigated only SCI patients. There is level 1 evidence of BONT-A efficacy and safety in DESD, but its application remains off-label.

Conclusion

The progressive nature of MS, which results in significant disability along with extensive shifting of urodynamic parameters, makes patients different from those with idiopathic and neurogenic DO. In this setting, BONT-A exerts significantly beneficial qualitative and quantitative effects in patients who are refractory to first-line therapy, with good levels of evidence. Intradetrusor and intrasphincteric injections are well-tolerated, with minimal risk of systemic adverse events.

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This paper has been peer-reviewed.

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