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ORIGINAL ARTICLE

Botulinum toxin for the management of spasticity in multiple sclerosis: the Italian botulinum toxin network study

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Abstract

Background Botulinum toxin (BT) is an effective and safe treatment for spasticity, with limited evidence in multiple sclerosis (MS). We aim to describe the use of BT for the management of MS spasticity in the clinical practice, its combination with other anti-spastic treatments in MS and possible MS clinical correlates.

Methods This is a multicentre cross-sectional observational study including 386 MS patients, receiving BT for spasticity in 19 Italian centres (age 53.6 ± 10.9 years; female 228 (59.1%); disease duration 18.7 ± 9.2 years; baseline Expanded Disability Status Scale (EDSS) 6.5 (2.0–9.0)).

Results BT was used for improving mobility ($n = 170$), functioning in activities of daily living ($n = 56$), pain ($n = 56$), posturing-hygiene ($n = 63$) and daily assistance ($n = 41$). BT formulations were AbobotulinumtoxinA ($n = 138$), OnabotulinumtoxinA ($n = 133$) and IncobotulinumtoxinA ($n = 115$). After conversion to unified dose units, higher BT dose was associated with higher EDSS (Coeff = 0.591; $p < 0.001$), higher modified Ashworth scale (Coeff = 0.796; $p < 0.001$) and non-ambulatory patients (Coeff = 209.382; $p = 0.006$). Lower BT dose was used in younger patients (Coeff = − 1.746; $p = 0.009$), with relapsing-remitting MS (Coeff = − 60.371; $p = 0.012$). BT dose was higher in patients with previous BT injections (Coeff = 5.167; $p = 0.001$), and with concomitant treatments (Coeff = 43.576; $p = 0.022$). Three patients (0.7%) reported on post-injection temporary asthenia/weakness ($n = 2$) and hypophonia ($n = 1$).

Conclusion BT was used for spasticity and its consequences from the early stages of MS, without significant adverse effects. MS-specific goals and injection characteristics can be used to refer MS patients to BT treatment, to decide for the strategy of BT injections and to guide the design of future clinical trials and observational studies.

Keywords Multiple sclerosis · Spasticity · Botulinum · Symptomatic treatment

Introduction

Spasticity is defined as an increase in the velocity dependent reflexes to phasic stretch, detected and measured at rest, and affects up to 80% people with multiple sclerosis (MS), causing difficulties in mobility and personal care [1–4], complications (e.g. pain) [1–3, 5–8] and poor quality of life [8, 9]. Spasticity management requires a multidisciplinary approach, combining nonpharmacological and pharmacological interventions, and has to account for clinical features, patient preference and availability of services [6]. A number of treatments for spasticity, such as cannabinoids, benzodiazepines, oral and

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intrathecal baclofen, are available but are frequently underused, with patients reporting on dissatisfaction with spasticity management [3, 10–13].

Intramuscular injection of botulinum toxin (BT) has proven effective and safe for spasticity of any aetiology, including MS [10, 14–21]. However, evidence on MS is based on few studies including small samples of MS patients followed-up for a relatively short time, whilst larger studies, exploring the efficacy of BT for spasticity from any aetiology, only included a limited proportion of MS patients [22]. Thus, in many countries (e.g. Italy, where the present study has been conducted), formal registrations for MS are currently lacking [14, 23], and authorization from the Hospital Pharmacy is necessary to obtain full coverage of expenses from the National Healthcare System. In other countries (e.g. Canada, US), BT use is limited by patient costs and insurance coverage [24]. BT clinical potential remains underestimated, with many MS guidelines suggesting BT only for focal spasticity in the lower limbs [10, 17, 22, 25, 26]. Moreover, studies conducted on other aetiologies of spasticity (e.g. stroke, cerebral palsy) [2, 10, 27] did not account for MS-specific clinical characteristics and potential injection goals [28–30]. Finally, the possibility of combining BT with other interventions for spasticity in MS has never been fully explored [17].

In the present multicentre cross-sectional study, we aim to describe (1) the use of BT for the management of MS spasticity in the clinical practice; (2) combinations of BT with different anti-spastic treatments in MS and (3) possible associations between MS clinical features and the use of BT.

Methods

Study design and population

This is a multicentre cross-sectional study, conducted in 19 BT injection clinics of the Italian Network for BT and of the Italian Study Group for MS of the Italian Society of Neurology. Data were collected from Sep 2017 to Sep 2018. Each patient was included for the most recent injection within the study period. All centres were requested to go through a structured questionnaire for data collection (Supplementary Material 1); all items of the questionnaire were mandatory.

Ethics approval was obtained from the committee of "Federico II" University of Naples, Italy. The study included anonymized data collected in the clinical practice and was conducted in accordance with good clinical practice and the Declaration of Helsinki.

Inclusion criteria were (1) diagnosis of MS [31] and (2) injection of BT for MS-related spasticity within the study period. Exclusion criterion was (1) incomplete medical records.

Demographics and MS-related clinical variables

At the time of study inclusion (BT injection), we collected demographics (age and sex) and MS-related clinical features: disease duration (years from reported disease onset to study inclusion, corresponding to current BT injection), Expanded Disability Status Scale (EDSS), clinical phenotype (relapsing/remitting [RR], secondary progressive [SP], or primary progressive [PP]) and current immunomodulatory treatment for MS (disease modifying treatment (DMT)). DMTs were classified as first- or second-line treatments according to the Italian regulatory agency.

BT injection and spasticity variables

Spasticity was clinically defined as an increase in the velocity dependent reflexes to phasic stretch, detected and measured at rest [4]; spasticity evaluation included separate assessment of the tone in specific muscle groups (e.g. shoulder, elbow, wrist, fingers, hip, leg, knee, ankle), by using the modified Ashworth score (MAS) (minimum MAS score for definition of spasticity was 1), performed at the time of study inclusion (BT injection). For each patient, the highest MAS score was used for statistical purposes; dominant spasticity pattern for upper and lower limbs was described (flexor or extensor for elbow and knee, abductor or adductor for shoulder and hip, mixed if a combination of previously-described spasticity patterns was found).

We collected BT injection history (date of current injection, date of first injection and total number of injections), main injection goal, formulation (AbobotulinumtoxinA [Dysport®], IncobotulinumtoxinA [Xeomin®], or OnabotulinumtoxinA [Botox®]), characteristics (dosage, dilution, injection sites and use of injection guidance) and adverse events (side effects occurring during the injection or reported by the patient from the most recent previous injection were systematically searched with a specific open question, within the structured questionnaire for data collection).

Injection goals were derived from the World Health Organization (WHO) International Classification of Functioning, Disability, and Health (ICF) (http://apps.who.int/classifications/icfbrowser/) [32], as from previous validation studies in MS [33–35]. Then, we grouped injection goals into:

1) ICF self-care goal areas d570 (daily assistance);
2) ICF self-care goal area 510, d520, d530, d540, d550 and d560 (posturing-hygiene);
3) ICF pain goal area b280 (pain);
4) ICF mobility goal area d410, d415, d420, d429, d430, d435, d440, d445, d449, d450, d455, d460, d465, d469, d470, d475, d480, d489, d498, d499 (mobility);

5) ICF domestic life goal area d610, d620, d629, d630, d640, d649, d650, d660, d669, d698 and d699 (functioning in activities of daily living).

For patients who received previous BT injections, current BT injection characteristics were compared with the most recent previous injection (e.g. changes in dosing, muscle/sites, BT formulation or dilution).

We recorded all medications that were used for the management of spasticity, as from the Italian consensus on treatment of spasticity in MS [26]. Procedures and/or prescriptions that were related to physiotherapy departments according to Italian regulations (e.g. physiotherapy, occupational therapy, orthotics) were recorded within physiotherapy. Invasive (e.g. intrathecal baclofen, orthopaedic surgery) or microinvasive interventions (e.g. phenol injection) for spasticity treatment were also collected.

In accordance with previous papers on the same topic, for comparison of patients using different BT formulations, doses were unified [36]. Because most of the patients had been treated with either IncobotulinumtoxinA [Xeomin®], or OnabotulinumtoxinA [Botox®], these doses were left unchanged, whilst AbobotulinumtoxinA [Dysport®] doses were divided by 2.5 to yield comparable unified dose units (uDU).

Statistics

Mean (and standard deviation), median (and range) and mode (most frequently reported value) were calculated for different study variables, as appropriate, to describe the use of BT (aim 1). Injection characteristics (e.g. total dose) were used as outcome measures and were associated with variables of concomitant anti-spastic treatments (aim 2), and of MS clinical features (aim 3), using linear regression models and ordered regression models (for EDSS and MAS), as appropriate. EDSS, centre of injection and BT formulation were included as covariates. Coefficients (Coeff) and 95% confidence intervals (95%CI) were calculated.

Statistical analyses were performed with Stata 15.0. Results were considered statistically significant for $p < 0.05$.

Results

Demographics, clinical features and BT injections

The present study included 386 MS patients from 19 Italian Centres within the Italian Network for BT and the Italian Study Group for MS. Among originally screened patients, we excluded one MS patient who received BT injection for other than spasticity (tremor), and two MS patients due to incomplete medical records. Demographic and clinical features of included patients are reported in Table 1. Repartition among centres is reported in the Supplementary Material 2.

Table 1 Demographics and clinical characteristics. The table shows demographics and clinical characteristics, recorded at study inclusion, corresponding to BT injection

		MS patients ($n = 386$)
Age, years		53.6 ± 10.9
Sex, female		228 (59.1%)
Disease duration, years		18.7 ± 9.2
EDSS, median (range)		6.5 (2.0–9.0)
	EDSS ≤ 3.5	46 (11.8)%
	EDSS 4.0–6.5	170 (44.1%)
	EDSS ≥ 7.0	170 (44.1%)
Clinical subtype	PPMS	88 (22.8%)
	RRMS	213 (55.2%)
	SPMS	85 (22.0%)
On treatment with DMT		204 (52.9%)
DMT type	1st line	109 (53.4%)
	Azathioprine	15
	Dimethyl Fumarate	16
	Glatiramer Acetate	24
	Interferon-beta	25
	Teriflunomide	29
2nd line		96 (46.6%)
	Alemtuzumab	13
	Cyclophosphamide	1
	Daclizumab	1
	Fingolimod	43
	Mitoxantrone	1
	Natalizumab	26
	Ocrelizumab	5
	Rituximab	4
	Siponimod	2
MAS, median (range)		3 (1–4)
BT naïve		81 (20.9%)
Total BT injections		5.6 ± 5.8
Injection goal	Daily assistance	41 (10.4%)
	Pain	56 (14.6%)
	Functioning	56 (14.6%)
	Posturing hygiene	63 (16.3%)
	Movement	170 (44.1%)
Reported side effects		3 (0.7%)

EDSS, expanded disability status scale (EDSS ≤ 3.5 corresponds to fully ambulatory patients; EDSS 4.0–6.5 corresponds to patients with limited ambulation; EDSS ≥ 7.0 corresponds to patients essentially restricted to wheelchair); *DMT*, disease modifying treatments; *MAS*, modified Ashworth scale; *BT*, botulinum toxin; BT naïve, patients of their first BT injection

On clinical examination, spasticity in the upper limbs was found in 136 patients (35.2%); the most frequent spasticity pattern in the upper limbs was elbow flexion ($n = 112$, 83.6%), followed by mixed ($n = 12$, 9.0%), elbow extension ($n = 5$, 3.7%) and shoulder adduction ($n = 5$, 3.7%). Spasticity in the lower limbs was found in 358 patients (92.7%); the most frequent spasticity pattern in the lower limbs was knee extension ($n = 161$, 45.0%), followed by knee flexion ($n = 86$, 24.0%), mixed ($n = 62$, 17.3%) and hip adduction ($n = 49$, 13.7%).

Eighty-one patients (20.9%) were on their first BT injection, whilst 305 patients (79.1%) already had 5.6 ± 5.8 BT injections (from 1 to 36), with 4.3 ± 3.0 months of interval between injections. MS Centre ($n = 349$, 90.4%) was the most frequent referring institution to BT injection, followed by physiotherapy departments ($n = 25$, 6.5%), general practitioner ($n = 10$, 2.5%) and other neurology clinics ($n = 2$, 0.6%). The most frequent injection goal was mobility ($n = 170$, 44.1%), followed by hygiene ($n = 63$, 16.3%), pain ($n = 56$, 14.6%), functioning in activities of daily living ($n = 56$, 14.6%) and daily assistance ($n = 41$, 10.4%).

BT formulations were AbobotulinumtoxinA (Dysport) ($n = 138$, 35.7%) with 876.2 ± 473.4 units injected in 2.9 ± 1.8 muscles/muscle groups across 7.0 ± 6.6 sites, OnabotulinumtoxinA (Botox) ($n = 133$, 34.5%) with 246.7 ± 147.9 units injected in 2.6 ± 1.3 muscles/muscle groups across 6.3 ± 3.8 sites and IncobotulinumtoxinA (Xeomin) ($n = 115$, 29.8%) with 236.9 ± 144.6 units injected in 2.8 ± 1.6 muscles/muscle groups across 6.3 ± 4.2 sites. Injected muscle (or muscle group), BT formulations, number of injection sites (per muscle or muscle group), doses, dilution (units of each BT formulation/mL of saline solution) and most commonly used guidance are reported in Table 2.

Among MS patients who received previous BT injections, 135 patients ($n = 44.4\%$) changed BT injection characteristics, when compared with the most recent previous injection, with increased dose ($n = 63$, 46.7%), reduced dose ($n = 34$, 25.2%), change in muscle/sites ($n = 30$, 22.2%), change in BT formulation ($n = 7$, 5.2%) or change in BT dilution ($n = 1$, 0.7%).

No side effects were reported during the current injection. After previous injection, temporary asthenia/weakness ($n = 2$) and hypophonia ($n = 1$) were reported by 3 patients (0.7%).

BT and spasticity management

One hundred sixty-eight patients (43.5%) were currently on treatment with BT alone, whilst 218 patients (56.5%) were treated with an average of 1.1 concomitant medications for spasticity, as from the Italian consensus on treatment of spasticity in MS. Concomitant treatments for spasticity are reported in Table 3. Concomitant spasticity treatments were associated with higher BT dosage (+ 43 uDU) (Table 4).

Three hundred twenty-eight patients (84.9%) were on physiotherapy, with outpatient long-term weekly physiotherapy sessions ($n = 286$, 87.2%) or inpatient 3-month intensive physiotherapy program ($n = 5$, 1.5%). A minority of patients were on inpatient short-term (2 weeks) intensive physiotherapy immediately after BT injection ($n = 37$, 11.3%). BT dosage was not associated with physiotherapy (Coeff = 8.045; 95%CI = − 50.112/66.202; $p = 0.785$).

Nine patients (2.3%) underwent invasive (baclofen pump implant $n = 5$; tendon lengthening $n = 1$) or microinvasive (phenol neurolysis $n = 3$) interventions due to spasticity. BT dosage was not associated with these interventions (Coeff = 51.418; 95%CI = − 66.541/169.378; $p = 0.867$).

BT and MS clinical features

Each EDSS point was associated with 59 BT uDU more (Fig. 1a), with wheelchair-bound patients having 209 BT uDU more, than fully ambulatory patients. No association was found between disease duration and BT dose. Each MAS point was associated with 79 BT uDU more (Fig 1b) (in line with pre-defined injection goal, the muscle/muscle group with the highest MAS score was always injected). Lower BT dosage was used in younger patients (− 1.7 uDU/year), RRMS patients (− 60 uDU), when compared with PPMS and SPMS, in patients currently on DMT (− 53 uDU), when compared with those not on DMT, and in patients on their first BT injection (− 66 uDU), when compared with those who have received previous BT injections. Among MS patients who received previous BT injections ($n = 305$, 79.1%), when including the total number of BT injections in the regression model, BT dosage was 5 units higher on each BT injection (across 5.6 ± 5.8 injections). Lower BT dosage was used to treat spasticity-related pain (− 113 uDU), poor functioning in activities of daily living (− 146 uDU) and mobility difficulties (− 119 uDU), when compared with posturing hygiene and daily assistance. Reported side effects were associated with higher BT dosage (+ 269 uDU). Aforementioned units should be considered for OnabotulinumtoxinA (Botox®) and IncobotulinumtoxinA (Xeomin®), whilst 2.5 higher dose changes should be considered for AbobotulinumtoxinA (Dysport®). Results are reported in Table 4..

Discussion

We described BT injection characteristics, MS clinical correlates and concomitant treatments for the management of spasticity in the clinical practice of 19 Italian centres. The aforementioned results might provide useful information to treat spasticity in MS, with the ultimate goal of tailoring BT treatment according to patient-specific clinical features, and to design future clinical trials and observational studies

Table 2 Injection targets and characteristics. The table shows number of injection sites (per muscle or muscle group, with number of patients treated), doses, dilution (units of each BT formulation/mL of saline solution) and most commonly used guidance (mode), for each BT formulation, within each injected muscle or muscle group

Muscle or muscle group	Formulation	Sites Mean ± sd (range)	Dose Units ± sd (range)	Dilution (units/mL)	Guidance
Upper limb					
Adducted shoulder					
Pectoralis *(n = 28)*	oBTnA	1.7 ± 0.5 (1–2)	83.3 ± 23.5 (50–100)	100/2	EMG
	aBTnA	2.0 ± 0.7 (1–3)	193.3 ± 6.2 (125–300)	500/2.5	EMG
	iBTnA	2.2 ± 1.1 (1–4)	65.5 ± 43.2 (15–200)	100/2	EMG
Extended elbow					
Triceps *(n = 14)*	oBTnA	1.4 ± 0.5 (1–2)	58.1 ± 21.3 (25–100)	100/2	US
	aBTnA	1.0 ± 0.0 (1–1)	100.0 ± 50.0 (50–150)	500/2.5	US
	iBTnA	1.3 ± 0.5 (1–2)	55.3 ± 29.7 (25–100)	100/2	US
Flexed elbow					
Biceps *(n = 63)*	oBTnA	1.9 ± 0.6 (1–4)	80.1 ± 35.0 (25–170)	100/2	US
	aBTnA	1.8 ± 0.7 (1–4)	250.7 ± 99.3 (50–500)	500/2.5	US
	iBTnA	1.9 ± 0.9 (1–4)	70.6 ± 42.7 (20–200)	100/2	US
Brachialis *(n = 10)*	oBTnA	1.0 ± 0.0 (1–1)	50.0 ± 0.0 (50–50)	100/2	US
	aBTnA	1.0 ± 0.0 (1–1)	75.0 ± 50 (50–150)	500/2.5	US
	iBTnA	2.5 ± 0.5 (2–3)	62.5 ± 12.5 (50–75)	100/2	US
Brachioradialis *(n = 25)*	oBTnA	1.0 ± 0.0 (1–1)	40.6 ± 10.1 (25–50)	100/2	US
	aBTnA	1.0 ± 0.0 (1–1)	169.3 ± 93.5 (80–350)	500/2.5	US
	iBTnA	1.2 ± 0.4 (1–2)	40.0 ± 14.8 (20–60)	100/2	US
Flexed wrist					
Flexor carpi radialis *(n = 8)*	oBTnA	2.1 ± 0.5 (1–3)	55.7 ± 27.4 (25–100)	100/2	US
	aBTnA	2.0 ± 0.0 (2–2)	500.0 ± 0.0 (500–500)	500/2.5	US
	iBTnA	2.3 ± 1.1 (1–4)	68.7 ± 32.4 (25–100)	100/2	US
Flexor carpi ulnaris *(n = 9)*	oBTnA	1.0 ± 0.0 (1–1)	50.0 ± 0.0 (50–50)	100/2	US
	aBTnA	2.0 ± 1.0 (1–2)	250.0 ± 0.0 (250–250)	500/2.5	US
	iBTnA	1.5 ± 0.5 (1–2)	35.0 ± 15.0 (20–50)	100/2	US
Flexor digitorum superficialis *(n = 31)*	oBTnA	1.6 ± 0.7 (1–3)	64.0 ± 36.9 (20–150)	100/2	US
	aBTnA	2.1 ± 1.4 (1–5)	153.3 ± 136.1 (30–500)	500/2.5	US
	iBTnA	1.5 ± 0.6 (1–3)	31.0 ± 12.3 (10–50)	100/2	US
Clenched fist					
Flexor digitorum profundus *(n = 34)*	oBTnA	1.9 ± 0.8 (1–3)	80.0 ± 29.8 (50–150)	100/2	EMG
	aBTnA	2.7 ± 1.5 (1–5)	147.1 ± 70.0 (30–250)	500/2.5	EMG
	iBTnA	1.5 ± 0.9 (1–4)	41.0 ± 23.5 (15–100)	100/2	EMG

Table 2 (continued)

Muscle or muscle group	Formulation	Sites Mean ± sd (range)	Dose Units ± sd (range)	Dilution (units/mL)	Guidance
Lumbricales *(n = 8)*	oBTnA	4.0 ± 0.0 (4–4)	43.3 ± 14.9 (10–50)	100/2	US
	aBTnA	n/a	n/a	n/a	n/a
	iBTnA	4.0 ± 0.0 (4–4)	42.5 ± 7.5 (35–50)	100/2	US
Thumb-in-palm					
Flexor pollicis brevis *(n = 4)*	oBTnA	1.0 ± 0.0 (1–1)	15.3 ± 23.4 (10–50)	100/2	US
	aBTnA	n/a	n/a	n/a	n/a
	iBTnA	1.0 ± 0.0 (1–1)	20 ± 21.2 (5–50)	100/2	US
Flexor pollicis longus *(n = 11)*	oBTnA	1.6 ± 0.8 (1–3)	58.0 ± 21.3 (20–80)	100/2	US
	aBTnA	n/a	n/a	n/a	n/a
	iBTnA	1.0 ± 0.0 (1–1)	30.7 ± 21.6 (15–80)	100/2	US
Lower limb					
Flexed hip					
Iliopsoas *(n = 14)*	oBTnA	1.6 ± 0.9 (1–3)	41.6 ± 23.5 (25–75)	100/2	EMG
	aBTnA	1. ± 0.4 (1–2)	220.0 ± 146.9 (60–500)	500/2.5	EMG
	iBTnA	1.8 ± 0.4 (1–2)	84.0 ± 32.0 (20–100)	100/2	EMG
Adducted thigh					
Adductor *(n = 112)* *(longus/brevis/magnus)*	oBTnA	2.7 ± 1.5 (1–9)	116.1 ± 56.5 (20–250)	100/2	US
	aBTnA	2.7 ± 1.3 (1–7)	323.5 ± 162.5 (100–750)	500/2.5	US
	iBTnA	2.4 ± 1.0 (1–5)	97.3 ± 53.5 (10–250)	100/2	US
Extended knee					
Quadriceps *(n = 103)* *(rectus femori, vastus medialis and lateralis, sartorius)*	oBTnA	2.0 ± 1.0 (1–5)	83.3 ± 47.6 (20–200)	100/2	US
	aBTnA	2.0 ± 1.2 (1–6)	310.4 ± 166.7 (10–1000)	500/2.5	US
	iBTnA	2.0 ± 1.0 (1.6)	84.0 ± 66.7 (20–400)	100/2	US
Flexed knee					
Hamstring *(n = 58)* *(biceps femori long and short head, semitendinosus, semimembranosus)*	oBTnA	3.1 ± 0.3 (3–4)	96.8 ± 35.1 (30–150)	100/2	EMG
	aBTnA	2.4 ± 1.6 (1–8)	306.0 ± 167.2 (60–550)	500/2.5	EMG
	iBTnA	2.5 ± 1.1 (1–5)	138.8 ± 82.4 (30–300)	100/2	EMG
Equine foot					
Triceps surae *(n = 179)* *(medial and lateral gastrocnemius, soleus)*	oBTnA	2.7 ± 1.6 (1–8)	108.9 ± 56.6 (10–270)	100/2	US
	aBTnA	2.7 ± 1.5 (1–8)	411.3 ± 247.0 (75 ± 1500)	500/2.5	US
	iBTnA	2.8 ± 1.7 (1–7)	109.1 ± 56.6 (10–300)	100/2	US
Tibialis posterior *(n = 92)*	oBTnA	1.9 ± 0.7 (1–4)	64.6 ± 30.4 (35–200)	100/2	EMG
	aBTnA	2.0 ± 1.0 (1–4)	271.2 ± 135.1 (100–750)	500/2.5	EMG
	iBTnA	1.5 ± 0.8 (1–4)	57.6 ± 23.7 (20–100)	100/2	EMG

Table 2 (continued)

Muscle or muscle group	Formulation	Sites Mean ± sd (range)	Dose Units ± sd (range)	Dilution (units/mL)	Guidance
Flexed toes					
Flexor digitorum longus (*n* = 3)	oBTnA	n/a	n/a	n/a	n/a
	aBTnA	2.3 ± 0.9 (1–3)	233.3 ± 188.5 (100–500)	500/2.5	EMG
	iBTnA	n/a	n/a	n/a	n/a
Hitch-hiker toe					
Extensor hallucis longus (*n* = 19)	oBTnA	1.2 ± 0.4 (1–2)	47.5 ± 11.9 (30–70)	100/2	US
	aBTnA	1.3 ± 0.4 (1–2)	115.6 ± 41.3 (50–200)	500/2.5	US
	iBTnA	1.0 ± 0.0 (1–1)	22.8 ± 7.4 (10–30)	100/2	US

oBTnA, onabotulinumtoxinA (Botox®); *aBTnA*, abobotulinumtoxinA (Dysport®); *iBTnA*, incobotulinumtoxinA (Xeomin®); *EMG*, electromyography; *US*, ultrasound; *n/a*, not assessed

The novelties of this study were (1) the gathering of Italian BT and MS specialists in order to collect both BT injection characteristics and MS-related clinical features; (2) the recruitment of the largest described sample of MS patients treated with different BT formulations for spasticity, from a variety of injection clinics, giving a broad view across different settings (e.g. university, hospital, and community-based services) and (3) BT injection characteristics on different muscle groups around different joints, including shoulder, elbow, wrist, hand, hip, knee and ankle, that have not been fully considered in previous studies [10, 20].

Our population of MS patients with spasticity is in line with previous studies, reporting on relatively high prevalence of pain and interference with activities of daily living, and on the use of a variety of interventions (e.g. medications, physiotherapy, invasive and microinvasive interventions) [24]. Also, our population was composed of rather advanced MS patients, with progressive features and high disability, as expected in the presence of spasticity [2]. The use of BT was modulated based on different clinical features, with lower doses being applied in younger, ambulatory patients, in early phases of the disease and with mild spasticity. Interestingly, early consequences of spasticity (e.g. pain, mobility difficulties, poor functioning in activities of daily living) are relatively easy to address with low-dose BT injections, when compared with more advanced disease (e.g. with difficulties in hygiene and daily assistance) [18]. In our population, BT was used from the early stages of MS; previous evidence suggests that spastic syndromes should be treated early, before contractures

Table 3 Concomitant treatments for spasticity. Concomitant treatments for the management of spasticity are presented, as from the Italian consensus on treatment of spasticity in MS

Medication	MS patients (*n* = 218)		
Benzodiazepines		21	8.8%
Alprazolam	1		
Clonazepam	13		
Diazepam	4		
Lorazepam	3		
GABAergics		18	7.6%
Gabapentin	9		
Pregabalin	9		
Cannabinoids		60	25.2%
THC:CBD oromucosal spray	57		
Other	3		
Muscle relaxants		137	57.6%
Baclofen	124		
Tizanidine	13		
Others		2	0.8%
4-Aminopiridine	2		

Table 4 Demographic and clinical correlates of BT total dose. The table shows demographic and clinical characteristics (recorded at study inclusion, corresponding to BT injection), and their associations with BT unified dose units (uDU). Coefficients (Coeff), 95% confidence intervals (95%CI) and *p* values are presented from linear regression models and ordered regression models (for EDSS and MAS), as appropriate (*$p < 0.05$); EDSS, centre of injection and BT formulation were included as covariates. Coeffients relate to OnabotulinumtoxinA [oBTnA, Botox®] and IncobotulinumtoxinA (iBTnA, Xeomin®) units, whilst 2.5 higher dose should be considered for AbobotulinumtoxinA (aBTnA, Dysport®)

		Coeff	95%CI		*p* values
			Lower	Upper	
Age		− 1.746	− 3.063	− 0.430	0.009*
Sex		− 17.475	− 46.549	11.598	0.238
Disease duration		− 1.148	− 2.825	0.529	0.179
EDSS		0.591	0.431	0.751	< 0.001*
EDSS ≤ 3.5		Reference			
EDSS 4.0–6.5		81.190	− 67.091	229.473	0.282
EDSS ≥ 7.0		209.382	61.874	356.893	0.006*
Clinical subtype	PPMS	Reference			
	SPMS	10.671	− 28.139	49.481	0.589
	RRMS	− 60.371	− 107.608	− 13.134	0.012*
On treatment with DMT		− 53.957	− 89.113	− 18.801	0.003*
DMT type	1st line	Reference			
	2nd line	− 47.319	− 171.930	77.291	0.455
MAS		0.515	0.172	0.859	0.003*
BT naïve		− 66.255	− 106.204	− 26.306	0.001*
Total BT injections		5.167	2.035	8.299	0.001*
Injection goal	Daily assistance	Reference			
	Pain	− 113.207	− 183.544	− 42.870	0.002*
	Functioning	− 146.006	− 216.099	− 75.912	< 0.001*
	Hygiene	− 40.024	− 108.567	28.518	0.252
	Movement	− 119.661	− 179.855	− 59.466	< 0.001*
Concomitant spasticity treatments		43.576	12.306	87.401	0.022*
Reported side effects		269.030	71.169	466.892	0.008*

EDSS, expanded disability status scale (EDSS ≤ 3.5 corresponds to fully ambulatory patients; EDSS 4.0–6.5 corresponds to patients with limited ambulation; EDSS ≥ 7.0 corresponds to patients essentially restricted to wheelchair); *PPMS*, primary progressive multiple sclerosis; *SPMS*, secondary progressive multiple sclerosis; *RRMS*, relapsing-remitting multiple sclerosis; *DMT*, disease modifying treatments; *MAS*, modified Ashworth scale; *BT*, botulinum toxin; BT naïve, patients of their first BT injection; total BT injections, total number of reported BT injections

arise, spastic postures turn fixed and BT becomes ineffective [10, 37–39]. Indeed, early BT treatment could prevent fixed contractures, especially for muscles prone to shortening, so that the number and extent of later surgical interventions can be reduced [10, 37–39]. As such, disease duration was not associated with BT total dose, further suggesting that BT use largely depended on symptoms, rather than merely being a function of the disease duration. However, we cannot exclude that the uncertainty of disease duration in a retrospective study could be responsible, at least in part, for the lack of association.

Over time, higher BT doses were injected, in particular in wheelchair-bound patients, with higher disability (EDSS) and spasticity levels (MAS), and with the progressive phenotypes of the disease, also in combination with other anti-spastic medications. In such advanced disease stages, immunomodulatory treatments (DMTs) are not as effective as in the early phases of MS, and symptomatic treatments, including BT, remain of utmost importance to improve everyday functioning in activities of daily living and quality of life [3, 10–12]. In a survey of participants in the North American Research Committee on MS (NARCOMS) registry, BT was currently used in < 2% of MS patients with spasticity [24], whilst our results would suggest BT could be used on a much larger number of MS patients with spasticity.

In keep with the progressive nature of MS, injection goals were almost equally divided between the effects of spasticity on locomotor impairment (e.g. decreased mobility/function), and its consequences (e.g. hygiene issues, pain, difficulties in daily assistance). This result can be of particular relevance for

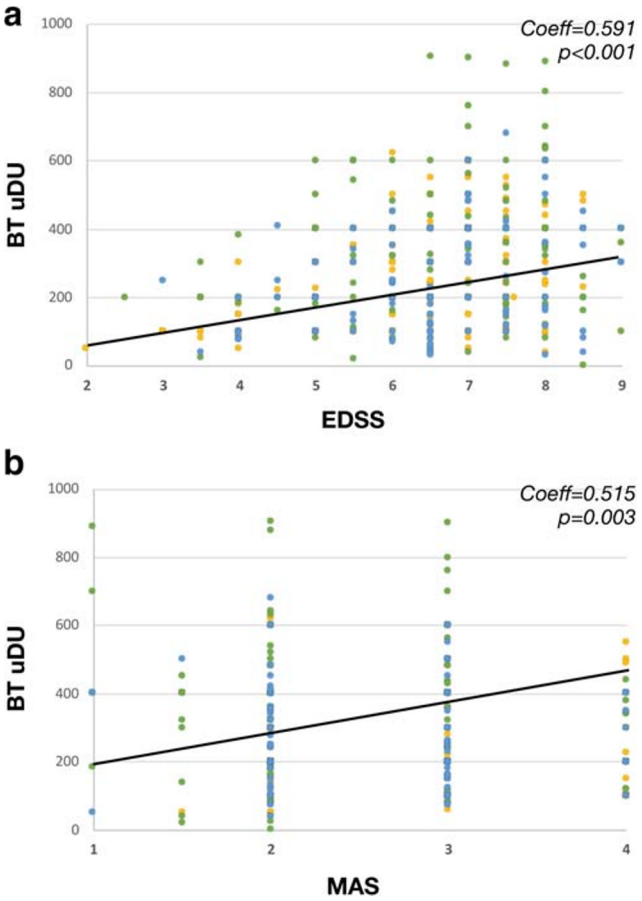

Fig. 1 Clinical correlates of BT dosage. Scatter plots show associations between BT dosage (unified dose units (uDU)) and EDSS (**a**), and highest MAS score (**b**). Coefficients (Coeff) and *p* values are reported from ordered regression models, adjusted by centre of injection, BT formulation and, for MAS, by EDSS. AbobotulinumtoxinA (Dysport®) is in green, IncobotulinumtoxinA (Xeomin®) is in blue or OnabotulinumtoxinA (Botox®) is in yellow

MS specialists, who often take into account the effects of spasticity on the motor system (e.g. EDSS), but not its broad-range clinical consequences that could be effectively treated with BT. Therefore, MS neurological interview and examination should include not only muscle rigidity and spasms, but also associated features of spasticity, uncovering symptoms that patients might not mention spontaneously [3]. Unfortunately, the cross-sectional design of the present study did not allow to evaluate whether the injection goal was actually achieved, which is warranted for future studies.

This study provided BT specialists with a detailed report of the preferred injection characteristics for MS patients. We presented sites of injection, dosage, most commonly used dilution and guidance, for each BT formulation, within each muscle or muscle group across all body segments (Table 2). These data could be used for designing future clinical trials and longitudinal studies aiming to specifically target MS-related spasticity with BT. In particular, future studies should define the main outcome measure based on specific muscles/muscle groups and injection goals, and should consider using average injection parameters we suggested. Moreover, inclusion/exclusion criteria should account for demographic and MS clinical features affecting BT injections (e.g. the same clinical effect could be achieved with lower dosage in younger RRMS patients, on their first BT injection). Not least, following our classification, clinical trials should include patient-reported outcome measures specific for each injection goal, providing regulatory agency also with perceived efficacy of BT on activities of daily life.

It is worth noting that BT injections were performed by using EMG and US guidance, possibly determining better muscle localization and clinical outcomes [40]; differences in EMG and US guidance could be explained by injection characteristics, with EMG generally preferred for injections in deep muscles (e.g. *tibialis posterior*). Also, we found a very limited number of patients reporting on transient side effects (e.g. weakness and hypophonia) that were associated with higher injection dosage; however, we must acknowledge that side effects were searched with an open question, possibly limiting side effects to most obvious and/or severe, and that concomitant DMTs (e.g. injectable medications) could have acted as confounding in side effect collection.

Similarly to other aetiologies of spasticity (e.g. stroke) [41], we observed the combination of nonpharmacological and pharmacological treatments. BT was used in combination with different medications, in particular anti-spastic agents acting on the GABAergic system (baclofen, pregabalin and gabapentin), and cannabinoids. In a limited number of cases, invasive or microinvasive interventions were also performed (phenol injection, baclofen pump implant). BT was frequently combined with physiotherapy that is generally thought to make people achieve the maximum benefit from the injection [18, 27, 39, 42]. However, BT dosage was not associated with concomitant physiotherapy, suggesting that the main goal of physiotherapy could have been mobility, active function and/or other MS symptoms (e.g. balance), along with spasticity. Adjuvant (nonpharmacological) treatments were not reported in our population [43].

The present study highlights the need of MS-specific knowledge for BT injections. In our MS population, BT dosage increased over time, possibly as a consequence of MS progression, rather than loss in BT efficacy, and exceeded regulatory suggestions, and national and international consensus statements. On the contrary, in nonprogressive aetiologies of spasticity (e.g. stroke), BT injections generally remain at lower dosage, and more pronounced effects have been described over time [19]. Interval between BT injections (4.3 ± 3.0 months) was higher than general recommendation of 90 days, possibly in relation to a number of factors that can affect spasticity over time in MS (e.g. weather, fatigue, stress, anxiety and, not least, disease progression) [44–46]. As such, spasticity should be carefully assessed on each injection and,

if necessary, BT injections could be delayed and/or require up-to-date characteristics. Not least, BT specialists should be aware of MS-specific clinical features possibly affecting injection characteristics (e.g. EDSS, disease course).

The main limitation of the present study is its cross-sectional design, not assessing injection effects (e.g. change in MAS before and after 10 days/9 weeks), and patient satisfaction. However, we aimed to describe the clinical practice of BT use and, based on this, further longitudinal studies could be better planned. Also, BT is used to treat MS symptoms other than spasticity (e.g. neurogenic detrusor overactivity and tremor) [47, 48] that were out of the scope of this paper. BT structure (large double-stranded protein) could be antigenic and could interfere with MS inflammatory activity [10], but this would need to be investigated prospectively. Not least, the use of the highest MAS score artificially inflated the reported severity of the spasticity, and more reliable scales could have been used for the global load of spasticity (e.g. REsistance to PASsive movement (REPAS) scale) [49]. Follow-up would have been necessary also to evaluate long-term efficacy of BT in MS, considering that a previous study described a relatively high discontinuation rate to BT in MS (56% after 1.2 years) [27]. We included different clinical settings (e.g. university, hospital, and community-based services), but did not evaluate differences in practice characteristics; however, this was not an objective of our study, and could be examined in the future by including BT injections for different indications and a more detailed description of injection centre characteristics.

In conclusion, we described the clinical practice for treating MS spasticity with BT. BT is a common treatment for the management of a variety of spasticity-related symptoms in patients with MS. MS specialists and everyone involved in the management of MS patients (e.g. physiotherapy departments, GPs) should be aware that BT therapy can be used from the early stages of MS, when spasticity is more focal, also as a stand-alone treatment, and can be continued as symptoms progress, along with additional anti-spastic treatments. MS-specific goals and injection characteristics can be used to tailor BT treatment, moving towards personalized medicine. In the future, based on present findings, longitudinal studies are warranted to better profile the therapeutic spectrum of BT in the management of MS spasticity symptoms.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethics approval was obtained from the committee of "Federico II" University of Naples, Italy. The study included anonymized data collected in the clinical practice and was conducted in accordance with good clinical practice and the Declaration of Helsinki.

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