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Efficacy and safety of higher doses of botulinum toxin type A NT 201 free from complexing proteins in the upper and lower limb spasticity after stroke

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Abstract Botulinum toxin type A (BTX-A) represents the gold standard therapy for focal spasticity after stroke, with low prevalence of complications, reversibility, and efficacy in reducing spastic hypertonia. Current guidelines suggest the employment of a dosage up to 600 units (U) of BTX-A to treat spasticity after stroke, to avoid important adverse effects and the development of antibodies against the neurotoxin. In recent years, NT 201, a new BTX-A free of complexing proteins, has been used for treating several movement disorders, showing safety and efficacy in upper limb spasticity. In a prospective, non-randomized, open-label study, we studied the efficacy and safety of higher doses of BTX-A NT 201 (up to 840 U) in 25 consecutive patients with upper and lower limb spasticity after stroke, evaluated at 30 and 90 days after injections. Before and after the treatment, the grade of spasticity, the disability, and spasticity-related pain were extensively measured. After 30 days of follow-up, a great reduction of spasticity and pain with improvement of disability was observed. The effects were still present at 90 days of follow-up. No major adverse events were observed. Higher doses of BTX-A NT 201 appeared to be safe and efficacious in patients with upper and lower limb spasticity after stroke. However, further investigations are needed to determine its reproducibility in larger case series or randomized clinical trials and to observe the absence of antibodies against the neurotoxin also after repeated injections.

Keywords Botulinum toxin type A free of complexing proteins · NT 201 · Spasticity · Disability · Higher doses · Stroke

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Introduction

Several studies have been published on the employment of incobotulinum toxin A (NT 201; Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany), free of complexing proteins, for the treatment of spasticity of various etiologies such as stroke, brain injury, multiple sclerosis, or cerebral palsy (Barnes et al. 2010; Kaňovský et al. 2011). All these reports showed the safety and efficacy of this new formulation of botulinum toxin type A (BTX-A) with few and transitory adverse events. In particular, for post-stroke spasticity, the patients enrolled in a recent study were submitted to administration of BTX-A NT 201 to treat wrist and elbow spasticity in a clinical picture with clenched fist and thumb in palm and with a maximum dose injected of 400 units (U) (Kaňovský et al. 2011). After the treatment, the patients reported a reduction of muscle tone

and an improvement of functional disability measured, respectively, with Ashworth Scale (AS) (Ashworth 1964; Brashear et al. 2002a) and Disability Assessment Scale (DAS) (Brashear et al. 2002a). NT 201, a highly purified BTX-A formulation, is free from complexing proteins and thus expected to be associated with a lower risk of immunogenicity and reduced numbers of secondary non-responders (Frevert 2009). To the best of our knowledge, at present, only one cross-over study investigated the effect of higher doses of BTX-A NT 201 in post-stroke spasticity (Dressler 2009). In the present prospective, non-randomized, open-label study, we described the safety and efficacy of higher doses (up to 840 U) of BTX-A NT 201 in patients with upper and lower limb spasticity after stroke.

Methods

Consecutive outpatients with stable upper and lower limb spasticity resulting from a stroke at least 6 months before the enrollment, attending the Department of Physical Medicine and Rehabilitation, University of Foggia, Foggia, Italy from January 2010 to July 2011 were invited to participate in the study and were screened for study eligibility. A clinical pattern with AS $\geq$2 concerning spasticity of elbow (E), wrist (W), finger (F), and ankle (A) flexors was considered for treatment (Ashworth 1964; Brashear et al. 2002a). Patients were also evaluated considering their disability related to spasticity and measured with DAS, and spasticity-related pain measured with visual analog scale (VAS) (Price et al. 1994). At the screening, patients together with investigators chose their individual primary therapeutic target among dressing, limb position, pain, or hygiene (Brashear et al. 2002a). A DAS score $\geq$2 was the primary therapeutic target. Patients pre-treated with other formulations of botulinum toxin were included if they were stable responders.

Subjects were excluded from the study if they met any of the following criteria: fixed contractures and/or deformities at the shoulder, elbow, and wrist, previous fractures of the paretic upper limb, cognitive impairment, peripheral nervous system disorders/myopathies, and medications that could have had an impact on the study findings (e.g., intrathecal baclofen, benzodiazepines, muscle relaxants, previous treatment of spasticity with phenol or alcohol injection ,or surgery in the target limb). Moreover, no patients with structural alterations in the soft tissue as fibrosis were enrolled. To exclude the patients, during the first evaluation, a sonographic measurement was performed on the spastic muscle of upper and lower limbs. At the end of evaluation, 25 of 40 consecutive patients (16 men and 9 women, age range 45–71 years) who fulfilled the selection criteria were enrolled in the study. After complete description of the study, written informed consent was obtained from all subjects and/or their relatives.

Patients received one set of injections of BTX-A NT 201, in their hypertonic upper and lower limb. The dose was chosen considering previous studies describing a dose ratio of 1:1 for BTX-A NT 201 to another conventional BTX-A complex product (Botox®) (Jost et al. 2005; Dressler 2009) and considering several muscles involved in the individual clinical picture. NT 201 was administered with 2 mL of 0.9 % dilution saline and the maximum total dosage in the upper and lower limbs was 840 U (ranged from 750 to 840 U) (Table 1). NT 201 was injected into the upper limb muscles using a dosage of maximum 540 U distributed in the shoulder adductor major pectoralis (ranged from 50 to 80 U), elbow flexors (biceps brachii and brachioradialis) (ranging from 130 to 200 U), pronators teres (ranging from 50 to 70 U), wrist flexors (flexor ulnaris carpi and flexor radialis carpi) (ranging from 80 to 140 U), finger and thumb flexors (flexor superficialis digitorum, flexor profundus digitorum, flexor longus pollicis, and abductor pollicis brevis) (ranging from 120 to 240 U, totally) (Table 1). A dosage of maximum 340 U was administered into the lower limbs (ranging from 250 to 340 U) distributed in the ankle plantar flexors (gastrocnemius medialis, gastrocnemius lateralis, and soleus) (ranging from 140 to 230 U), adductor longus–brevis–magnus (ranging from 50 to 80 U), rectus femoris (50 or 60 U), biceps femoris (50 U), posterior tibialis (ranging from 30 to 50 U), anterior tibialis (30 U), flexor digitorum longus (30 or 40 U), flexor hallucis longus (ranging from 20 to 40 U), and extensor hallucis longus (30 or 40 U) (Table 1). The number of injection sites per muscle and the dose injected into each muscle were determined at the discretion of the investigator. Injections were performed under sonographic guide. Then, the patients participated in a rehabilitation program consisting of stretching exercises of the muscles injected for 10 days to improve the paralytic effect of neurotoxin. All the 25 patients who entered in the study protocol completed the study. To evaluate the effect of BTX-A NT 201, changes in AS and DAS scores were analyzed after 30 and 90 days, considering a reduction of about $\geq$1 point of score as efficacy of treatment, similar to other studies on spasticity measurement (Brashear et al. 2002b). Before treatment and during follow-up, each patient was examined by the same investigator. Investigators and patients rated the efficacy of the treatment using a nine-point scale (global assessment of treatment response, GATR) ranging from $+4$ = very marked improvement to -4 = very marked worsening after 1 month. A physical and neurological examination was performed after 2 weeks to evaluate safety, excluding adverse events.

All analyses were performed using SPSS for Windows, version 6.1. Difference between baseline (t_0) and post-

Table 1 Individual dosages (in units, U) of botulinum toxin type A NT 201 administered in single muscles patients with upper and lower limb spasticity after stroke

Patients	MP	BB	BR	PT	FSD	FPD	FUC	FRC	FLP	ABP	ADD LBM	RF	BF	GM	GL	SOL	PT	AT	FDL	FHL	EHL	Total
1		100	50	50	70	50	100		30					70	70	80	40		40	40		790
2	50	80	50	50	100	100	80		30		60			70		80			40	30		820
3	80	100	50	60	100	50	100		30					70	70	80	40					820
4		100	50	50	80	50	100			30				80	70	80	30	30	30	20		800
5	50	100	50		70	70		100		30				80		80	50	30	40	30		780
6	50	80	50	50	80	50	80				80	60		70		70	40				40	800
7	80	100	50		100		80			30			50	70	70	80	30		40	30		810
8	50	100	50	70	80	50	100		30		60			70	70	70					30	830
9	80	100	70		100		80	50				50		70		80	50	30				790
10		80	80	60	80	80	80		30					70		80	40				40	820
11	60	100	50		100	50	100		30				50	70	50	70			40	30		800
12	80	100	50	60	80	50	100		30		80			70		80	40					820
13	50	100	50	50	80		80	80						70	70	70	30	30	40	30		830
14		100	50		80	80	80	70	30		50	60		70	70	70						810
15	40	100	50	50	80	70	80		30			50		70	70	80					30	800
16		80	80	60	100	50		100			80			70		80	50		40			790
17	50	150	50		100	50	100	50	30					70	70	80						800
18	60	100	100	40	70	50	100							70	70	70	40	30				800
19	80	150		50	100		50	50						70		80	50		40	30		750
20		150	50	50	80	80	80		30		60			70	70	80						800
21	50	80	80		100	50	100							70		80	50	30	40	30		760
22	50	100	50	60	80	70	70	70						70		80	50		40	30		820
23	60	80	80	60	100	50	80		30		80			70	70	80						790
24	50	100	50		100	100	100		40		80			70	70	80						840
25	50	150	50		100	50	80	80						80		80	50	30				800

MP major pectoralis, *BB* biceps brachii, *BR* brachioradialis, *PT* pronator teres, *FSD* flexor superficialis digitorum, *FPD* flexor profundus digitorum, *FUC* flexor ulnaris carpi, *FRC* flexor radialis carpi, *FLP* flexor longus pollicis, *ABP* abductor pollicis brevis, *ADD LBM* adductor longus–brevis–magnus, *RF* rectus femoris, *BF* biceps femoris, *GM* gastrocnemius medialis, *GL* gastrocnemius lateralis, *SOL* soleus, *PT* posterior tibialis, *AT* anterior tibialis, *FDL* flexor digitorum longus, *FHL* flexor hallucis longus, *EHL* extensor hallucis longus

treatment outcome measure scores (t_1 30 days and t_2 90 days) was computed by t Student's test. The level of statistical significance was set as $p < 0.05$.

Results

The majority of patients injected were classified as treatment naïve (64 %). In fact, of the 25 patients enrolled, only 9 were treated previously with another BTX-A formulation. The maximum dose use for these patients in the previous BTX-A treatment was 580 U distributed into the upper and lower limbs from about 2 years, every 3 months. The mean time (standard deviation, SD) between the last BTX-A injection and the administration of NT 201 was 3.3 (1.2) months. The mean time (SD) from the onset of stroke in months was 32.4 (8.3). In Table 2, we reported individual baseline (t_0) and post-treatment (t_1 30 days and t_2 90 days) outcome measure scores (AS, DAS, VAS, and GATR) in patients with upper and lower limb spasticity after stroke treated with higher doses of BTX-A NT 201. Patients reported an improvement of their clinical picture concerning spasticity of muscles injected evaluating the decrement of at least 1 point on the AS for elbow, wrist, fingers, and ankle flexor muscles. In fact, the analysis showed a statistically significant decrease evaluated after 30 and 90 days from the treatment ($p < 0.05$) (Table 3). For functional disability measured with DAS, 48 % of patients chose limb position as main target, following by pain (24 %), hygiene (16 %), and dressing (12 %). An improvement of DAS score and spasticity-related pain measured with VAS were observed for all patients. Table 1 shows the mean DAS and VAS score with a statistically significant decrease evaluated after 30 and 90 days from the treatment ($p < 0.05$). Both patients and investigators considered the treatment to be effective. However, the rate of response was higher for investigators than patients. In fact, considering spasticity, pain, and other primary targets on DAS, 40 % of investigators and 28 % of patients rated their clinical picture as "marked improvement" (Fig. 1). Adverse events were monitored 2 weeks after treatment with BTX-A NT 201, and only four patients (16 %) experienced treatment-emergent adverse events (injection site pain 1, muscular weakness 4). All these adverse events were mild and resolved in a few days.

Discussion

The present study with higher doses of BTX-A NT 201 in patients with upper and lower limb spasticity after stroke confirmed previous findings suggesting that BTX-A NT 201 injections can improve functional disability and muscle tone in patients with spasticity of various etiologies (Barnes et al. 2010; Kaňovský et al. 2011).

Many studies and meta-analyses demonstrated that BTX-A injections represent the gold standard for the treatment of focal spasticity (Brashear et al. 2002b; Simpson et al. 1996; Rosales and Chua-Yap 2008; Simpson et al. 2009). A recent European consensus established that a dose of about 600 U may be safe and well tolerated in post-stroke spasticity (Wissel et al. 2009). Other studies suggested that higher doses of BTX-A can increase the risk of the development of antibodies to extraneous clostridial proteins present in the toxin preparation, directed against the core neurotoxin, interfering with pharmacological activity, potentially leading to loss of clinical efficacy, and reducing the therapeutic effect partially or completely (Jankovic and Schwartz 1995). NT 201, a highly purified BTX-A formulation, is free from complexing proteins, and thus might be associated with a relatively low risk of immunogenicity. This may be of therapeutic advantage for a long-term treatment with higher doses (Jost et al. 2007; Frevert 2009). Usually, higher doses of BTX-A can be used to treat severe spasticity, although controversy also exists about improvement in motor function relative to improvement in spasticity. It is known that low doses of BTX-A can be used to increase motor function in those patients affected by spasticity graded 1 or 2 as measured by AS. This scale represents a useful tool to measure muscle tone and a higher score of AS suggests severe spasticity related to a few motor functions of involved limbs as measured also by DAS. Although in the case of severe spasticity, the improvement in active performance is sometimes difficult to obtain, higher doses can be used, for example, to improve limb posture, to apply splinting, to consent to manage personal hygiene, to increase passive articular range of motion, and to walk and stand in patients with spastic equinovarus foot deformities, improving joint range of motion and muscle extensibility (Hesse et al. 1996) or to reduce spasticity-related pain.

In the present study, treatment with doses of BTX-A NT 202 up to 840 U resulted in statistically significant improvement in muscle tone and spasm reduction, as well as in patients' primary functional disability domains or principal therapeutic intervention targets. Previous reports have shown that BTX-A NT 201 was safe and efficacious as other neurotoxin formulations in the treatment of movement disorders, also reducing muscular tone (Jost et al. 2005; Benecke et al. 2005; Roggenkamper et al. 2006), whereas other recent studies have confirmed the safety and efficacy of a dose of about 400 U to treat upper limb spasticity as measured with AS and DAS (Barnes et al. 2010; Kaňovský et al. 2011). To the best of our knowledge, at present, the employment of higher doses of this new BTX-A formulation was investigated only in one

Table 2 Individual baseline (t_0) and post-treatment (t_1 30 days and t_2 90 days) outcome measure scores in patients with upper and lower limb spasticity after stroke treated with higher doses of botulinum toxin type A NT 201

Patients	AS E t_0	AS E t_1	AS E t_2	AS W t_0	AS W t_1	AS W t_2	AS F t_0	AS F t_1	AS F t_2	AS A t_0	AS A t_1	AS A t_2	DAS t_0	DAS t_1	DAS t_2	VAS t_0	VAS t_1	VAS t_2	P GATR t_1	I GATR t_1
1	3	2	2	3	2	2	2	1	1	4	3	3	3	2	2	5	1	3	0	2
2	3	2	2	3	2	2	3	1	1	3	2	2	3	2	2	5	1	2	0	3
3	4	3	3	3	2	2	3	2	2	4	2	3	3	2	2	7	2	2	−1	3
4	4	3	3	4	3	3	3	1	1	4	4	4	2	1	1	5	2	2	4	3
5	4	2	2	4	2	2	3	2	2	4	2	2	2	2	2	6	3	3	0	4
6	3	1	2	3	1	1	2	1	1	3	1	1	2	1	2	5	2	2	2	4
7	4	3	3	4	2	2	2	1	1	4	2	2	3	2	2	4	2	3	2	4
8	4	2	3	4	3	3	3	2	2	4	2	2	3	2	1	3	2	3	−2	2
9	4	3	2	4	3	2	3	2	2	4	3	2	3	2	2	4	1	1	−1	2
10	3	3	2	3	2	2	4	3	3	3	2	2	3	2	2	4	3	3	3	3
11	4	3	3	4	2	2	4	3	3	4	3	2	2	1	2	5	1	1	3	2
12	4	3	3	4	3	3	3	2	2	4	3	3	3	2	3	7	3	3	3	4
13	4	2	3	4	3	3	2	1	1	4	2	3	3	2	2	5	2	2	0	2
14	4	2	3	4	2	3	3	1	1	4	2	3	3	2	3	7	2	4	2	3
15	3	2	2	3	1	1	3	1	1	3	2	2	2	1	2	4	2	3	−1	3
16	3	2	1	3	1	1	3	3	2	3	2	1	2	2	2	4	2	2	−1	2
17	4	2	2	4	3	3	3	2	2	4	3	2	2	1	1	7	3	3	3	3
18	4	2	3	3	2	2	2	1	1	4	3	3	3	2	2	3	1	2	3	3
19	3	2	1	2	1	1	2	1	1	3	2	1	3	1	1	5	3	2	3	4
20	4	3	3	2	2	2	3	2	2	4	3	3	2	1	1	7	2	2	2	4
21	3	1	1	3	1	2	3	2	2	3	2	2	3	3	3	4	3	3	2	4
22	3	1	1	3	2	2	3	2	2	3	2	2	2	2	2	6	3	3	4	3
23	3	3	2	2	1	1	3	2	2	3	3	2	3	2	2	5	4	3	-1	3
24	4	2	3	3	2	2	4	3	3	4	2	3	3	1	1	7	4	3	3	2
25	4	3	3	3	2	2	4	3	3	4	2	2	3	1	1	5	2	2	4	4

AS Ashworth Scale, *E* elbow, *W* wrist, *F* finger, *A* ankle, *DAS* disability assessment scale, *VAS* visual analog scale, *GATR* global assessment of treatment response, *P* patients, *I* investigators

Table 3 Difference between baseline (t_0) and post-treatment outcome measure scores (t_1 30 days and t_2 90 days) in all outcome measures in patients with upper and lower limb spasticity after stroke treated with higher doses of botulinum toxin type A NT 201

	t_0 ($N = 25$)	t_1 ($N = 25$)	t_2 ($N = 25$)
AS E			
Mean ± SD	3.6 ± 0.5	2.3 ± 0.7	2.3 ± 0.7
95 % CI	3.4–3.8	2–2.6	2–2.6
T		7.8	7.1
p value		0.0000	0.0000
AS F			
Mean ± SD	2.8 ± 0.6	1.7 ± 0.7	1.7 ± 0.6
95 % CI	2.6–3.1	1.4–2	1.4–2
T		5.8	6.2
p value		0.0000	0.0000
AS W			
Mean ± SD	3.3 ± 0.7	2 ± 0.7	2 ± 0.7
95 % CI	3–3.6	1.7–2.3	1.7–2.3
T		6.5	6.5
p value		0.0000	0.0000
AS A			
Mean ± SD	3.6 ± 0.5	2.4 ± 0.6	2.2 ± 0.7
95 % CI	3.4–3.8	2.1–2.6	1.9–2.6
T		7.9	7.6
p value		0.0000	0.0000
DAS			
Mean ± SD	2.6 ± 0.5	1.7 ± 0.6	1.8 ± 0.6
95 % CI	2.4–2.8	1.4–1.9	1.6–2.1
T		6.5	5
p value		0.0000	0.0000
VAS			
Mean ± SD	5.2 ± 1.3	2.2 ± 0.9	2.5 ± 0.7
95 % CI	4.6–5.9	1.9–2.6	2.2–2.8
T		9.4	9.1
p value		0.0000	0.0000

E elbow, *F* fingers, *W* wrist, *A* ankle, *AS* Ashworth Scale, *DAS* disability assessment scale, *VAS* visual analog scale

AS, DAS, and VAS values are shown as mean ± SD. Values after 30 days (t_1) and 90 days (t_2) of administered treatment (t_3) for AS, DAS, and VAS were compared with baseline (t_0)

cross-over study in which 74 patients with post-stroke spasticity were previously treated with Botox® for at least 1 year in stable condition before entering into the study and converted in a blinded fashion to BTX-A NT 201 (the maximum dose applied was 840 U), throughout a 3-year period and using a 1:1 conversion ratio and identical treatment parameters (Dressler 2009). This study showed no subjective or objective differences between these two neurotoxin formulations with respect to onset latency, maximum duration of their therapeutic effects, and their adverse effect profiles, with long-term use not revealing additional relevant safety concerns (Dressler 2009). In the present report, considering as responders patients with a reduction ≥1 point of AS and DAS scores from baseline (clinical improvement), a great reduction was obtained after only one set of injections, and these effects lasted for 90 days with a few adverse events. Comparing the present findings with other open-label studies with similar outcome measures and injection intervals (70–90 days), we found a higher proportion of patients reporting a clinical improvement in muscle tone and functional status than patients treated with 400 U of BTX-A NT 201 (Kaňovský et al. 2011) or 255 U of Botox® (Slawek et al. 2005). In a follow-up of 30 days, both patients and investigators considered efficacious the treatment, as measured with GATR. However, the rate of response was higher for the investigators than the patients. This finding can be explained with the expectations of the patients who would like to obtain a very marked improvement with the treatment with BTX-A on their main targets. The efficacy of treatment of post-stroke spasticity with 400 U of BTX-A NT 201 was rated as very good or good by the majority of investigators, patients, and carers also in another recent open-label study (Kaňovský et al. 2011). Safety was analyzed for all patients enrolled in the present study after 2 weeks. All adverse effects related to the treatment were mild, i.e., injection site pain and muscular weakness. Thus, several reports described these side effects also with low doses of BTX-A injections. These adverse effects usually resolved in a few days (Barnes et al. 2010; Kaňovský et al. 2011).

Spasticity-related pain is one of the main targets for BTX-A treatment, with potential worsening of activities of daily living. In fact, an effect on spasticity-related pain is required also as one of the primary targets of DAS in patients enrolled in many studies on spasticity. The analysis of VAS in our patients treated with higher doses of neurotoxin showed a reduction of the score. Sjölund (2002) referred that pain may be due to processes in sensory systems equivalent to those causing spasticity in motor systems. Other authors suggested that pain in spasticity could be generated in case of complex regional pain syndrome, based on central sensitization of pain transmission in neurons throughout the nervous system effected by *N*-methyl-D-aspartic acid complex mechanisms and a major immune contribution from activated glial and astrocyte secretion of chemokines and cytokines that maintained and augmented the process (Schwartzman et al. 2006). Several reports showed the analgesic effect of BTX-A on central pain, inhibiting neurogenic inflammation by attenuation of neurotransmitter release (glutamate, substance P, and calcitonin-gene related peptide), prevention of capsaicin receptor increase, and therefore resulting in the inhibition of peripheral sensitization. The inhibition of peripheral

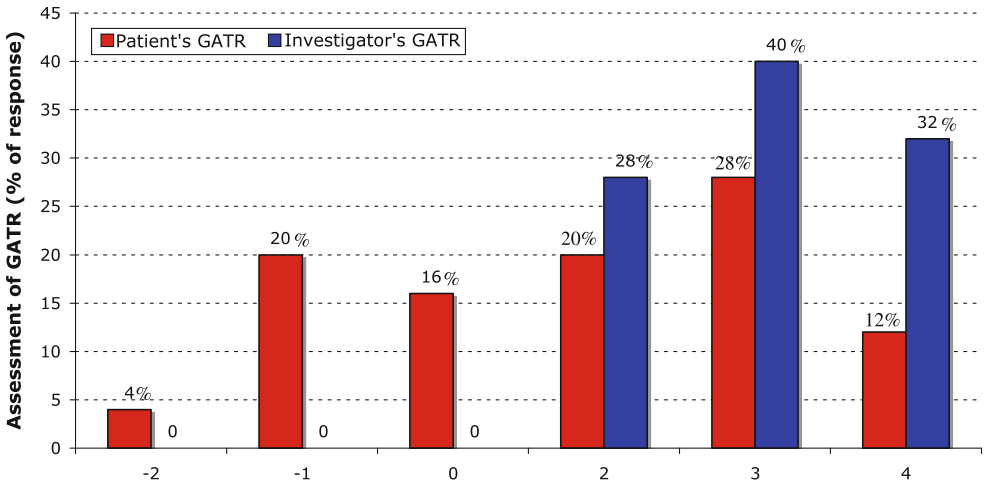

Fig. 1 Global assessment of treatment response (GATR) of patients and investigators at day 30 compared with baseline (full analysis set). GATR scale: −4 = very marked worsening, −3 = marked worsening, −2 = moderate worsening, −1 = mild worsening, 0 = no change, +1 = mild improvement, +2 = moderate improvement, +3 = marked improvement, +4 = very marked improvement

sensitization would reduce the transmission of nociceptive signals into the spinal cord (Aoki 2005).

A recent European consensus on the use of BTX-A in adult spasticity suggests that, at present, there is little information on the measures that can modify and/or increase the efficacy of botulinum toxin injections (Wissel et al. 2009). Electrical stimulation of the nerve or the injected muscles and muscle activity itself can increase the efficacy of BTX-A. Also, physiotherapy including muscle stretching, casting, taping, or splinting is able to act in the same way (Wissel et al. 2009). In the present study, the patients participated in a rehabilitation program consisting of stretching exercises of the muscles injected for 10 days to improve the paralytic effect of neurotoxin. For the length of stretching exercises, at present, there is no golden standard both for this kind of intervention alone or after BTX-A injections in patients with spasticity. A systematic review on this issue suggested that stretching protocols without previous BTX-A treatment were generally inadequately described and poorly standardized, with a wide diversity in studies investigating the effects of stretching on spasticity (Bovend'Eerdt et al. 2008). In particular, some randomized clinical trials (RCTs) for the treatment of spasticity in post-stroke (Baricich et al. 2008; Carda et al. 2011) or multiple sclerosis (MS) patients (Giovannelli et al. 2007) used a rehabilitation program of stretching exercises after BTX-A injections with a range from 7 to 15 days, therefore consistent with the length of our rehabilitation program.

Among limitations of this study, we must acknowledge the lack of a control group, a brief period of follow-up, and the open-label nature of the study in patients' evaluation and assessment and treatment. Furthermore, a recent European consensus on the use of BTX-A in adult spasticity suggested that some RCTs had shown deeply localized or small muscle needle placement, based solely on anatomical landmarks, was unsatisfactory and most muscles were only correctly located in less than 50 % of cases (Wissel et al. 2009). Therefore, injection guidance with electrical stimulation/EMG or sonography for deep-seated muscles may be a better alternative and should be a standard practice. In the present study, injections were performed under sonography guidance, an approach in which the needle is inserted more precisely, knowing the muscle depth, avoiding other near muscles, and identifying muscle fibrosis for injecting BTX-A in other muscle areas. Although there are only few studies comparing electrical stimulation/EMG or sonography (Yelnik et al. 2010), muscle targeting by EMG or electrical stimulation, while effective, can be difficult, is time-consuming, and may cause discomfort and thus is not always carried out in a routine clinical setting (Wissel et al. 2009), although practice does vary between countries. Moreover, several sets of higher doses of BTX-A NT 201 must be administered to exclude with certainty the adverse events and the development of toxin's antibodies evoked by higher doses. In conclusion, similarly to previous studies, with a maximum dose of 400 U of incobotulinum toxin A, also the administration of one set of higher doses of BTX-A NT 201 resulted in substantial improvements in functional disability, spasticity-related pain, and muscle tone with few and transitory adverse effects.

Conflict of interest The authors report no conflicts of interest.

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