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# Safety and efficacy of incobotulinum toxin type A (NT 201-Xeomin) for the treatment of post-stroke lower limb spasticity: a prospective open-label study

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***Background*. In recent years, NT 201, a new botulinum toxin type A (BTX-A) free of complexing proteins, has been used for treating several movement disorders, showing safety and efficacy in upper limb spasticity.**
***Aim*. To assess the safety and evaluate the effects of BTX-A NT 201 free from complexing proteins for the treatment of post-stroke lower limb spasticity evaluating spasticity grade, passive ankle dorsi-flexion motion, and muscle's spasms, as well as its efficacy and rate of satisfaction for patients and for the physicians.**
***Design*. Prospective open-label study.**
***Population*. Patients (71) with post-stroke lower limb spasticity at least 5 months by the event.**
***Methods*. Intramuscular injections of BTX-A NT 201 in soleus, medial, and lateral gastrocnemius with a maximum total dose of 180 U. Each patients was assessed at baseline, 30, and 90 days after treatment using Modified Ashworth Scale, Spasm Frequency Scale, evaluating passive ankle dorsi-flexion motion, and the rate of satisfaction for patients and investigators.**
***Results*. Patients treated with BTX-A NT 201 reported a statistically significant reduction in muscle tone and spasms daily increasing passive ankle dorsi-flexion at 30 days, persisting also at 90 days of follow-up.**
***Conclusion*. BTX-A NT 201 for the treatment of post-stroke lower limb spasticity was safe and efficacious reducing muscle tone and spasms, and improving passive ankle dorsi-flexion movement.**
***Clinical rehabilitation impact*. These results confirmed the safety and effectiveness of a new type of BTX-A, with low immunogenity, useful to improve rehabilitative treatment of post-stroke lower limb spasticity**

**KEY WORDS:** Botulinum toxins, type A - Muscle spasticity - Spasm.

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In patients with lower-limb spasticity after stroke, spastic equinus foot represents a prolonged abnormal lower limb posture and can leads to substantial deformity, affecting gait, standing, mobility, transfer, and hygiene, contributing to pressure sores and pain, and interfering with the activities of daily living and tolerance of orthoses.[1]

In the rehabilitation setting of stroke survivors, the main goal is the reduction of hypertonia, so to increase the mobility and range of motion, and improve hygiene, and other functional activities.[2] Many approaches are available even if botulinum toxin type A (BTX-A) is proposed as the pharmacological treatment of first choice for focal spasticity. Botulinum toxin reduces spasticity in selected muscles blocking acetylcholine release at the neuromuscular junction.[3, 4] The effect lasts for about 3-4 months. The temporary reduction of muscle tone allows physical and occupational therapy, such as

muscle strengthening and facilitation, increasing articular range of motion, retraining of ambulation and gait, improving function in the activities of daily living, and the tolerance of orthoses. A lot of muscles are responsible of spastic equinus foot (*e.g.*, medial and lateral gastrocnemius, soleus, posterior tibial, flexor longus digitorum, and extensor hallucis) even if both gastrocnemius and soleus are most frequently involved in this typical pattern and then treated with BTX-A, to reduce plantar flexion forces and the drive to plantar flexion.[5] Past randomized controlled trials (RCTs) have investigated the effects of lower limb BTX-A injections on spasticity and walking in post-stroke patients and have found significant reductions in spasticity but no significant improvements in walking ability.[6-9] Only one RCT demonstrated a significant improvement in walking speed and function; however, it was a small change.[10] Other open-label studies used complex gait analysis to determine changes in walking ability post-BTX-A injections in stroke patients [11] and upper motor neuron syndrome,[12] with trends towards improvement in walking speed and function but no significant changes.

In the last years, a new type of BTX-A, with low immunogenity has been produced to reduce the risk of secondary non-responders patients. 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 after stroke.[13, 14] In these reports, the safety and the efficacy of this new formulation of BTX-A with few and transitory adverse events have been demonstrated. The patients enrolled in these studies were submitted to administration of BTX-A NT 201 to treat upper limb spasticity, with a maximum dose injected of 400 U. After the treatment, the patients reported a reduction of muscle tone and an improvement of functional disability measured respectively with Modified Ashworth Scale (MAS) [15] and Disability Assessment Scale. To the best of our knowledge, at present, there was a lack of studies investigating the effect of BTX-A NT 201 injections for the treatment of lower limb spasticity after stroke. The present open-label study was designed to assess the safety and effects of the administration of BTX-A NT 201 in the treatment of post-stroke lower limb spasticity evaluating muscle tone, passive ankle dorsi-flexion motion, spasms frequency, and also considering the rate of patient's and physician's satisfaction after the treatment.

## Materials and methods

Consecutive naïve outpatients with stable lower limb spasticity resulting from a stroke at least five months before the enrollment, attending the Department of Physical Medicine and Rehabilitation, University of Foggia, Italy and Arìa, Neurological Rehabilitaion Center, Agazzi, Arezzo, Italy from January 2010 to December 2011 were invited to participate in the study and were screened for study eligibility. A clinical pattern with MAS=2 concerning ankle plantarflexor muscles spasticity was considered for treatment. Patients were also evaluated considering the frequency of daily spasms measured with Spasms Frequency Scale (SFS) [16] and passive ankle dorsi-flexion grade of motion (PADFM).

Subjects were excluded from the study if was present one of the following criteria: previous BTX-A injection into plantarflexor muscles, peripheral nervous system disorders/myopathies, 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, surgery in the target limb), fixed contractures, fibrosis, atrophy and/or deformities at the ankle (during the first evaluation, a sonographic measurement was performed on spastic muscles of lower limb). At the end of evaluation, 71 of 102 consecutive patients (46 men and 25 women, age range 28-80 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.

The clinical and demographic characteristics of patients are summarized in Table I. The dose was chosen considering previously studies that describe a dose ratio of 1:1 for BTX-A NT 201 to another conventional BTX-A complex product (Botox®) [17] and considering several muscles involved in individual clinical picture. BTX-A NT 201 was administrated with 2 mL of 0.9% saline of dilution and injected in to ankle plantarflexors muscles (lateralis/medialis gastrocnemius, and soleus) in relationship on spastic hypertonia; the dose ranged between 25 U and 100 U for each muscle (mean dose into

TABLE I.—*Demographic and clinical characteristics of stroke patients at baseline.*

| | |
|---|---|
| Mean age (SD) in years | 58.5 (12.2) |
| Mean time (SD) since onset of stroke in months | 28.8 (12.9) |
| Sex | |
| Female (N.) | 25 |
| Male (N.) | 46 |
| Stroke type | |
| Thrombotic (N.) | 49 |
| Hemorrhagic (N.) | 22 |

medialis gastrocnemius: 36.4±9.7; mean dose into lateralis gastrocnemius: 19.8±16.1; mean dose into soleus: 64.8±11.1). Immediately after injection, passive ankle flexion-extension was performed for 20', to enhance the spreading of BTX-A. 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 ultrasonography and electromyographic guide. Then, the patients participated for five days in a rehabilitation program consisting only in stretching exercise of muscle injected to improve the paralytic effect of neurotoxin. To evaluate the effect of BTX-A NT 201, changes in MAS, PADFM (measured with a goniometer while the patient was lying in a supine position), and SFS were analyzed after 30 and 90 days, considering a reduction of about 1 point of score as efficacy of treatment, similar to other studies on spasticity measurement,[18] even if for upper limb spasticity. Before treatment and during follow-up, each patient was examined by the same investigator.

### *Statistical analysis*

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 one month. A physical and neurological examination was performed after two weeks to evaluate safety, whereas adverse effects were assessed using a semi-quantitative scale (0: no adverse effects; 4: serious adverse effects). All analyses were performed using STATA for Mac OS, version 10.1. Difference between baseline ($t_0$) and post-treatment outcome measure scores ($t_1$,30 days and $t_2$, 90 days) was computed by *t*-student test for PADFM and Kruskal-Wallis test for two groups for MAS and SFS. The level of statistical significance was set as $p<0.05$. For statistical purposes the MAS score '1' was considered as 1, MAS score '1 +' as 2 and so on until 5.

## Results

Table II showed MAS, PADFM, and SFS values after 30 days of follow up ($t_1$) respect to the baseline ($t_0$). Patients reported an improvement of their clinical picture concerning spasticity of muscles injected evaluating the decrement of at least 1 point on the MAS score for ankle plantarflexor muscles. In fact, the analysis showed a statistically significant MAS score decrement ($t_1$=2.5±1; $t_0$= 3.9±0.6; Kruskal-Wallis H=67.9; P=0.0000) with an increase of PADFM ($t_1$=-2.4±7.2; $t_0$=-14.3±5.2; t=11.3; P=0.0000). A reduction of SFS score was also observed for all patients ($t_0$=1.1±1.2; $t_1$=0.1±0.5; Kruskal-Wallis H=38.0; P=0.0000). Table III reported MAS, PADFM, and SFS values after 90 days of follow-up ($t_2$) respect to the baseline ($t_0$). The MAS value reduction persisted also after 90 days of treatment ($t_2$=3±0.9; $t_0$=3.9±0.6; Kruskal-Wallis H=46.4; P=0.0000), as well as the increase of PADFM ($t_2$=-5.7±6.9; $t_0$=-14.3±5.2; t=8.3; P=0.0000). The SFS score decrement persisted in all patients ($t_2$=0.5±0.8; $t_0$=1.1±1.2; Kruskal-Wallis H=11.8; P=0.0001). Both patients and investigators considered effective the treatment. However, the rate

TABLE II.—*Difference between baseline ($t_0$) and post-treatment outcome measure scores ($t_1$, 30 days) in all outcome measures (Modified Ashworth Scale [MAS], passive ankle dorsi-flexion motion [PADFM], and Spasm Frequency Scale [SFS])] in patients with post-stroke lower limb spasticity treated with botulinum toxin type A NT 201. MAS, PADFM, and SFS values are shown as means ± SD. Values after 30 days ($t_1$) were compared with baseline ($t_0$).*

| | | $t_0$ | $t_1$ |
|---|---|---|---|
| MAS | mean±SD | 3.9±0.6 | 2.5±1.0 |
| | 95% IC | 3.8-4.1 | 2.2-2.7 |
| | Kruskal-Wallis H | | 67.9 |
| | p value | | 0.0000 |
| PADFM | mean±SD | -14.3±5.2 | -2.4±7.2 |
| | 95% IC | -15.5 - -13.1 | -7.2 - -0.7 |
| | t | | 11.3 |
| | p value | | 0.0000 |
| SFS | mean±SD | 1.1±1.2 | 0.1±0.5 |
| | 95% IC | 0.8-1.4 | 0.04-0.3 |
| | Kruskal-Wallis H | | 38.0 |
| | P value | | 0.0000 |

TABLE III.—*Difference between baseline ($t_0$) and post-treatment outcome measure scores ($t_2$, 90 days) in all outcome measures (Modified Ashworth Scale [MAS], passive ankle dorsi-flexion motion [PADFM], and Spasm Frequency Scale [SFS]) in patients with post-stroke lower limb spasticity treated with botulinum toxin type A NT 201. MAS, PADFM, and SFS values are shown as means ± SD. Values after 90 days ($t_2$) were compared with baseline ($t_0$).*

| | | $t_0$ | $t_2$ |
|---|---|---|---|
| MAS | mean±SD | 3.9±0.6 | 3.0-0.9 |
| | 95% IC | 3.8-4.1 | 2.8-3.2 |
| | Kruskal-Wallis H | | 46.4 |
| | P value | | 0.0000 |
| PADFM | mean±SD | -14.3±5.2 | -5.7±6.9 |
| | 95% IC | -15.5 - -13.1 | -7.4 - -4.0 |
| | t | | 8.3 |
| | P value | | 0.0000 |
| SFS | mean±SD | 1.1±1.2 | 0.5±0.8 |
| | 95% IC | 0.8-1.4 | 0.3-0.7 |
| | Kruskal-Wallis H | | 11.8 |
| | P value | | 0.0001 |

of response was higher for investigators than patients. In fact, considering spasticity, muscle spasms and passive dorsi-flexion motion, 36.6% of investigators and 25.4% of patients rated their clinical picture as "marked improvement" (Figure 1). Adverse events were monitored two weeks after treatment with BTX-A NT 201, and only eight patients (11%) experienced treatment-emergent adverse events (injection site pain for three patients, muscular weakness for five patients). All these adverse events were mild and were resolved in a few days.

## Discussion

The present study on post-stroke lower limb spasticity confirmed previous finding suggesting that BTX-A NT 201injections can reduce muscle tone in patients with spasticity of various etiologies.[13, 14] The reduction of hypertone is the main clinical goal for rehabilitation of stroke patients, increas-

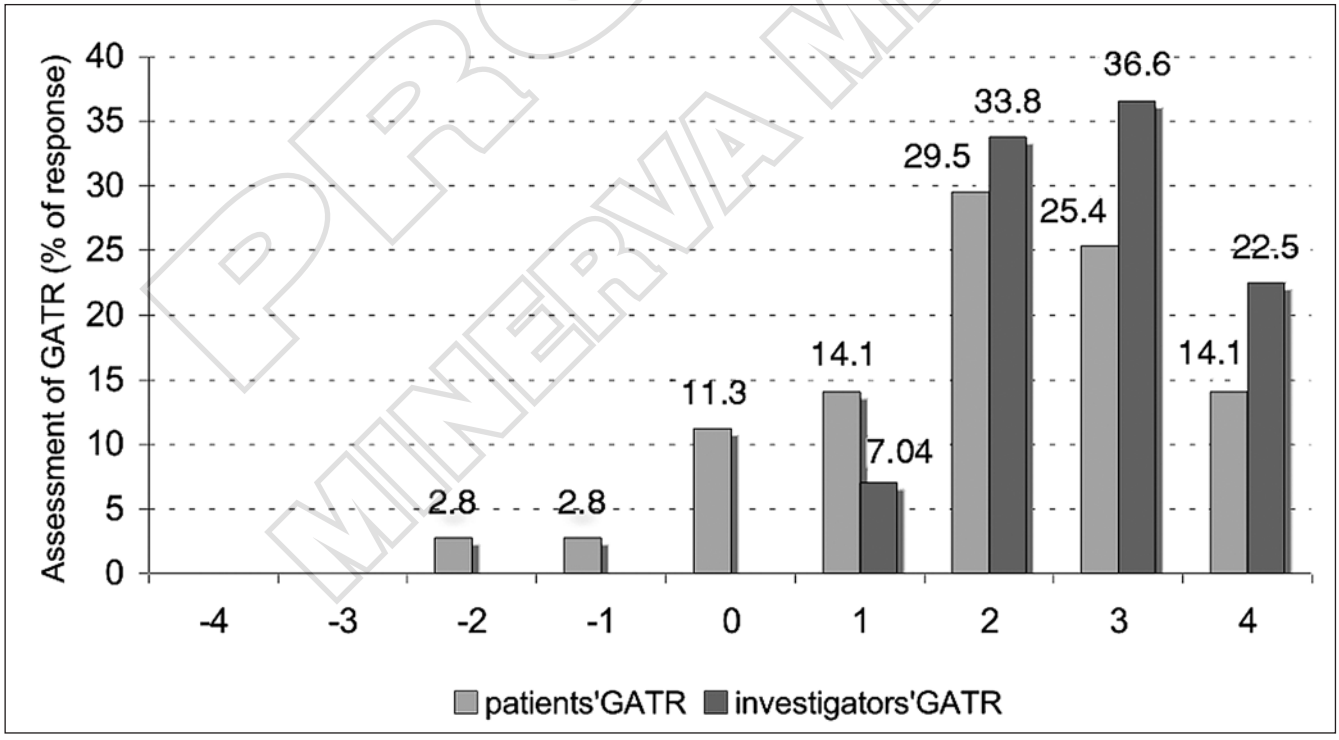


Figure 1.—Global assessment of treatment response (GATR) of patients and investigators at day 30 compared with baseline (full analysis set). GATR scale: - 4 = very marked worsening, -3 = marked worsening, -2 = moderate worsening, -1 = mild worsening, 0 = no change, +1 = mild improvement, +2 = moderate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

ing passive articular range of motion, reducing substantial deformity, and consenting also the employment of orthoses. Many studies demonstrated that BTX-A injections represent the gold standard for the treatment of focal spasticity.[18, 19] However, lower limb spasticity, especially interesting ankle plantarflexor muscles, represents a severe problem in stroke patients. In fact, the limited active ankle dorsi-flexion compromises the recovery of walking function and postural balance, increasing falls risk, also reducing the patients' participation and quality of life.

BTX-A injected in ankle spastic plantarflexor muscles consents to reduce hypertone even if its effect is less evident comparing with BTX-A effect in upper limb spasticity. In fact, in case of wrist or elbow spasticity, BTX-A injection permits to enhance the active and passive movement more than lower limb injections. The difficulty to observe BTX-A hypertone reduction of ankle plantarflexor muscles can be explained also considering that the leg extension in hemiparetic patient during the gait cycle increases the medial and lateral gastrocnemius' tension, further reducing active ankle dorsi-flexion motion, and the presence of Achilles tendon retraction and clonus contrast the ankle movements. Despite difficulties to obtain hypertone reduction after BTX-A injection, several studies emphasized the employment of BTX-A treatment for post-stroke lower limb spasticity,[6-9] especially associated to taping, casting, and physical therapies.[20, 21] Moreover, controversy also exists about functional improvements such as greater walking speed associated to the improvement in spasticity, and treatment benefits appear to be specific for the patient and it is difficult to identify clinical measures suitable to value the effects on individual outcome.[22]

Another important aspect is the dose of BTX-A injection to treat lower limb spasticity. It is known that fixed-dosage BTX-A regimen used does not reflect the current clinical practice, which is to use personalized dosages. In fact, in a randomized, double-blind, dose ranging study, comparing the effects of high, medium and low BTX-A doses, the injection of medium doses in spastic muscle is to be preferred, reaching a mean total dose of 320 U to avoid a decrease of strength also in to non-injected muscles.[23] Despite the employment of sonography and electromyographic guide consents to reduce BTX-A doses identifying precisely the muscles to be injected, medium doses (250-350 U) are safe and efficacious to reduce ankle plantarflexor muscles spasticity.[23] Although all of the plantarflexor muscles are known to contribute to the ankle plantarflexor spasticity,[5] different injection localizations can be chosen, after accurate clinical evaluation. The effect of BTX-A administrated into lateral/medial gastrocnemius and soleus muscles can be evaluated considering also only the grade of passive or active ankle dorsi-flexion motion, independently if patients are or not able to walk. Moreover, MAS represents actually an useful tool to consider the grade of spasticity before and after a rehabilitative treatment.[15]

In the present study, treatment of ankle plantarflexor muscles with BTX-A NT 201 resulted in statistically significant improvements in spasticity and spasms reduction increasing also passive ankle dorsi-flexion. These findings are similar to other studied showing that BTX-A NT 201 is safe and efficacious in the treatment of movement disorders,[24-26] whereas other recent studies confirmed safety and efficacy of a dose of about 400 U to treat upper limb spasticity after stroke.[13, 14] Recently, a case report concerning the employment of a total dose of 150 U to treat pes equines deformity after brain injury occurred to a 48 year-old female has been published.[27] In the present report, a MAS reduction about 2 points is obtained after only one set of injections, and this effect lasted for 90 days, confirming the findings on upper limb spasticity.[13, 14] In all these studies, the mean dose injected was administrated considering previous results that compare this new formulation with other drug preparations,[17, 28] confirming the same pharmacological effect. Safety was analyzed for all patients enrolled in the study after two weeks. 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 investigators than 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, whereas for investigators MAS and SFS scores reduction with passive ankle dorsi-flexion improvement represents an optimal target for stroke survivors' rehabilitation. A few mild adverse effects were reported, related to injection site pain and muscular weakness, with a complete resolution in a few days.

*Limitations of the study*

Among study limitations, we must acknowledge the limited sample size and that, given the open-label design of the study, the lack of a control group may affect the generalizability of the results. Moreover, another important limitation was the lack of a functional assessment in these patients with lower limb spasticity after stroke. On the other hand, while several studied have shown improvements in spasticity rating,[6-9] the gait and mobility measures did not reflect these changes in lower limb spasticity.[29, 30] Only one RCT found a significant improvement in walking speed.[10] This lack of convincing change on gait and mobility measures contrasts with the perceptions of participants in these RCTs, two-thirds of whom reported important improvements in their walking.[30] Although in the case of post-stroke lower limb spasticity the improvement in functional performance is sometimes difficult to obtain, the reduction of hypertone can be used, for example, to improve limb posture, to apply splinting, to increase passive articular range of motion, to walk and stand improving joint range of motion and muscle extensibility or to reduce spasticity-related pain.

## Conclusions

The present findings confirmed the safety and efficacy of BTX-A NT 201 in patients with post-stroke lower limb spasticity showing an optimal efficacy and tolerability after a single administration. This study was limited by little sample size and the lack of functional assessment and a control group, so limiting interpretations of the magnitude of effect. However, the present findings with BXT-A NT 201 may lead to promising new therapeutic options to treat lower limb spasticity after stroke. NT 201 is a new preparation of BXT-A potentially with low immunogenity, but further studies are needed to confirm its effectiveness also after repeated injection excluding the development of toxin neutralizing antibodies.

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*Conflicts of interest*.—Dr R. Spidalieri works as a consultant for Merz.

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