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EDITORIAL

High doses of incobotulinumtoxinA for the treatment of post-stroke spasticity: are they safe and effective?

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1. Introduction

Botulinum toxin type A (BoNT-A) represents the gold standard therapy for focal spasticity and related disorders also in acquired brain injury including stroke. Since 1989, the effectiveness of BoNT-A in reducing poststroke spasticity showed reversibility and low prevalence of complications [1], obtaining the approval of U.S. Food and Drug Administration for upper limb spasticity after stroke in 2010. In the following years, many studies have been published demonstrating its safety and effectiveness [2,3]. However, the role of BoNT-A in the management of poststroke spasticity has been modified, changing from muscle chemodenervation (nerve block) to become an useful tool for improving limb posture, applying splint, consenting hygiene, standing, and walking in patients with spastic equino-varus foot deformities with also improvement joint range of motion and muscle extensibility or reduction of spasticity-related pain.

The correct evaluation of the patient to be injected is necessary to increase the efficacy of BoNT-A considering that there is a high response for improving passive function, but controversy also exists about the improvement in motor function relative to the improvement of spasticity. There are proposals on dosages, injection techniques, patient selection, and outcome measures, but a consensus about the employment of adjunctive therapies after the BoNT-A injection, considered necessary to increase the effect on spasticity reduction, has not been reached, considering the time to start, the duration of adjunctive therapies, and the type of rehabilitation procedures [4]. So, at present, the injection sites, the choice of muscles, the dosage, the dilution, and the rehabilitation programs after BoNT-A treatment are often identified by injector's decision-making without specialized training.

BoNT-A has clearly been recommended as first-line treatment for focal spasticity by several European consensus statements and the American Academy of Neurology [4,5] and current guidelines suggested the employment of a dose up to 600 units (U) of onabotulinumtoxinA (Botox®, Allergan, Inc., Irvine, CA, USA) and incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany) or up to 1500 U of abobotulinumtoxinA (Dysport®, Ipsen, Slough, UK/Galderma, Paris, France) per injection session to treat spasticity after stroke [5]. However, in recent years, higher doses have been used, especially in case of upper and lower limb severe spasticity considering the low prevalence of complications and the reversibility of the BoNT-A [6,7]. The possibility to employ high doses is strictly related to the precision of the injection. A correct muscle identification with instrumental guide (i.e. electrical stimulation or ultrasonography) may reduce the spread of the toxins to the nearby tissues and the risk of adverse effects.

2. Therapeutic response and adverse effects of BoNT-A for treating spasticity

BoNT-A is effective for spasticity reduction [1–3], even if a reduction or absence of response of therapeutic effect can occur [8]. A condition of transient nonresponse was identified, in which the first application of BoNT-A could be not efficacious, but subsequent injections may produce the desired clinical effects. There was also a condition of permanent nonresponse, in which both the first and subsequent treatments may be ineffective. Moreover, two different conditions have been identified as primary and secondary nonresponse. Primary nonresponse after the first application may occur in patients with a clinical subtype that has reduced sensitivity to botulinum toxin. Moreover, inadequate dosing, handling errors during drug storage or preparation, or problems with drug administration (e.g. incorrect muscles to inject or spread

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Table 1. Key and reviewed studies on higher doses of incobotulinumtoxinA for the treatment of upper and lower limb poststroke spasticity.

First author and year of publication	Study design	IncobotulinumtoxinA doses units (U)	Patients characteristics and outcome measures	Clinical results and adverse effects
Santamato et al. [7]	Prospective, open-label, nonrandomized study	≤840	25 stroke patients with upper and lower limb spasticity. DAS, VAS for spasticity-related pain for patients, and GATR for investigators and patients	Disability, pain and spasticity reduction; one patient reported injection site pain, four patients experienced muscular weakness
Dressler et al. [13]	Prospective, noninterventional, randomized study	≤1200	About 90% of 33 stroke subjects suffering from hemispasticity, arm, and leg spasticity. Patients were submitted to STQ, CSTF, NE, and LS	None of the patients showed signs of motor or autonomic dysfunction distant from the target muscles and attributable to incobotulinumtoxinA. LS did not show any remarkable abnormalities for serum chemistry
Invernizzi et al. [14]	Case–control study	> 600	11 stroke survivors with spastic hemiplegia. Heart rate variability measures derived from ECGs	The use of incobotulinumtoxinA in adult patients at doses up to 12 units/kg seems to be safe regarding autonomic heart drive

CSTF: complete secondary therapy failure; DAS: Disability Assessment Scale; ECG: electrocardiogram; GATR: global assessment of treatment response; LS: laboratory screening; NE: Neurological Questionnaire; STQ: Systemic Toxicity Questionnaire; VAS: Visual Analog Scale.

over the targeted muscles) can also cause either a primary or secondary nonresponse. An important reason for secondary treatment failure is the antibodies (Ab) formation against therapeutic neurotoxin-protein evoked by booster (high dosing frequency injections) and high doses [8].

Regarding adverse effects, they can be distinct as localized and generalized. Localized effects comprised those directly associated with the injection as swelling, hematoma, bruising, and pain at injection site, lasting few days with resolution without any complications. The generalized adverse events were related to spread of toxin distant from the site of injection: botulism-like syndrome, exaggerated muscle weakness, dysphagia, breathing or speech difficulty, and severe allergic reaction can result in death in very rare cases, also at low doses [9].

3. High doses of incobotulinumtoxinA for the treatment of poststroke spasticity

Among BoNT-A formulations, incobotulinumtoxinA is a150 kDA neurotoxin free from complexing proteins indicated for the treatment of neurological disorders such as blepharospasm, cervical dystonia, and upper limb spasticity in stroke survivors at the dosage of 400 U [10]. Although incobotulinumtoxinA is not licensed for lower limb spasticity or increased muscle tone caused by other central nervous system disorders, there is good evidence that BoNT-A improves spasticity in the lower limb after stroke [7,11] or upper limb spasticity due to other neurological disorders such as seen with multiple scleroses, cerebral palsy, or brain injury. Four weeks after a maximum dosage of 450 U of incobotulinumtoxinA, these patients showed substantial improvement of 57 % in functional disability and muscle tone regardless of the etiology [12]. A particular feature of incobotulinumtoxinA was the absence of accessory complexing proteins, so the therapeutic effect was mediated by the neurotoxin purified, maintaining an elevated specific biological activity. The advantage of the absence of complexing proteins could be related to a lower risk of immunogenicity, but this effect is not yet demonstrated. However, the hypothetical reduced risk of Ab formation has been the reason for many clinicians to use more than the 400 U recommended by the European incobotulinumtoxinA product label, so overcoming the limit of 600 U of BoNT-A previous established [5]. There are some studies describing the employment of high doses of incobotulinumtoxinA for spasticity reduction in stroke patients, with more than 600 U can be used in case of severe spasticity of upper and lower limbs (Table 1). In a prospective, nonrandomized, open-label study, 25 consecutive subjects have been treated with incobotulinumtoxinA administrated under ultrasound guide, with a dosage ranged from 750 to 840 U [7]. The patients reported after 30 days a significantly reduction of spasticity, pain, and disability lasting at 90 days of follow-up. In this report, with the limit of the nonrandomized, open-label study design, only 16% of patients experienced treatment-emergent adverse events as injection site pain and muscular weakness resolved in a few days. In a prospective, open-label noninterventional study, Dressler evaluated the safety outcomes in 15 suffered with hemispasticity, 13 with arm spasticity, and 5 with leg spasticity due to stroke for 90% of the patients treated up to 1200 U of incobotulinumtoxinA (dose range: 400–1200 U; mean dose ± standard deviation: 570.1 ± 158.9 U). No signs of motor or autonomic dysfunction have been reported and no patient developed Ab production and secondary treatment failure [13]. The safety of 600 U of incobotulinumtoxinA has been also tested in 11 spastic stroke survivors evaluating possible changes in autonomic heart drive. No relevant effects on autonomic drive directed to the heart have been showed with an electrocardiographic exam performed 24 h before and 10 days after the injections, demonstrating an absence of systemic diffusion also at high doses [14]. Finally, a Phase III, nonrandomized, single arm, multi-center trial (TOWER) (ClinicalTrials.gov Identifier: NCT01603459) to investigate the efficacy and safety in a dose titration study with incobotulinumtoxinA in upper and lower limb spasticity of cerebral causes in 155 subjects deemed to require total body doses of 800 U of neurotoxin has been completed in September 2014, but results have not been yet published [10].

4. Conclusion

A European consensus established that a dose of about 600 U of onabotulinumtoxinA and incobotulinumtoxinA or up to 1500 U of abobotulinumtoxinA may be safe and well-tolerated in poststroke spasticity [5]. There is the possibility to use higher doses of incobotulinumtoxinA, given that this neurotoxin is free of accessory complexing proteins and its employment could reduce the risk of Ab formation, even if this possibility is not yet demonstrated, and it does not exclude the possibility to have generalized adverse effects. However, as described in previous studies, generalized botulism-like syndrome for subjects treated can occur also for recommended doses of BoNT-A or increasing the frequency of the injections [9]. Therefore, the clinicians recommend careful consideration for reinjection period with doses greater than 600 U of BoNT-A: a reduction in systemic side effects may be obtained with a reinjection frequency greater than four months. Although systemic BoNT-A toxicity clearly is a quantitative problem and as such not necessarily fatal, fear of systemic toxicity is still the most vigorous concern against application of increased BoNT-A doses. The few studies focusing on the employment of high doses of incobotulinumtoxinA suggested that a single treatment superior to 600 U appeared to be effective in reducing spasticity after stroke, with adverse effects similar to those reported with lower doses. To the best of our knowledge, no data existed about long-term treatment of high doses of BoNT-A therapy, so further studies on several sets of high doses toxin should be carried out to exclude certainly the adverse events and the development of toxin Ab evocated by higher doses. This issue should be carried out for an improved knowledge of the therapeutic and adverse effects of high doses of incobotulinumtoxinA.

5. Expert opinion

An increasing and cumulative body of evidence suggested that incobotulinumtoxinA as well as onabotulinumtoxinA and abobotulinumtoxinA appeared to be safe and efficacious in reducing spasticity due to several neurological disorders with rare and mild adverse effects [10]. The recommended doses of BoNT-A in the product label reflect older clinical trials, performed with the use of lower BoNT-A doses. As time has passed, many experienced clinicians have employed high BoNT-A doses, as evidenced by recommendations in expert consensus panel reviews. The interest on more than 600 U of BoNT-A is increased with the marketing of incobotulinumtoxinA free of accessory complexing proteins and potentially with low immunogenicity even if with the same risk of generalized side effects, as for other BoNT-A formulations. Considering this issue related to the employment of high neurotoxin doses, the reason for its use must be carefully indicated. In fact, BoNT-A therapy not only reduces the spasticity, but also decreases the motor control of injected muscles. High doses can spread to near muscles, so reducing the residual motor function of the patients. However, high doses can be employed to reduce severe spasticity improving hygiene, pain, posture, gait, and balance. Finally, a correct guide of injection, as electrical stimulation or ultrasonography, is needed to reduce the possibility of diffusion to near tissue and to identify the correct muscles. In fact, as reported in previous studies [6,7], many muscles were injected in case of severe spasticity, so the precision of needle insertion is basic for small and deep-seated muscles and to reduce the risk of failure of the therapy [15]. However, the evidence coming from the few studies available and reviewed about the safety of elevated incobotulinumtoxinA doses in treating poststroke spasticity should be treated cautiously (Table 1). In fact, it is necessary to choose an individual primary functional target before starting, considering that spasticity reduction is not always related to improvement of motor function in upper or lower limbs. Further systematic reviews based on metanalytic findings and larger studies focusing on long-term treatment are mandatory to confirm that high doses of incobotulinumtoxinA may be safe and efficacious for treating spasticity after stroke.

Declaration of interest

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(•) or of considerable interest
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