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Do flexible inter-injection intervals improve the effects of botulinum toxin A treatment in reducing impairment and disability in patients with spasticity?

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ABSTRACT

In patients treated with botulinum toxin-A (BoNT-A), toxin-directed antibody formation was related to the dosage and frequency of injections, leading to the empirical adoption of minimum time intervals between injections of 3 months or longer. However, recent data suggest that low immunogenicity of current BoNT-A preparations could allow more frequent injections. Our hypothesis is that a short time interval between injections may be safe and effective in reducing upper limb spasticity and related disability. IncobotulinumtoxinA was injected under ultrasound guidance in spastic muscles of 11 subjects, who were evaluated just before BoNT-A injection (T0), and 1 month (T1), 2 months (T2) and 4 months (T3) after injecting. At T1, in the case of persistent disability related to spasticity interfering with normal activities, patients received an additional toxin dose. Seven subjects received the additional dose at T1 because of persistent disability; 4 of them had a decrease of disability 1 month later (T2). Rethinking the injection scheme for BoNT-A treatment may have a major impact in the management of spasticity and related disability. Future studies with larger sample sizes are warranted to confirm that injection schedules with short time intervals should no longer be discouraged in clinical practice.

Introduction

The management of spasticity is a major challenge in neurorehabilitation. Primary goals are the improvement of patients' comfort and their functional level. Several effective procedures are now available, among which botulinum toxin-A (BoNT-A) treatment represents the first choice for focal spasticity [1].

While botulinum toxin is a highly effective treatment for spasticity, treatment effects are temporary and many patients experience partial to complete reemergence of symptoms towards the end of each injection cycle as the benefits of the previous dose begin to wear off. In the early days of BoNT-A treatment, if the first set of injections induced unsatisfactory effects patients were injected additional doses of toxin 2–4 weeks later [2]. Unfortunately, the early years of BoNT-A treatment were burdened by treatment failure due to the development of antibodies able to neutralize the toxin (neutralizing antibodies) [3]. The risk of BoNT-A antibody formation was directly related to the toxin dosage and the frequency of injections. Indeed, patients who experienced antibody-induced treatment failure had received injections with higher frequency (shorter time intervals) than patients who did not develop toxin resistance [4]. These observations marked the end of the use of additional doses of BoNT-A, and led to the empirical detection of injection intervals of 3 months or longer, still adopted in the nowadays clinical practice [5].

Clinical observations that led to the recommendation of ≥3 months injection interval were performed on patients treated with early formulations of onabotulinumtoxinA, known to be much more immunogenic than the current onabotulinumtoxinA [6] As a result, an obvious question is whether the availability of recent toxin formulations with reduced immunogenic potential

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[7] should prompt a reappraisal of the debate on whether the clinical benefits of adopting shorter and more flexible inter-injection intervals could be worth the risk of neutralizing antibody formation, at the moment recognized as significantly lowered [8].

We conjectured that this issue would be best analyzed having data on the immunogenic risk of neutralizing antibody formation on the one hand, but more meaningfully, by providing evidence on the clinical benefits deriving from the adoption of short inter-injection intervals on the other. Certainly, if adopting short injection intervals produced no increase in clinical benefit (an eventuality that cannot be excluded a priori), performing large clinical studies to investigate the risk of antibody formation would be inappropriate. As a matter of fact, recent data in children with lower limb spasticity show that increasing the inter-injection intervals from 12-monthly to 4-monthly confers no clinical advantage [9].

Therefore, we hypothesize that in patients with upper limb spasticity the clinical benefit induced by botulinum toxin treatment improves when adopting a short inter-injection interval. If this is the case, impairment and disability evaluated after administering an additional dose of incobotulinumtoxinA one month after a first set of injections, should be found reduced. Having this information would strengthen the rationale for designing and planning multicentre studies investigating the immunogenic risk of neutralizing antibody formation.

Methods

We designed this pilot study in patients with upper limb spasticity to test the hypothesis that adopting short inter-injection intervals improves the clinical benefit induced by botulinum toxin treatment on impairment and disability in patients with spasticity.

Patients' selection

Patients were included in the study based on the following criteria: 1) upper limb spasticity resulting from a lesion in the brain or in the spinal cord; 2) evidence of difficulty, mainly caused by spasticity, in dressing or maintaining personal hygiene, pain or malposition of the upper limb, as demonstrated by a score $\geq$2 in at least 1 of the 4 domains of the Disability Assessment Scale (DAS); 3) a stable clinical picture in the 6 months preceding enrollment.

Exclusion criteria were: cognitive impairment interfering with the ability to provide informed consent; joint retractions and major muscle contractures in the affected upper limb; significant cutaneous or joint inflammation in the affected upper limb; ongoing neuromuscular diseases; a change in oral medication for spasticity in the previous three months; treatment with intrathecal baclofen.

The present study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; a written informed consent was obtained from all participants.

Study design

IncobotulinumtoxinA was injected in the upper limb muscles affected by spasticity under ultrasound guidance. Muscles to be injected and toxin doses were determined in each single subject, according to the clinical picture, in the aim to reduce spasticity and related disability. The subjects were evaluated just before BoNT-A injection (T0), and 1 month (T1), 2 months (T2) and 4 months (T3) after injecting. At T1, in the case of persistence of selection criterion number 2, an additional BoNT-A dose was injected.

All subjects underwent physiotherapy during the two months following the first set of injections (from T0 to T2). Physiotherapy, which included muscle stretching and muscle training, was organized in three weekly sessions lasting 45 min each (24 sessions in total). Functional task-specific activities were incorporated.

Outcome measures

Muscle tone was evaluated using the *Modified Ashworth Scale (MAS)*, a 6-point scale ranging from 0 (no increase in tone) to 4 (limb rigid in flexion or extension) [10].

To evaluate the functional disability we used the *Disability Assessment Scale (DAS)* [11]. Four areas of disability were assessed (hygiene, dressing, limb position and pain) according to the following classification: 0 = no disability; 1 = mild disability not interfering significantly with normal activities; 2 = moderate disability (normal activities require increased effort and/or assistance); 3 = severe disability (normal activities limited). The scores of the 4 areas were summed.

The overall response to treatment was evaluated together by investigators, patients, and caregivers using the *Global Assessment Scale (GAS)* [12]. The GAS is a 9-point scale ranging from 0, unchanged, to +4, very marked improvement, or to −4, very marked worsening.

MAS and DAS were administered at each examination (T0, T1, T2 and T3), while GAS and adverse effects were evaluated only after the BoNT-A injection (T1, T2 and T3).

All measures of variability are reported as standard deviation.

Endpoints

Endpoint 1: number of enrolled subjects showing persistence of spasticity and related disability at T1 with DAS score $\geq$ 2 in at least 1 of the 4 domains.

Endpoint 2: number of subjects injected at T1 with DAS score at T2 < DAS score at T1.

Results

Table 1 shows the demographic and clinical features of the 11 enrolled subjects.

The mean dose of incobotulinumtoxinA injected at T0 was 220 ± 81 units (Table 2).

At T1, all the subjects showed a MAS score reduction of at least 1 point in at least 1 treated muscle (Table 3). Eight subjects (patients 1–8) underwent a reduction in DAS score, and all the 11 subjects had a positive GAS score (Table 4).

In subjects 1–4 (mean dose of BoNT-A at T0 215 ± 39 units), DAS score at T1 was <2 in all the 4 domains; therefore, they received no additional dose. In contrast, subjects 5–11 (mean dose of BoNT-A at T0 224 ± 101 units) showed persistence of spasticity and related disability at T1 with DAS score $\geq$ 2 in at least 1 of the 4 domains (***endpoint 1: 7 out of 11 subjects***) (Table 4). These 7 subjects received an additional dose of incobotulinumtoxinA (137 ± 73). In 3 of those subjects (6, 8 and 10), the additional dose was injected in the same muscles treated at T0. In other 3 subjects (5, 7 and 11), the early additional dose was injected both in muscles treated and not treated at T0. Subjects 9 received the additional dose only in a muscle not treated at T0 (Table 2).

At T2, subjects 1–4 (not receiving the additional dose) showed same DAS and GAS scores as those collected at T1. In contrast, among those who received the additional dose, 4 subjects (5–7 and 10) showed reduced DAS score (***endpoint 2: 4 out of 7 subjects***), and 5 subjects (5–7, 9 and 10) increased GAS score.

All subjects denied any adverse event.