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Brief Communication

A phase II, open-label, non-comparative study of Botulinum toxin in Restless Legs Syndrome

Imad Ghorayeb [a,*], Antoine Bénard [b], Alexandre Vivot [b], François Tison [c], Pierre Burbaud [a]

[a] Service des Explorations Fonctionnelles du Système Nerveux, Hôpital Pellegrin, Place Amélie Raba-Léon, 33076 Bordeaux cedex, France
[b] Unité de soutien méthodologique à la recherche clinique et épidémiologique, Service d'Information Médicale, CHU de Bordeaux, Bordeaux, France
[c] Department of Neurology, University Hospital Bordeaux, Bordeaux, France

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ABSTRACT

Objective: To assess the efficacy of intradermally injected botulinum neurotoxin type A (BoNT/A) in patients with Restless Legs Syndrome (RLS).
Methods: We conducted an optimal two-stage, phase II exploratory, open label, non-comparative clinical trial. The primary outcome measure was the efficacy of BoNT/A defined by the proportion of patients (responders) with ⩾50% improvement of their RLS severity score at week 2 following injections compared to baseline score at inclusion. Twenty-seven patients were to be included in the first stage of the trial, which was to be stopped if less than nine responders were documented. Selected patients had a minimum score of 21 on the International RLS Rating Scale. They all received a series of 20 intradermal injections of 0.05 ml of BoNT/A in symptomatic areas in their lower limbs. Change of RLS severity was evaluated over a 6 months period.
Results: Of the 27 selected patients, only six achieved the primary endpoint at week 2. In these six patients, the median duration (Inter-Quartile Range) of the IRLSRS score improvement of at least 50% was 46 days (42–126).
Conclusions: Considering the proportion of responders as the primary endpoint of this trial, BoNT/A showed no efficacy in alleviating RLS sensory symptoms.

1. Introduction

The Restless Legs Syndrome (RLS) is a chronic sensorimotor disorder with still no accepted understanding of its pathophysiology. The evidence for a dopaminergic involvement is to be found in the excellent efficacy of dopaminergic medications. Although effective, non-ergot derivative D2-D3 dopamine receptor agonists (DA) may induce serious side effects such as impulse control disorders and RLS augmentation [1,2]. Loss of efficacy also represents a potential major problem during long-term treatment of RLS with DA [3,4]. Alternative new treatment strategies are, therefore, mandatory to expand the treatment arsenal of RLS. Experimental evidence suggests that botulinum neurotoxin type A (BoNT/A) may modulate afferent sensory fiber firing and thereby reduces central sensitization [5,6]. As evidence suggests, an enhanced sensitization of central pain processing in RLS [7], it has been hypothesized that BoNT/A may be effective in decreasing its sensory discomfort [8,9]. Few reports have investigated the benefit of BoNT/A in patients with recalcitrant RLS, but controversies persist otherwise [10–13]. In these reports, BoNT/A was delivered intramuscularly (IM), which in RLS may not be an optimal scheme of administration. The efficacy of intradermal injection of BoNT/A has been shown in neuropathic pain [14,15].

In this study, we investigate the efficacy of intradermal BoNT/A injection for the treatment of severe RLS.

2. Methods

This study was conducted at Bordeaux University Hospital and was approved by regional ethical committee. The ClinicalTrials.gov Registration Identifier is NCT00949806.

2.1. Patients

Consecutive patients with primary RLS diagnosis based on the presence of a characteristic clinical history and on the International Restless Legs Syndrome Study Group (IRLSSG) essential definition criteria were screened [16]. Patients were selected if they were ⩾18 years, had daily RLS symptoms, a baseline severity score ⩾21 on the International Restless Legs Syndrome Rating Scale

* Corresponding author. Address: Clinical Neurophysiology Department, Pellegrin Hospital, Place Amélie Raba-Léon, 33076 Bordeaux cedex, France. Tel.: +33 5 57 57 16 07; fax: +33 5 56 98 61 82.
E-mail address: imad.ghorayeb@u-bordeaux2.fr (I. Ghorayeb).

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(IRLS) [17], were stable on RLS medications for more than 6 weeks prior to enrollment and could clearly delineate the area of sensory unpleasantness in their legs.

The exclusion criteria were abnormal neurologic examination, medical history of diabetes, ongoing untreated depression, kidney failure, iron deficiency, pregnancy, lactation, woman of childbearing age without efficient contraceptive method, patient undergoing aminosid antibiotherapy or BoNT/A injection for other indication, any contra-indication to BoNT/A injection and participation to another clinical study within 30 days prior inclusion.

All patients were informed of the investigational nature of this study and that any current RLS medication modification was forbidden throughout the study. Written informed consent was obtained from all patients.

2.2. Protocol design

We conducted an optimal two-stage, phase II, non-comparative clinical trial. In this design the second phase takes place if a minimal efficacy is observed in the first phase.

A total of five follow-up visits were scheduled at 2-week (W2), 6-week (W6), 12-week (W12), 18-week (W18) and 24-week (W24) intervals after the BoNT/A injection.

2.3. Intradermal BoNT/A injection

Intradermal BoNT/A injection was administered at inclusion after symptoms location were mapped. A single-use, sterile 500 Unit vial (Dysport®, Ipsen Pharma) were reconstituted with 2 ml of 0.9% Sodium Chloride to yield a solution of 250 units/ml. To standardize the protocol of BoNT/A administration, symptomatic areas at the lower limbs were selected as follows: anterior and posterior tights, and anterior and posterior legs. Injections were distributed in a grid distribution pattern covering a total of 20 equidistant sites matched to the extent of the symptomatic area [15]. Each area received 20 injections of 0.05 ml, each injected dose corresponding to 12.5 units, so as to cover the whole symptomatic area according to a procedure adapted from that used in the treatment of painful peripheral neuropathies [14,15]. Each participant received a total of 250 unit injection into each symptomatic zone and both legs were systematically injected. Depending on the extent of RLS symptoms, a minimum of 500 units and a maximum of 1000 units were delivered per patient.

2.4. Outcome measures

The primary outcome measure was the efficacy of BoNT/A in the treatment of RLS defined by the proportion of responders, (i.e. patients with an improvement $\geqslant$50% of their RLS severity score at W2 compared to baseline) [18]. The RLS severity score was measured at inclusion and on follow-up visits. Secondary outcomes measures included mean RLS severity score change from inclusion to W2, W6, W12, W18 and W24, the clinician's overall impression of change on the Clinical Global Impression-Improvement (CGI-I) 7-point scale (from very much improved = 1 to very much worse = 7) and efficacy duration, (i.e. maintenance of at least $\geqslant$50% improvement of the RLS severity score on follow-up visits).

The safety of BoNT/A, particularly for systemic adverse effects, was documented at each visit.

2.5. Sample size determination

The principle of a two-stage non-comparative clinical trial is to determine the adequate sample size to have a high probability of rejecting an ineffective treatment and a high probability of further developing (in phase III clinical trials) treatment with efficiency greater than a predetermined level. In this trial, the percentage of responders beyond which efficacy of BoNT/A could be considered was set at 50%. A proportion of responders <30% was not considered sufficient for a further evaluation of the treatment.

With an alpha-error of 2.5% and a power of 90%, the sample size was estimated at 27 patients for the first stage of the trial. The accrual was to stop the trial if less than nine remissions were observed in the first 27 selected patients (<30%).

2.6. Statistical analysis

The proportion of responders at W2 was estimated with its 95% binomial confidence interval. RLS severity scores at W2, W6, W12, W18 and W24 were compared to the score at inclusion using Wilcoxon (rank signed) test for paired data.

Analyses were conducted using SAS, version 9.1 (SAS Institute Inc., Cary, NC). Statistical significance was set to 0.05.

3. Results

A total of 58 patients with RLS were screened. Out of the 27 patients included, only 6 (22%, 95% confidence interval: 6.5–37.9) were responders at W2.

3.1. Patients' characteristics

Of the 27 included patients, 26 completed the full 6-month trial. One patient withdrew from the study after completing the W12 visit. The reason for withdrawal was a lack of efficacy of BoNT/A and the need to rapidly proceed to RLS treatment modification. For this patient, data collected at inclusion, W2, W6 and W12 were included in the statistical analysis. Table 1 shows relevant characteristics of patients at inclusion (responders vs. no responders). The mean (±standard deviation) age of the patients at inclusion was 57.6 ± 14.3 years, with a median disease duration (Inter-Quartile Range [IQR]) of 11 years (6–25) and a mean IRLS score at inclusion of 31.1 ± 4.7. There were 15 men and 12 women and 14 (52%) of the patients reported a family history of RLS.

3.2. IRLSRS score reduction

BoNT/A improved average IRLS score of the whole group. The mean RLS severity baseline score dropped from 31.1 ± 4.7 to 23.2 ± 8.9 at W2 ($p < 0.0001$), with a 15% (IQR 4–41) median relative reduction of the RLS severity score at W2. At W6, the mean RLS severity score reached its lowest value (22.3 ± 8.5, $p < 0.0001$), with a 19% (IQR 6–45) median percentage reduction of the score. At W24, the mean RLS severity score was 26.1 ± 7.2 ($p = 0.001$), with a persisting median percentage improvement of 8% (IQR 0–26).

Of the 6 responders at W2, the median duration of the RLS severity score improvement of $\geqslant$50% was 46 days (IQR 42–126).

3.3. CGI-I change

The CGI-I scores evolution did not strictly parallel that of the RLS scores. At W2, 10 patients (37%) were considered much to very much improved by the clinician. They were 11 at W6. Their number declined to 9 at W12 and W18, and to 4 at W24.

3.4. Safety

The only significant adverse effect was moderate transient limb weakness in seven patients with one having also complained from transient diplopia.

Table 1
Descriptive characteristics of the 27 patients with RLS according to their RLS severity score modification following BoNT/A injection.

	Non responders (<50% IRLSRS score decrease)		Responders (⩾50% IRLSRS score decrease)	
Number (%)	*N* = 21 (78%)		*N* = 6 (22%)	
Age (years)	59	(49–67)	62	(56–68)
Men	11	(52)	4	(67)
Family history of RLS	11	(52)	3	(50)
RLS age of onset (years)	41	(26–54)	41	(39–58)
RLS symptoms duration (years)	10	(6–28)	14	(6–25)
Mean baseline IRLSRS severity	31	(27–35)	34	(25–34)
Body mass index (kg/m^2)	25	(22–29)	29	(28–32)
Site of maximal RLS symptoms and of BoNT/A injection				
Anterior tight	5	(24)	3	(50)
Posterior tight	4	(19)	1	(17)
Anterior leg	5	(24)	1	(17)
Posterior leg	19	(91)	6	(100)
Concomitant treatment	12	(57)	5	(83)
Type of concomitant treatment*				
Weak analgesics/anti- inflammatory	5		6	
Opioid analgesics	0		4	
Antidepressants	3		2	
Antiepileptic	2		0	
Hypnotics	2		0	
Others	29		16	

Data are numbers (*N*), percentages (%) or median (IQR).
* Some patients were taking more than one concomitant treatment.

4. Discussion

This is the first trial on the efficacy of intradermal BoNT/A in patients with severe RLS. We observed a significant decrease of the RLS severity score after BoNT/A administration, but failed to prove BoNT/A efficacy as only six patients out of the nine expected in the first phase of the trial were responders. Moreover, the average IRLS score reduction of the whole group was very similar to the usual placebo response in clinical trials with RLS.

Previous studies on the efficacy of BoNT/A in RLS were mostly case series and all used IM injections of BoNT/A. Results were conflicting as only two studies out of four reported efficacy [10–13]. Due to the wide extent of RLS sensory symptoms, IM injection may not be a relevant route of BoNT/A administration and may in part explain these results.

Unlike its function at the neuromuscular junction, the mechanism of action of BoNT/A on pain relief is not clear. Animal studies suggested mediation of a direct antinociceptive effect involving neurogenic inflammation blockade [5,6]. This same neurogenic inflammation blockade by BoNT/A was suggested to contribute to its effects on pain in clinical conditions such as migraine [19]. Evidence in humans did not find any effect of BoNT/A on pain perception [20], thereby indicating no direct analgesic effect of BoNT/A and suggesting that pain reduction after BoNT/A treatment is rather mediated through its effect on muscle tone.

The IRLS score is currently the most used primary endpoint as, unlike the CGI, it contains specific questions for RLS symptoms [18]. In our study, although both patients and clinician perceived a change in the severity of the RLS symptoms following BoNT/A injection, the magnitude of this change was not the same depending on whether the IRLS or the CGI-I has been used. Although this shows that the patients' perception of the severity of their RLS symptoms do not always parallel that of the clinician [10,11] it most probably reflects the placebo nature of the patients' response.

5. Conclusion

In conclusion, our results show no indication for a BoNT/A treatment benefit in RLS.

Study funding

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Conflict of Interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2012.08.019.

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