Botulinum Toxin Type A Improves Function According to Goal Attainment in Adults with Poststroke Lower Limb Spasticity in Real Life Practice

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Keywords

Stroke · Spasticity · Type A botulinum toxin · Goal attainment scaling · Cohort study

Abstract

Introduction: Botulinum toxin type A (BoNT-A) is an effective and well-tolerated treatment for adult lower limb spasticity. However, data are inadequate to determine BoNT-A efficacy for active function. This study evaluated functional goal achievement (measured by goal attainment scaling [GAS]) following lower limb BoNT-A injection in clinical practice. **Methods:** Phase 4, postmarketing, multicenter, prospective, observational study (NCT01444794) in adults with poststroke lower limb spasticity receiving one BoNT-A injection cycle. Assessments were at baseline (pretreatment), 1 month $\pm$ 7 days (visit 1), and 3–5 months posttreatment (visit 2). Primary outcome measure was GAS; additional assessments included Modified Ashworth Scale, Demeurisse Motricity Index, 10-meter walk test, and Disability Assessment Scale. **Results:** Of 100 enrolled patients, 94 completed the study. Most common primary treatment goals at baseline were improving mobility (57.5%) and positioning (18.1%). At visit 2, 88.3% achieved their primary goal; 87.0%

($n = 47/54$) for mobility, and 100.0% ($n = 17/17$) for positioning. In total, 79.1% of patients achieved their secondary goals. Two factors were predictive of primary goal achievement: time since stroke onset (OR 0.907; 95% CI 0.827–0.995; $p = 0.038$); and absence of stiff knee spasticity pattern (OR 0.228; 95% CI 0.057–0.911; $p = 0.036$). All functional scales showed improvements; walking speed (mean [SD]) improved by 0.06 (0.13) and 0.05 (0.20) m/s at visits 1 and 2, respectively. **Conclusions:** BoNT-A injection for lower limb spasticity led to high goal achievement rates in patient-centered GAS evaluation and functional and symptomatic improvements. BoNT-A may therefore deliver clinically meaningful functional improvements in real-life practice.

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Introduction

Stroke is the leading cause of disability in adults in Europe and the second most common cause of death worldwide, ranking ahead of cancer and only second to heart disease [1, 2]. In Spain, there are 120–350 cases of stroke per 100,000 inhabitants each year [3]. The resulting central nervous system damage causes upper motor

neuron syndrome, leading to loss of strength and skills; spasticity; and abnormal posture [4, 5]. At 12 months after a first stroke, 17–39% of patients have spasticity and this is disabling in up to 4% of cases [6, 7].

Lower limb spasticity, which commonly manifests as equinovarus foot deformity, is characterized by reduced ankle dorsiflexion and increased forefoot inversion [8]. In patients with lower limb spasticity after stroke, spastic equinus foot represents a prolonged abnormal lower limb posture and affects gait, standing, and transfer [9]. Muscles involved may include the tibialis anterior, tibialis posterior, the long toe flexors, medial and lateral gastrocnemius, soleus, and extensor hallucis longus [8].

Botulinum toxin type A (BoNT-A) is a specific formulation of a locally injected muscle relaxant produced by the bacterium *Clostridium botulinum*. BoNT-A blocks acetylcholine release at neuromuscular junctions, an action that accounts for its therapeutic effect in relieving dystonia and spasticity [10]. The integral role of BoNT-A in the management of focal spasticity is recognized in guidelines around the world [11–13].

BoNT-A has been established as safe and effective for the treatment of adult lower limb spasticity (multiple Class I studies) [14]. However, limited data are available to determine their efficacy in the improvement of active function [14]. Clinical research into the effects of BoNT-A in the lower limbs has focused mainly on deficits, such as muscle tone (measured using the Modified Ashworth Scale [MAS]) or range of movement. However, the goals of rehabilitation programs often involve different fields of the International Classification of Functioning, Disability and Health, such as activity, participation, quality of life, and environmental factors. A recent open-label study of abobotulinumtoxinA for the treatment of lower limb spasticity in adults demonstrated progressive improvements in active function and quality of life following repeated injections [15].

Goal attainment scaling (GAS) is a method for writing personalized evaluation scales, for quantifying progress toward defined goals. This approach is attracting growing interest in clinical practice because it enables the assessment of treatment efficacy based on goals set by the patient themselves, rather than using generic scales, which may not always include the problem that is most pertinent to the patient [16].

GAS can be used to cover all the fields of the International Classification of Functioning Disability and Health, including those relating to activity, participation, quality of life, and environmental factors. Involving the patient and their family and carers in the choice of treatment goals may enable better integration into activities of daily living, by em-

bedding these goals in the patient's usual context [16]. Patients undergoing rehabilitation are more motivated when their goals are clearly defined and consistent with their life project. Furthermore, rehabilitation outcomes are better when the patient is involved in setting their own goals [16].

To the best of our knowledge, real-world evidence on the application of GAS in the management of spasticity with BoNT-A has been only collected for the upper limb [17].

The aim of this study is to evaluate the achievement of goals agreed with the patient/caregiver (measured by GAS) in the treatment of lower limb spasticity with one cycle of BoNT-A injection, used in accordance with standard clinical practice. Secondary objectives are focused on assessing standardized measures of voluntary movement and ambulation, such as the 10-meter walk test (10-MWT).

Methods

Study Design

We ran a multicenter, prospective, observational, longitudinal, single-cohort study (Valoración GAS [VALGAS]; NCT01444794), conducted in 23 neurology and rehabilitation departments in Spanish hospitals between September 2011 and August 2012. All patients received one cycle of BoNT-A injections. Patients were assessed at baseline (pre-BoNT-A treatment), at 1 month $\pm$ 7 days (visit 1), and at 3–5 months post-treatment (visit 2; final visit). As the study is observational, it was designed to reflect, as accurately as possible, real-life clinical practice. Hence, investigators had complete freedom to choose target muscles, BoNT-A product, dose, volume, and number of injections per point.

The study was approved by the Spanish Medicine Agency as a post-authorization study with prospective follow-up. It was also approved by the Ethics Committees of all participating sites. Patients' personal data were confidential and delivered to third parties according to European Directive 95/46/CE on the protection of persons regarding personal data processing and Spanish Law 15/1999 on Personal Data Protection.

Study Population

Adults diagnosed with poststroke lower limb spasticity with no prior BoNT-A exposure, or exposure >12 weeks prior to study entry, were eligible for inclusion. In addition, all patients had a functional ambulation classification of 2–5. Treating physicians were required to confirm that patients were able to follow the study protocol and procedures.

Patients were excluded if they were under 18 years of age; had received BoNT-A for <12 weeks prior to study entry; had suspected botulinum toxin antigen positivity or had received any medication that could interfere with neuromuscular transmission; had any sign of motor neuron disease; had severe muscle atrophy at the injection site; had any other diagnosis that could impact on rehabilitation or outcome assessment; had any nonstroke-related spasticity; were pregnant or lactating women; or had previously participated in studies using GAS scores.

All participating patients provided written informed consent.

Assessments

The primary outcome measure was response rate, based on achievement of the patient's primary GAS objective after one cycle of BoNT-A injection (GAS score at least 0 at visit 2). At baseline, one primary treatment goal and up to 2 secondary goals were set in agreement with the patient/caregivers. Goals were weighted based on their importance and difficulty (from very to moderately).

The achievement of goals was evaluated at visit 2, with scores of +2, +1, 0, -1, or -2 given depending on the level of achievement. If the expected level of achievement was attained, a score of 0 was assigned. Better outcomes were scored +1 (better) or +2 (much better), and worse than expected outcomes were scored -1 (worse) or -2 (much worse) [18]. A responder was a patient who achieved a GAS score of at least 0 at visit 2 (final visit).

The T-score was used to enable GAS scores to be normalized and then analyzed with parametric statistics [16]. T-score was calculated by applying an equation that transforms the raw scores from the individual scales into a single number, T:

$$T = 50 + \frac{10 \sum WiXi}{\sqrt{[(1-\rho)\sum Wi^2 + \rho(\sum Wi)^2]}}$$

where Xi is the GAS score, Wi is the weighting of each goal attainment scale, and rho is the correlation coefficient between the various scales [16]. If all goals have the same weight or the T-score is unweighted, this equation simplifies to:

$$T = 50 + C \sum Xi$$

where C is a coefficient that depends on the patient's number of scales (and thus the number of scores). C is 10 for 1 scale, 6.2 for 2 scales, 4.56 for 3 scales, 3.63 for 4 scales, and 3.01 for 5 scales [16].

Muscle tone was evaluated using MAS, which is considered reliable for grading the resistance of a relaxed limb to rapid passive stretch in 6 stages: [19] from 0, which indicates normal or lowered muscle tone, up to 4, which indicates a state in which passive movement of the affected limb is impossible.

In addition to MAS, investigators and patients/caregivers were invited to complete a number of other assessment scales to provide a broader set of data points. These included the functional ambulation classification, Demeurisse Motricity Index, 10-MWT, Disability Assessment Scale, Spasm Frequency Scale, and the Tardieu Scale [20]. Completion of these scales was optional and was conducted according to local standard clinical practice.

Clinical and demographic parameters were also collected, as well as information on the BoNT-A injection dose, volume, injection sites, and the use of electromyography, electrical stimulation or echography at each center.

Statistical Analysis

A sample size of 100 patients was deemed sufficient to estimate the proportion of responders with $\geq 9.6\%$ precision in the 95% CI.

Statistical analysis was performed by the Biostatistics Department of Nuvisan Pharma Services, Spain, using SAS version 9.2 [21] following the procedures specified in the Statistical Analysis Plan prepared and approved before database lock. Descriptive statistics were applied to all demographic data. Prognostic factors were assessed with a logistic regression analysis.

Analyses were conducted on the primary analysis set ($n = 94$), comprising patients who received treatment and underwent a postinjection visit, including GAS assessment (Fig. 1). Analysis of the primary endpoint was also performed in a number of patient subgroups, including those with documented time since onset of spasticity.

Results

A total of 100 patients received treatment with BoNT-A for poststroke lower limb spasticity. One patient did not complete the study due to comorbidities (pancreatitis and heart failure) and 5 others did not complete a GAS assessment postinjection (Fig. 1). No other major deviations from the protocol were reported.

Baseline Characteristics

Baseline characteristics are provided in Table 1. The mean age (SD) of treated patients was 58.2 (12.5) years, and 65.0% were male. The most commonly reported lower extremity characteristics were increased muscle tone (98.0%) and paresis (92.0%; Table 1); additionally, 29.0% of patients experienced contractures in the lower extremities. The most frequently reported spasticity pattern was clubfoot in 94% of patients; 22 and 21% of patients had striatal foot and stiff knee, respectively. Most patients were living in their own home (71.0%), and 60.0% had a relative who took the role of caregiver. The majority of patients (93.0%) had received prior physical therapy for spasticity. AbobotulinumtoxinA was the most commonly used BoNT-A (92.0%), followed by onabotulinumtoxinA (6.0%) and incobotulinumtoxinA (2.0%; Table 1); median (range) doses injected were 250 units (100; 1,000), 50 units (50; 250), and 100 units (100; 100), respectively. The median number of injected muscles was three. Electromyography and electrical stimulation were used in at least one muscle in 18.0 and 25.0% of patients, respectively. Altogether, 74.0% of patients received one single point injection in at least one muscle, and 85.0% of patients received injections at multiple points.

GAS Goals

At baseline, the most common primary goal of treatment was to improve mobility (57.5%), followed by improving positioning (18.1%; Table 2). Among secondary objectives, the most common goal set was to improve mobility (24.8%), followed by improving positioning (19.4%) and decreasing pain (17.8%).

Fig. 1. Patient disposition. BoNT-A, botulinum toxin type A; GAS, goal attainment scaling.

The overall response rate (the proportion of patients who achieved their primary GAS goal) at 3–5 months (visit 2) was 88.3%. Secondary goals were achieved in 79.1% of cases.

A subanalysis of patients who received abobotulinumtoxinA ($n = 86$) found a response rate for the primary GAS goal of 88.4%. In the subgroup of patients who had better mobility as their primary goal, the response rate was 87.0% ($n = 47/54$), and in those with better positioning as the primary goal, the response rate was 100% ($n = 17/17$). Among patients with onset of spasticity <1 year ago ($n = 37$), 1–3 years ago ($n = 29$), and ≥ 3 years ago ($n = 24$), the primary treatment goal was achieved by 91.9, 89.7, and 83.3%, respectively.

Two factors were found to be predictive of a lower rate of primary goal achievement: time since the onset of stroke (OR 0.907; 95% CI 0.827–0.995; $p = 0.038$) and absence of stiff knee spasticity pattern (OR 0.228; 95% CI 0.057–0.911; $p = 0.036$).

The mean (SD) weighted GAS T-score improved by 17.84 (11.96) points, from 36.17 (3.74) at baseline to 54.02 (10.36) at study end. Similar improvements were recorded for unweighted GAS T-scores.

Muscle Tone, Functional Scales, and Benefit Evaluation

All scales demonstrated improvements in symptoms and function between baseline and study end (Table 3). Mean (SD) MAS decreased from 2.42 (0.65) at baseline to 1.85 (0.73) at visit 1 and 1.91 (0.77) at visit 2; mean De-meurisse Motricity Total Score improved from 57.32 (17.01) at baseline to 61.23 (15.77) at visit 1 and 60.60 (17.37) at visit 2; the 10-MWT showed a mean improvement in walking speed of 0.06 (0.13) m/s at visit 1 and 0.05 (0.20) m/s at visit 2; there were also improvements in all 4 dimensions of the Disability Assessment Scale at visit 2. Patients also reported fewer spontaneous spasms on the Spasm Frequency Scale at study end compared with baseline.

A total of 81.7% of investigators and 78.5% of patients rated their global assessment of benefit to be “some” or “great.”

Discussion

To the best of our knowledge, this is the first observational study to determine responder rate based on GAS in patients with lower limb spasticity. The study illustrated that in patients with poststroke lower limb spasticity, one cycle of BoNT-A administered according to the usual clin-

ical practice of participating centers led to a high rate of achievement of primary and secondary objectives (88.3 and 79.1%, respectively) using the GAS evaluation system.

If goals are set in an unbiased fashion, and are neither overambitious nor overcautious, the mean GAS T-score should be around 50 ($\pm$ SD 10) [22]. The mean (SD) GAS T-score of 54.02 (10.36) at study end in the present work provides a useful quality check of investigators' ability to set achievable goals. Previous authors have suggested that GAS score changes >10 are clinically meaningful [23, 24]. In this study, the mean improvement from baseline to study end was 17.84 (11.96).

Two predictive factors were identified for the attainment of objectives. A progressive decrease in objective attainment was observed with increasing years since the onset of spasticity. This was evidenced in a multiple logistic regression model, in which increasing time since the onset of stroke was associated with lower response rates. This is a logical finding and confirms similar results from previous studies [25–28]. The second predictive factor identified was the absence of a stiff knee, which could reflect the impact of this spasticity pattern on the difficulty of achieving the primary goal – most commonly improvement in mobility.

All symptom assessments and functional scales assessed showed clear improvements after one cycle of BoNT-A injections, including the MAS, Demeurisse Motricity Total Score, 10-MWT, and the Disability Assessment Scale. In addition, the Spasm Frequency Scale revealed that patients reported fewer spontaneous spasms at study end compared with baseline. All these measurements showed greater improvements at 1 month (visit 1) compared with 3–5 months post-BoNT-A injection (visit 2). This aligns with the known process of gradual recovery of impulse transmission from 6 to 8 weeks, as new nerve terminals sprout [29]. However, although the improvements were less marked at 3–5 months, there was still evidence of a good effect relative to baseline. In particular, improvement in walking speed (10-MWT) was notable. A systematic review and meta-analysis on the impact of BoNT-A treatment on gait velocity revealed a small improvement (Hedges' g 0.193 ± 0.081 ; 95% CI 0.033 – 0.353 ; $p < 0.018$), equivalent to an increase of 0.044 m/s [30]. Similarly, a recent study with repeat BoNT-A injections showed a progressive increase in comfortable barefoot walking speed across injection cycles, with a mean (95% CI) improvement of $+0.05$ (0.03 – 0.07) and $+0.04$ (0.03 – 0.06) m/s after a single injection of 1,000 or 1,500 U abobotulinumtoxinA, respectively, followed by an overall least squares mean (95% CI) improvement from baseline of $+25.35\%$ (17.48 – 33.21) by

Table 1. Baseline patient, disease, and treatment characteristics

Characteristic	Patients ($n = 100$), n (%)
Age, years, mean (SD)	58.2 (12.5)
Gender	
Male	65 (65.0)
Female	35 (35.0)
Patient autonomy*	
Lives in own home	71 (71.0)
Lives with a relative as a caregiver	43 (43.0)
Has the assistance of a relative as caregiver	17 (17.0)
Time since stroke onset, years, mean (SD)	4.1 (5.3)
Stroke type*	
Ischemic	64 (64.0)
Hemorrhagic	40 (40.0)
Stroke sequelae*	
Hemiparesis	93 (93.0)
Impaired balance or coordination	46 (46.0)
Depression	33 (33.0)
Aphasia	22 (22.0)
Time since spasticity onset, years, mean (SD)	2.4 (4.1)
Upper extremity involvement	
Yes	89 (89.0)
No	11 (11.0)
Lower extremity involvement (all)*	
Ankle	95 (95.0)
Foot	81 (81.0)
Knee	43 (43.0)
Hip	20 (20.0)
Spasticity pattern*	
Clubfoot	94 (94.0)
Striatal foot	22 (22.0)
Stiff knee	21 (21.0)
Lower extremity characteristics*	
Increased muscle tone	98 (98.0)
Paresis	92 (92.0)
Hypertonia	81 (81.0)
Babinski sign	81 (81.0)
Fatigue	77 (77.0)
Loss of selective motion control	75 (75.0)
Prior nondrug therapies for spasticity*	
Physical therapy	93 (93.0)
Antispastic positions	65 (65.0)
Orthosis	60 (60.0)
Muscular facilitation techniques	54 (54.0)
Electrical stimulation	15 (15.0)
Biofeedback	11 (11.0)
Prior drug therapies for spasticity*	
Botulinum toxin	62 (62.0)
Baclofen	31 (31.0)
Diazepam	5 (5.0)
Tizanidine	4 (4.0)
BoNT-A treatment	
AbobotulinumtoxinA	92 (92.0)
OnabotulinumtoxinA	6 (6.0)
IncobotulinumtoxinA	2 (2.0)
Functional ambulation category [†]	
2 – walks with intermittent assistance by 1 person	17 (18.1)
3 – walks with monitoring. The patient needs verbal assistance without physical contact	17 (18.1)
4 – walks independently on plain paths, but does not climb stairs	60 (63.8)

All treated population.

* Responses were not mutually exclusive.

[†] Only assessed in the primary analysis set ($n = 94$).

BoNT-A, botulinum toxin type A.

Table 2. Primary and secondary goal areas at baseline and achievement (PAS population)

Goal area	Primary goals		Secondary goals	
	at baseline, <i>N</i> (%)	achievement <i>n/N</i> (%)	at baseline, <i>N</i> (%)	achievement <i>n/N</i> (%)
Better mobility	54 (57.5)	47/54 (87.0)	32 (24.8)	24/32 (75.0)
Better positioning	17 (18.1)	17/17 (100.0)	25 (19.4)	20/25 (80.0)
To decrease pain	8 (8.5)	7/8 (87.5)	23 (17.8)	19/23 (82.6)
To decrease spasms	6 (6.4)	5/6 (83.3)	10 (7.8)	9/10 (90.0)
To enhance brace	4 (4.3)	3/4 (75.0)	19 (14.7)	19/19 (100.0)
To enhance range of motion	5 (5.3)	4/5 (80.0)	19 (14.7)	10/19 (52.6)
To delay or prevent surgery	0 (0)	0/0 (0)	1 (0.8)	1/1 (100.0)

PAS, primary analysis set; *N*, number of patients who set goal at baseline; *n*, number of patients who achieved their goal.

Table 3. Functional scales assessed as secondary objectives (PAS population, *n* = 94)

Measure	Baseline	Visit 1		Visit 2	
		mean value	change from baseline	mean value	change from baseline
MAS, mean (SD)	2.42 (0.65)	1.85 (0.73)	−0.55 (0.65)	1.91 (0.77)	−0.51 (0.63)
Demeurisse Motricity Total Score, mean (SD)	57.32 (17.01)	61.23 (15.77)	2.69 (9.00)	60.60 (17.37)	3.28 (11.59)
10-MWT, m/s, mean (SD)	0.46 (0.30)	0.50 (0.34)	0.06 (0.13)	0.49 (0.34)	0.05 (0.20)
Disability Assessment Scale, mean (SD)					
Hygiene	0.95 (0.95)	N/A*	N/A*	0.82 (0.91)	−0.08 (0.77)
Dressing	1.21 (0.86)			0.98 (0.92)	−0.22 (0.67)
Limb position	1.33 (0.76)			1.02 (0.91)	−0.29 (0.70)
Pain	0.91 (0.87)			0.53 (0.68)	−0.37 (0.75)
Spasm Frequency Scale, <i>n</i> (%)					
Spontaneous spasms	11 (18.6)	N/A*	N/A*	5 (8.5)	
Fewer than 1 spontaneous spasm/hour	8 (13.6)			4 (6.8)	
One or more spontaneous spasms/hour	2 (3.4)			1 (1.7)	
More than 10 spontaneous spasms/hour	1 (1.7)			1 (1.7)	

* This scale was optional at visit 1.

PAS, primary analysis set; N/A, not available; MAS, Modified Ashworth Scale; 10-MWT, 10-meter walk test.

week 4 of injection cycle 4 [15]. In our study, mean walking speed increased by 0.06 m/s at 1 month and 0.05 at 3–5 months. Hence, the results align with previous data, supporting the notion that BoNT-A can increase gait velocity in patients with poststroke lower limb spasticity.

The mean number of patients recruited per center was only 4, which is too low a number to reflect the diversity of patients treated at present with BoNT-A. However, a large number of centers involved in the study indicate a high degree of uniformity in clinical practice and support generalization of the findings in Spain. A similar percentage of investigators and patients rated their global assessment of benefit as “some” or “great.” This may reflect the

process of agreement between patients and healthcare providers in the setting of primary and secondary goals, providing a model for the evaluation of achievement in other studies.

Overall, this study confirms that patients treated with one cycle of BoNT-A injections (predominantly abobotulinumtoxinA) for lower limb spasticity had a high response rate, as measured by patient-centered goal attainment using GAS. Symptoms and function, measured using standardized scales, were also improved. Hence, BoNT-A treatment may deliver clinically meaningful improvements at a functional level in the treatment of spasticity in real-life practice.

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Statement of Ethics

All participating patients provided written informed consent. The study was approved by the Spanish Medicine Agency as a post-authorization study with prospective follow-up. It was also approved by the Ethics Committees of all participating sites. Patients' personal data were confidential and delivered to third parties ac-

cording to European Directive 95/46/CE on the protection of persons regarding personal data processing and Spanish Law 15/1999 on Personal Data Protection.

Disclosure Statement

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Author Contributions

All authors made a substantial contribution to the concept and design of the study, acquisition of data, critical revision of the draft and interpretation of data, and provided approval of the present version for submission to publication.

Data Availability

Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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