An international, multicenter, prospective, randomized, evaluator-blinded study comparing different botulinum toxin injection strategies for treatment of upper limb spasticity

Tiina Rekand,[1] Bo Biering-Sørensen,[2] Jun He,[3] Ole Jakob Vilholm,[4] Peter Brøgger Christensen,[5] Trandur Ulfarsson,[6] Roger Belusa,[7] Torbjörn Ström,[7] Peter Myrenfors,[7] Pascal Maisonobe,[8] Torben Dalager,[9]

1. Dept. Of Neurology, Haukeland Unversity Hospital, Bergen, Norway 2. Dept. of Neurology, Spasticity Clinic, Rigshospitalet Glostrup, Glostrup, Denmark 3. Dept. of Neurology, University Hospital of Copenhagen, Roskilde Hospital, Denmark 4. Dept. Of Neurology, Vejle Hospital, Vejle, Denmark 5. Dept. of Neurology, Aarhus University Hospital, Denmark. 6. Dept. Of Rehabilitation Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden. 7. Institut Produits Synthèse (Ipsen AB), Stockholm, Sweden 8. Ipsen Pharma, Boulogne, France 9. Clinic of Dystonia, Bispebjerg Hospital, Copenhagen, Denmark

Scan here to view a PDF of this poster

Copies of this poster obtained through Quick Response Code are for personal use only

QR code to be provided by Toxins

Introduction

Patients with spasticity suffer from decreased active movement, increased disability and impaired function. Intramuscular injections with botulinum toxin (BoNT) is a safe and efficacious established treatment option for these patients. Studies with abobotulinumtoxinA (ABO, Dysport) have demonstrated benefits such as decreased resistance to passive movement, improvement in pain, and goal attainment. Several factors such as injection technique and targeting of neuromuscular junctions (NMJ), concentration of BoNT and volume of injected solution as well as stimulation of BoNT uptake in targeted cells can influence efficacy.

Animal and human studies indicate that targeting these NMJ zones increase the effectiveness of BoNT-A injections. Gracies et al (2009) suggested that NMJ targeted injections in combination with a low-concentration dilution of BoNT are superior to a non-targeted injection technique with a high-concentration dilution.

The hypothesis for this study was that one high volume and low-concentration ABO injection per muscle result in the same effect as several injections. The only injection should be centrally located in the area of the NMJ zones. The ABO will spread to and block the surrounding NMJ zones and be as effective as a technique with several injections with lower volume and higher concentration. A randomized, multicenter, international, evaluator-blinded study was performed to evaluate non-inferiority between these two different injection treatment strategies.

Methods

Patients

39 medical centers from Finland, Norway, Denmark and Sweden participated in the study. Inclusion criteria were: provision of written informed consent, male or female, aged 18 or older, suffering from upper limb spasticity as a result of stroke or traumatic brain injury, spasticity position pattern type 1, 3 or 4, elbow flexor muscles spasticity MAS 2 to 3, at least 2 consecutive previous treatment cycles of ABO for treatment of the current diagnosis, the latest treatment cycle demonstrating good treatment efficacy according to investigator judgement, ABO dose administered was considered to be adequate according to investigator judgement, need for the same treatment modality in m. brachialis, m. biceps brachii, m. brachioradialis, m. flex. carpi ulnaris, m. flex. carpi radialis as the previous treatment cycle and last ABO treatment 12-24 weeks ago. Main exclusion criteria were: a need for ABO doses >800 units in the upper limb, is likely to start other spasticity treatment during the study, is likely to start physiotherapy treatment during the study, other ongoing neurological disorder and use of agents interfering with neuromuscular transmission.

Design and treatment

This is a non-inferiority study (ClinicalTrials.gov, number NCT01682148). Patients were randomly allocated to two injection strategies in a ratio of 1:1 (stratified for spac. pattern and country). The two groups were named current clinical practice (group 1) and NMJ targeting technique (group 2) see table 1. The injection strategies are presented in table 1. The injection-points in group 2 were predefined according to the mapping of NMJ zones. All injections were guided using electromyography (EMG) and/or ultrasound (US).

Study endpoints and assessments

The primary variable was change in modified Ashworth scale (MAS) between baseline and 4 weeks post injection for elbow flexors muscles. The primary endpoint is defined as one level decrease on the MAS and evaluated as the proportion of patients with at least 1 level improvement. The treatment was blinded to the evaluator. MAS was assessed at baseline and week 4 and 12.

Table 1. Injection strategies

	Group 1	Group 2
m. biceps brachii*	2-4	1
m. brachialis*	2-4	1
m. brachioradialis*	1-2	1
m. flexor carpi radialis / m. flexor carpi ulnaris*	2-3	1
Total no. of injections	7-13	4
Volume of injection	0.1- 0.7 mL per muscle	0.4- 2.0 mL per muscle
Conc. of ABO	300 units/ml	100 units/ml

*number of injection points

Table 2. Baseline characteristics

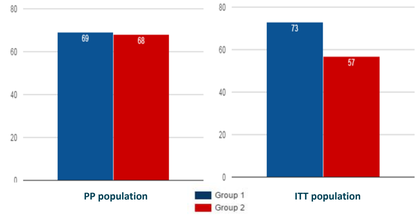
	PP population		ITT population	
	Group 1	Group 2	Group 1	Group 2
Number of subjects	29	25	44	44
Age, years (mean±SD)	60.9 ±13.2	58.7 ±10.0	60.3 ±14.4	57.1 ±11.4
Male, n (%)	18 (62.1%)	17 (68.0%)	28 (63.6%)	30 (68.2%)
Spasticity patterns % (I, II, IV)	6.9, 51.7, 41.4	12.0, 48.0, 40.0	9.1, 54.5, 36.4	11.4, 59.1, 29.5
Years since stroke/injury (median, range)	3 1--16	5,5 1--24	4 1--21	4 1--24
ABO units inj. upper limb (mean±SD)	537.8 ±130.2	579.4 ±180.5	566.4 ±169.8	588.0 ±200.3

The secondary study endpoints were: MAS of elbow flexors at 12 weeks, spasticity pain measured by VAS (scale 0-100), injection pain measured by VAS, achievement of the primary goal measured by Goal Attainment Scale (GAS, scale -2 +2), subjective global evaluation of treatment effect and investigator preference of injection technique.

Data analyses

Statistical methods: both the primary endpoint (MAS responders) and the design as a non-inferiority study were taken into account for sample size calculation. A two sided 95% confidence interval for the difference of the two clinical success rates was calculated using generalized linear model with treatment, spasticity position patterns, country and baseline MAS score as factors. Significance was set at p<0.025 one sided (non inferiority).

Figure 1. Proportion (%) responders (≥1 improvement in MAS)



Results

Patients

The final size of the treatment groups was not in line with the planned sample size, as 272 subjects were originally planned to be enrolled. Difficulty in recruitment and protocol violations were the main reasons. 20 centers included 88 patients who were randomised in the study (ITT population). 54 of these completed the study without protocol violation (PP population). Protocol violation was detected in 34 patients. In 23, study treatment was not injected as per protocol and 11 had other violations, e.g. 5 patients had missing MAS evaluations. Baseline characteristics and ABO units injected are shown in table 2.

Study endpoints

Primary endpoint

- Proportion of responders in the ITT population at week 4 (≥1 level improvement in MAS) was 72.7% in group 1 and 56.8% in group 2. The adjusted difference between the two clinical success rates (group 2 minus group 1) was -0.1673 (95% CI; -0.3630, 0.0284; p=0.0986) (figure 1).
- Proportion of responders (≥1 level improvement in MAS) in the PP population for elbow flexors at week 4 was 69.0% in group 1 and 68.0% in group 2 (figure 1).

Secondary endpoints

- Mean (SD) and median changes in MAS for elbow flexors at week 4 are presented in figure 2 (PP and ITT populations).
- At week 12 there was a slight numerical higher proportion of responders in group 1 (19 (48.7%)), than in group 2 (13 (33.3%)) (ITT population). Proportion difference -0.1324 (-0.3531, 0.0884), p-value: 0.2400. The improvement after injections were not different in the two injection strategies.
- Improved outcome GAS (score 0, +1 or +2), was shown for 21 subjects (63.6%) in group 2, and for 25 subjects (61.0%) in group 1 (ITT population), and there was no statistically significant differences between the treatment groups
- Evaluation of pain at week 4 using VAS (100 mm scale) for both spasticity and injection pain is shown in table 3 (ITT population). There were no statistically significant differences, in spasticity pain measured by VAS, shown between the groups, either at week 4 (p=0.9448; 95% CI: -7.5570, 7.0474) or at week 12 (p=0.5458; 95% CI: -7.1575, 13.4217). At baseline, the mean VAS for injection related pain was 30.68 mm (SD 27.33 mm) in group 1 and 25.67 mm (SD 25.37 mm) in group 2. There was no statistically significant difference shown between the groups (p=0.4006; 95% CI: -17.9809, 7.2784).
- Subject global evaluation of treatment effect did not differ between the treatment groups
- Physician preference of injection technique could not be evaluated due to too few reports

Safety

- Adverse events reported were consistent with known safety profile of ABO.
- Subjects that experienced any TEAEs: group 1 (11 (25.0%)) and group 2 (15 (34.1%)). Investigator assessed treatment related TEAEs: group 1 (2 (4.5%)) and group 2 (1 (2.3%)). In group 1: one patient with injection site hypersensitivity, assessed as mild and related to the study treatment and one patient with dysphagia and fatigue, both assessed as mild and related to the study treatment. In group 2: one patient experienced fatigue, assessed as moderate and related to the study treatment. Majority of events reported were of mild to moderate in intensity. Three subject experienced severe TEAEs in group 2 assessed by investigators as not related to ABO treatment and none in group 1. Two subjects in both groups experienced serious adverse events.
- There were no reported TEAEs leading to withdrawal or death.

Figure 2. Mean (SD) change in MAS in elbow flexors at week 4

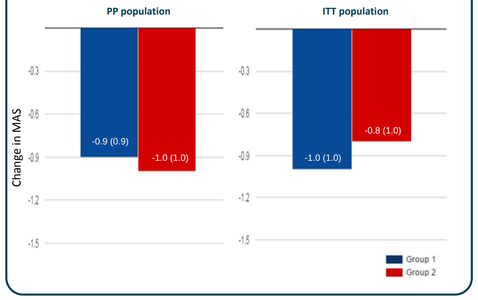


Table 3. Evaluation of pain (VAS 100 mm) at week 4. Spasticity related pain (a) and injection related pain (b).*

VAS (mean±SD)	Group 1 (a)	Group 2 (a)	VAS (mean±SD)	Group 1 (b)	Group 2 (b)
Baseline	14.32 ±22.64	21.66 ±28.97	Baseline	30.68 ±27.33	25.67 ±25.37
Week 4	10.30 ±19.99	14.05 ±27.50	Raw Difference		-5.01
Mean change	-4.35 ±12.29	-5.8 ±23.07	p-value		0.4006
% decrease of mean value	30.4	26.8			

*ITT population

Conclusions

- The study was terminated early due to slow recruitment and the predefined number (272) of patients was not met, hence statistical analysis is weak and the interpretation should be careful
- We could not detect any difference in MAS at the elbow flexors at 4 weeks between the two injection strategies. The primary endpoint of non-inferiority could not be shown due to insufficient number of included patients
- Both treatment strategies resulted in a high proportion of responders
- The experienced pain was mild or moderate. Reduction of pain was achieved in both groups
- The study did not reveal any new safety issues regarding treatment with ABO
- Due to premature termination of this study, further investigation is needed to confirm the hypothesis and the trend seen in the study that targeting the NMJ zones with a higher volume/lower concentration injection in spastic muscles could decrease the number of required injection points

Acknowledgments

The authors thank the investigators and patients participating in this study. The authors thank PCG for assisting in data management.

NMJ Study Group:

Tiina Rekand, Bo Biering-Sörensen, Jun He, Ole Jakob Vilholm, Peter Brøgger Christensen, Trandur Ulfarsson, Roger Belusa, Torbjörn Ström, Peter Myrenfors, Pascal Maisonobe, Torben Dalager, Jesper Gyllenborg, Jari Ylinen, Anna-Maija Saukkonen, Ottar Berg, Kjell Kullander, Ann Axelsson, Eilert Öhman, Magdalena Siberna-Grajnert, Miriam Morell-Larsen, Inge Bäckström.

References

1. Gracies JM, Lugassy M, Weisz DJ, Vecchio M, Flanagen S, Simpson DM. Botulinum toxin dilution and endplate targeting in spasticity: a double-blind controlled study. Arch Phys Med Rehabil 2009; 90: 9-16

Presented at the 3rd TOXINS Congress 18-21 January 2017, Madrid, Spain.

This study was sponsored by Ipsen