Botulinum Neurotoxin Revisited – An Individualised, Patient-centric Approach for the Treatment of Dystonia and Spasticity

Report of the Proceedings of Centro de Medicina de Reabilitação de Alcoitão Symposium at Toxins 2015, Lisbon, Portugal

Expert Review by:

Maja Relja,[1] Jorge Jacinto,[2] Joseph Jankovic[3] and Alberto Albanese[4]

1. University Hospital Center Zagreb, Croatia; 2. Centro de Medicina de Reabilitação de Alcoitão, Alcabideche, Portugal; 3. Baylor College of Medicine, Houston, Texas, US; 4. Istituto Nazionale Neurologico Carlo Besta, Milan, Italy

Abstract

Botulinum toxin A (BoNT-A) has become the first-line therapy in cervical dystonia (CD), blepharospasm and spasticity. However, the current guidelines for the clinical use of BoNT-A are based on data published more than 20 years ago and patient satisfaction with current treatment regimens is low. There is a striking difference between the injection intervals given in everyday clinical practice and the injection intervals preferred by patients. Recent data have indicated that shorter injection intervals may improve overall patient satisfaction since re-emergence of symptoms could be prevented. Three double-blind studies have demonstrated that incobotulinumtoxin A (incoBoNT-A) is suitable for use in a flexible, patient-centric approach in blepharospasm and CD, with injection intervals starting from 6 weeks. The efficacy, tolerability and safety of this regime were excellent. There is a need to optimise and individualise the treatment using the three available formulations of BoNT- A, as well as to define parameters for switching between the formulations.

Keywords

Botulinum toxin, blepharospasm, spasticity, cervical dystonia, incobotulinum toxin A

Disclosure: Maja Relja has no conflicts of interest to declare. Jorge Jacinto has received honoraria and support from Allergan, Ipsen and Merz for conferences, lectures, research projects, advisory and consultancy. He has no profit nor financial or other benefits from any of the companies. Joseph Jankovic has received research grants and is a consultant for Allergan, Ipsen and Merz. Alberto Albanese has received research grants and is a consultant for Allergan, Ipsen and Merz.

Acknowledgements: Editorial assistance was provided by Katrina Mountfort of Touch Medical Media, London, UK. This article reports the proceedings of a sponsored satellite symposium and as such has not been subject to the journal's usual peer-review process.

Received: 15 January 2015 **Accepted**: 9 April 2015 **Citation**: *European Neurological Review*, 2015;10(1):28–34 *DOI: 10.17925/ENR.2015.10.01.28*

Correspondence: Jorge Jacinto, Centro de Medicina de Reabilitação de Alcoitão, Serviço 3; Rua conde Barão, 2649-506 Alcabideche, Portugal. E: jor.jacinto@netcabo.pt

Support: The publication of this article was supported by Merz. The views and opinions expressed are those of the presenters and not necessarily those of Merz.

Introduction

Maja Relja

University Hospital Center Zagreb, Croatia

Since its introduction in the 1980s, botulinum toxin type A (BoNT-A) has become the first-choice treatment for most types of focal dystonia, including cervical dystonia (CD) and blepharospasm. It is also widely used in the treatment of spasticity arising from stroke, spinal cord injury, multiple sclerosis and traumatic brain injury, as well as in the treatment of pain e.g. chronic migraine. However, the current guidelines for the clinical use of BoNT-A are based on historical data, some of which was published more than 20 years ago,[1] and recent data suggest that patient satisfaction with current therapeutic regimes is low. A satellite symposium, co-chaired by Dr Maja Relja and Dr Jorge Jacinto, was held at Toxins 2015, Lisbon, Portugal, January 2015 organised by the Centro de Medicina de Reabilitação de Alcoitão, Portugal. Dr Relja presented the aims of the symposium: to review existing data on a patient-centric approach in spasticity and CD using BoNT-A; to provide information about recent clinical data; to consider how an individualised approach can be incorporated into clinical practice; and to provide practical expert guidance on evolving treatment strategies. ■

What do the Patients Want and What do they Expect from their Botulinum Neurotoxin Treatment?

Jorge Jacinto

Centro de Medicina de Reabilitação de Alcoitão, Alcabideche, Portugal

Dr Jacinto began with the Institute of Medicine definition of patient-centric care that is respectful of and responsive to individual patient preferences, requirements and values, ensuring that patient values guide all clinical decisions.[2] He proceeded to discuss the evaluation of patient-centric care in spasticity and dystonia. There is a need to establish what patients want and need, in addition to what healthcare professionals consider therapeutic goals and to provide a tool for to evaluate treatment.[3,4] Many people consider that there is a discrepancy between patients' and doctors' evaluations.

A recent online survey (n = 969) conducted in the US and EU showed that there is a need for an improvement in CD management in terms of patient satisfaction.[5] A patient-centric approach may necessitate a re-evaluation of how ambitious we should be for each treatment cycle in terms of number of muscles, doses and adjunctive treatments. Individual perception is very important in assessing treatment effect; the response to BoNT-A is multidimensional, and may be measured in terms of magnitude, duration, waning of effect, tolerability and safety. It is therefore difficult for the patients to accurately interpret treatment response. Furthermore, the response is not immediate, leading to memory bias. Therefore, it is important to evaluate treatment in an individualised manner and to manage patient's expectations.[6] In a 2005 study of 78 patients (mean age 54 years, 65 % female) with CD, patients' satisfaction with long-term BoNT-A treatment (median 5.5 years, range 1.5–10) was evaluated on a seven-point scale ranging from excellent to worsening. The independent evaluations of the treating neurologists broadly correlated with the patient's scores but differed in the excellent category (9 % of patients versus 17 % neurologists).[7]

Recommendations in national guidelines generally evaluate the effectiveness of BoNT-A treatment for spasticity in terms of improvement of the modified Ashworth scale.[8–10] Treatment effect is usually measured around the time of maximum effect (between 4 and 6 weeks after injection) and after 12 weeks (termination of the study or re-injection). There is no measurement of treatment effect in the time between the peak effect and the usual time point of re-injection. In addition, functional improvement is usually not adequately measured in most studies, partly due to the lack of sensitive assessment scales that relate to real-life tasks. Duration is typically not reported, since a routine injection interval is used (and/or single injection). Doses and injection patterns are pre-defined in most study protocols; studies are generally constrained in this aspect by the need to serve regulatory purposes. Patient-reported outcomes are usually limited to the Global Assessment of Efficacy and Tolerability at the end of the study (mostly single-injection studies). Sometimes the Disability Assessment Scale (DAS), and, more recently, the Goal Attainment Scale (GAS) have been used.[8–14]

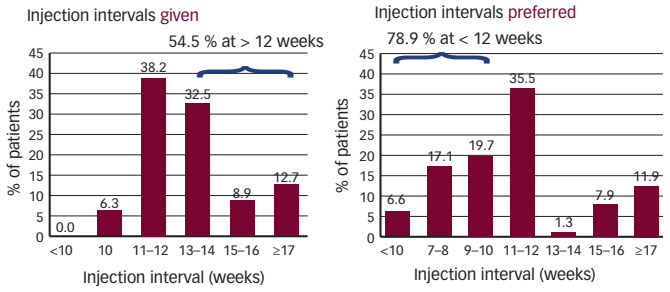
The interval between injections is a factor that has not been widely debated. Many reviews give no specific recommendations on injection interval and state that more research is required.[9–12,15] The French guidelines, however, recommend a 3-month interval although they agree that long-term studies are missing.[13] The UK guidelines state that although patients may become biologically resistant to BoNT-A as a result of antibody formation, it is rarely reported in practice. They recommend a review at three to four months post-injection, when the effect of the toxin is likely to have worn off.[8] Current product labelling of BoNT-A formulations recommends injection intervals of ≥10 weeks[16] (incobotulinumtoxinA in Europe only) to ≥12 weeks[17–21] for the treatment of CD. For spasticity, the current standard of care is injection intervals of at least 3 months.[22–24] However, some patients may experience re-emergence of symptoms before the next dose is administered. This may lead to reduced patient satisfaction during the latter part of the injection cycle. In practice, physicians compensate for this by giving larger doses, which may have adverse effects, or by giving adjunctive therapies.

Two recent surveys have evaluated patient satisfaction with current dosing regimens of BoNT-A for the treatment of CD and spasticity. These involved structured patient interviews that were conducted in Germany, France, the US and Canada. All participants had received ≥2 injection sessions with BoNT-A. In the survey in CD, patients receiving abobotulinumtoxinA (aboBoNT-A, Dysport®, Ipsen Ltd) or onabotulinumtoxinA (onaBoNT-A, Botox®, Allergan Inc) were included.[25] In the survey in spasticity, patients receiving aboBoNT-A, incobotulinumtoxinA (incoBoNT-A, Xeomin®, Merz Pharmaceuticals) and onaBoNT-A were included.[26] Interviews were conducted either at 7–8 weeks or 9–10 weeks after the patient's last injection session; these time frames were considered to allow sufficient time for the BoNT-A to confer peak clinical effects.

In the CD survey, patients (n=136) usually received BoNT-A treatment at intervals of every 9–10 weeks (4.4 %), every 11–12 weeks (42.7 %), every 13–14 weeks (27.2 %), every 15–16 weeks (10.3 %) or >17 weeks (15.4 %). The mean (standard deviation [SD]) interval between injection sessions was 14.0 (3.7) weeks.[25] Patient satisfaction tended to follow the peak and waning of treatment effect. Satisfaction was greatest when patients were recalling the time of peak treatment effect. At this time point, the majority of patients (77.5 %) were very satisfied with treatment. Fewer patients were very satisfied at the time of the interview (7–10 weeks after the previous injection session; 50.7 %), and fewer again recalled being very satisfied just prior to the last injection session (13.7 %), when the effects of the previous dose would be diminishing.[25] At this time point, 39.2 % of patients reported not being satisfied at all. When asked for their preferred injection interval preferences, patients' responses varied, with a mean preferred injection interval of 12.9 weeks, although 46 % of patients would have preferred intervals of ≤10 weeks. Around half of patients stated that, given the choice, they would have a re-injection on the day of the interview (31.6 % somewhat; 22.1 % very much).[25]

In the spasticity survey (n=79), when asked about the interval at which they normally receive injection sessions, 54.5 % of patients stated they received injections at intervals of more than 12 weeks.[26] When asked about their preference for injection intervals, 78.9 % stated that they

Figure 1: Contract between Injection Intervals Given and Injection Intervals Preferred in the Treatment of Spasticity with BoNT-A



BoNT-A = botulinum toxin A. Source: Bensmail et al., 2014.[26]

would prefer an interval shorter than 12 weeks, and 43.4 % would prefer intervals of 10 weeks or less. The majority of patients stated a preference for re-injection on the day of their interview (36.7 % somewhat; 36.7 % very much so). Interviews were conducted 7–10 weeks after the most recent injection. As seen in the CD survey, patient satisfaction tended to follow the peak and waning of treatment effect. Satisfaction was greatest when patients recalled the time of peak treatment effect. For this time point, the majority of patients (68.2 %) were very satisfied with treatment. Few patients recalled being very satisfied just prior to the last injection session (9.1 %), when the effects of the previous dose would be diminishing. There was a striking difference between the injection intervals given (54.5 % >12 weeks) and the injection intervals preferred (78.9 preferred an interval of <12 weeks, see *Figure 1*). The majority of patients stated that, given the choice, they would have a re-injection on the day of their interview (31.6 % somewhat; 22.1 % very much so).[26]

In summary, the mean BoNT-A injection interval for patients is approximately 14 weeks. However, nearly the half of patients with CD and spasticity would prefer intervals of 10 weeks or less. Patient satisfaction levels generally follow the onset, peak and trough of clinical effect. Satisfaction was lowest just prior to the next injection session, which may have been due to symptom re-emergence. Shorter injection intervals may therefore improve overall patient satisfaction. ■

Do We have Data to Treat According to Individual Needs?

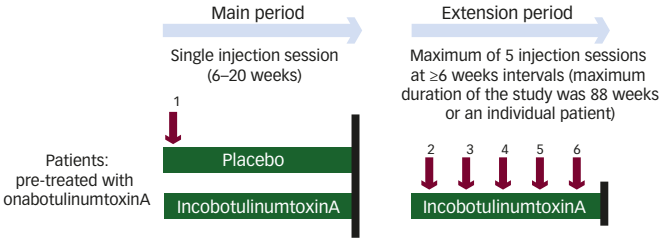
Joseph Jankovic

Baylor College of Medicine, Houston, Texas, US

Dr Jankovic began by reinforcing the conclusion of the previous presentation: that some patients might benefit from more frequent injections than the currently recommended minimum injection intervals of ≥12 weeks, which is based on data published more than 20 years ago.[1] Three recent double-blind clinical trials have, for the first time, investigated on-demand, flexible injection intervals to allow treatment individualisation.[27–29] In these trials, patients were able to visit the physician when they felt a repeat injection was necessary. The physician then objectively verified the need for a repeated injection, and retreated where indicated. In two trials, the study design was a randomised, placebo-controlled, double-blind main period, in which patients received a single injection of placebo or incoBoNT-A,[30,31] and in one study this was followed by an open-label extension period comprising a maximum of five injection sessions at ≥6-week intervals (the maximum study duration was 88 weeks for an individual patient; see *Figure 2*).[27,28] The third study evaluated the safety of two different doses of incoBoNT-A in a randomised, double-blind fashion as an extension to the CD placebo-controlled study. The study permitted flexible injection intervals as short as 6 weeks if patients had a clinical need for re-injection. Important inclusion criteria were Jankovic Rating Scale (JRS)[32] severity subscore ≥2 in blepharospasm and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) 33 total score ≥20 in CD.

The mean study duration of the blepharospasm extension study was 52.6 weeks (range 6.3–75 weeks); 79.4 % received at least four of the maximum five possible injections. The mean (SD) injection interval was 12.6 (4.5) weeks (median 12 weeks). The majority (94.9 %) of re-injections were administered after intervals of 6 to 20 weeks: 23.7 % were 6 to ≤10 weeks; 32.2 % >10 to ≤12 weeks; 24.7 % >12 to ≤14 week; and 19.4 % >14 weeks. The mean total doses (SD) of incoBoNT-A ranged from 64.7 (22.4) U (unit of biological activity) at the first injection to 72.7 (22.0) U at the fifth injection visit, range: 15.0 to 100.0 U.[28] The mean JRS sum scores significantly improved from each injection visit to the respective control

Figure 2: Design of Study Investigating Flexible Dosing of BoNT-A in Blepharospasm

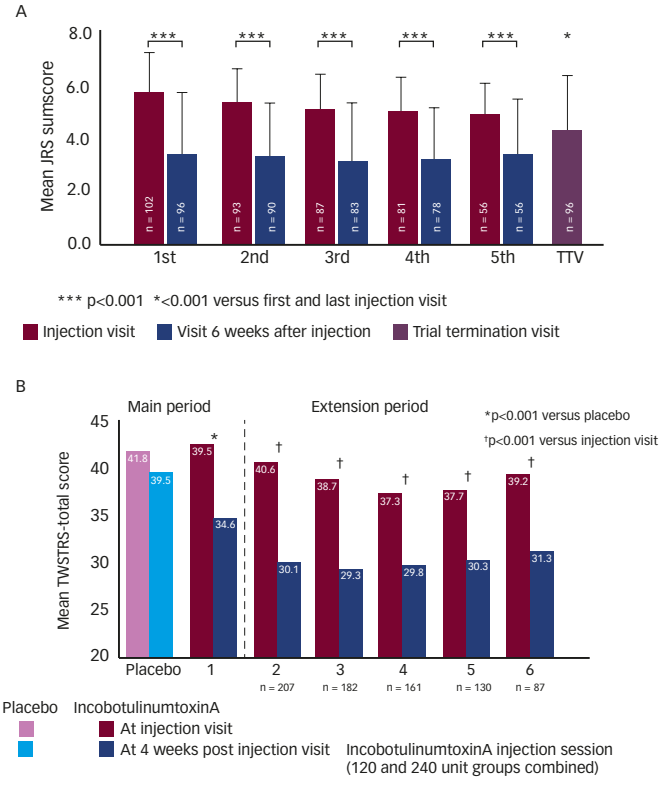


BoNT-A = botulinum toxin A.

visit 6 weeks later (p<0.001 for all sessions; see *Figure 3*), with mean (SD) improvements at the control visits ranging from –1.6 (1.8) to –2.4 (2.2). The mean (SD) JRS sum scores at the injection visits decreased across the study duration from 5.9 (1.4) to 4.9 (1.2). The mean JRS sum score at the trial termination visit (TTV) was significantly lower than at the first and the fifth injection visit (p<0.001). Similar patterns were seen for the JRS severity and frequency subscores (p<0.001 for all changes from injection to control visit; p≤0.002 for all changes from first or fifth injection visit to the TTV). The mean Blepharospasm Disability Index (BSDI) mean scores significantly improved from each injection visit to the respective control visit (p≤0.001 for all). BSDI mean score at the TTV was significantly lower than at the 1st injection visit (p=0.043). Improvements from injection to control visits were significant for each single item score of the BSDI (p≤0.038 for all).

Investigators rated the tolerability of treatment for each injection cycle at the subsequent injection visit and at the TTV (for the fifth or last injection session) Investigator Global Assessment of Tolerability (IGAT) scale ranges from 1 (very good) to 4 (poor). The tolerability was rated 'good' or 'very good' for the vast majority of patients (≥96.4 % for each

Figure 3: Efficacy of incoBoNT-A in Clinical Trials Investigating On-demand, Flexible Injection Intervals



A. Blepharospasm study: Jankovic Rating Scale (JRS) sum scores at each injection. Source: Truong et al., 2013;[28] B. CD study: Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores at each injection. incoBoNT-A = incobotulinumtoxin A; TTV = trail termination visit. Source: Evidente et al., 2013.[27]

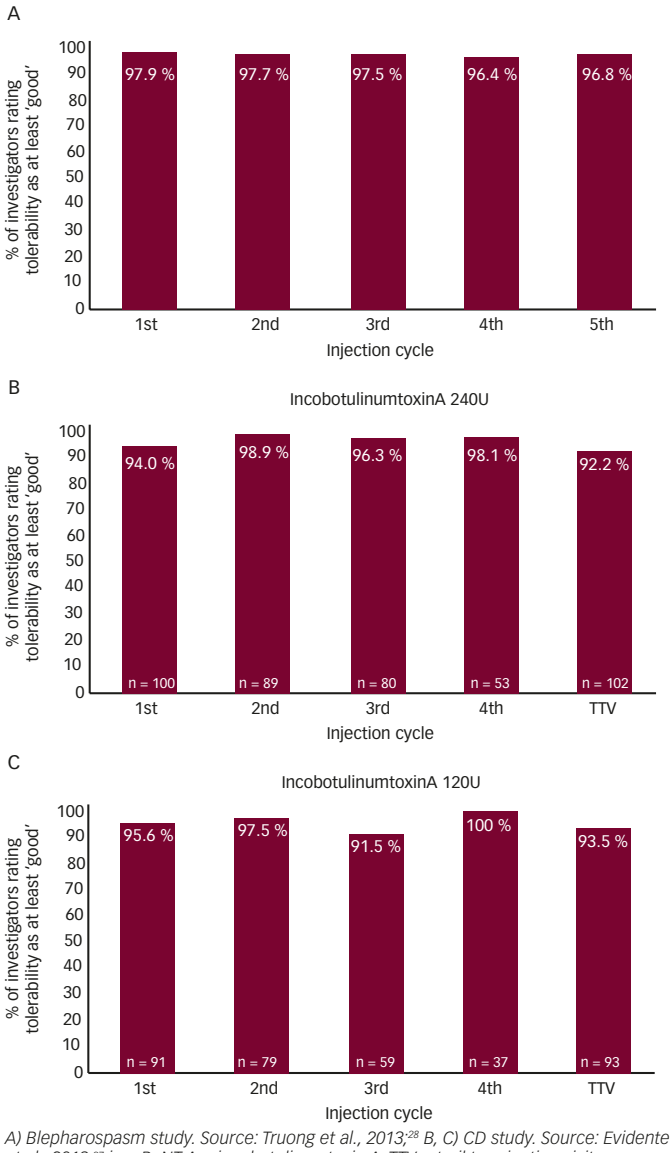
injection cycle, see *Figure 4*). At each contact, patients were directly questioned about adverse events (AEs) that could indicate toxin spread (stomach and bowel disturbances, drooping of eyelids, vision problems, dry mouth, swallowing difficulties, speech problems, shortness of breath, respiratory infection, local weakness, facial weakness and general body weakness). The most frequently reported AEs were eyelid ptosis and dry eye symptoms as expected. Frequencies of drug-related AEs per injection cycle ranged from 7.1 % to 11.8 % for eyelid ptosis and from 3.6 % to 6.9 % for dry eye symptoms. In total, 43.1 % of patients reported ≥1 AE over all five injection visits during the open label extension phase.

In the CD studies, patients (n=219 completing the main randomised, double-blind, placebo-controlled period; 214 in the extension randomised, double-blind study) were randomised to at the beginning of the studies to 240 U or 120 U (or placebo in the main phase). Evaluation of TWSTRS scores showed a significant improvement over the extension period (see *Figure 3*).[27] At every contact, patients were questioned about AEs; the most frequently reported treatment related AEs were dysphagia, injection-site pain, neck pain, muscular weakness and musculoskeletal pain (see *Table 1*). No serious treatment-related AEs were reported.

There was a wide range of injection intervals: ≤10 weeks (22.5 %), >10 to ≤12 weeks (24.6 %), >12 to ≤14 weeks (19.4 %) and >14 weeks (33.5 %) No differences were seen in the overall occurrence of AEs between the injection groups (p=0.1117).[27]

An additional safety analysis in the CD study evaluated the incidence of dysphagia, muscular weakness, neck pain and injection site pain

Figure 4: Tolerability of incoBoNT-A in Clinical Trials Investigating On-demand, Flexible Injection Intervals



A) Blepharospasm study. Source: Truong et al., 2013;[28] B, C) CD study. Source: Evidente et al., 2013.[27] incoBoNT-A = incobotulinumtoxin A; TTV = trail termination visit.

Table 1: Safety Analysis of In-clinical Trials Investigating On-demand, Flexible Injection Intervals of incoBoNT-A in Cervical Dystonia

Injection interval	6–7 weeks	8–9 weeks	10–11 weeks	12–13 weeks	14–15 weeks	16–17 weeks	18–20 weeks
Number of injection	n=65	n=177	n=127	n=196	n=116	n=71	n=69
Dysphagia (%)	3.1	5.6	8.7	6.1	7.8	8.5	10.1
Muscular weakness (%)	1.5	2.8	3.1	2.6	2.6	7.0	0
Neck pain (%)	3.1	4.5	4.7	3.6	4.3	5.6	7.2
Injection-site pain (%)	1.5	5.6	3.1	2.6	2.6	2.8	1.4

incoBoNT-A = incobotulinumtoxin A. Source: Evidente et al., 2014.[29]

according to injection interval. The frequency of AEs per injection session was lower in the 6–7 week injection interval than the AE rate

in longer injection intervals and in comparable single injection trials.[29] Investigators rated treatment tolerability for each injection cycle at the subsequent injection visit or at the TTV (up to 20 weeks after the last injection). Using the IGAT scale, tolerability was rated 'good' or 'very good' for the vast majority of patients (≥91.5 % for all treatments) in both dose groups.[27]

Antibody assays were performed at screening, control visit day 6, final visit of main phase, reinjection visits and TTV. These were assessed by a validated fluorescence immunoassay for antibodies (FIA-AB). Positive FIA-AB samples were tested with a validated mouse *ex vivo* hemidiaphragm assay (HDA). No patients had developed neutralising antibodies (nAbs) at study termination, including those patients that required reinjection at week 6. It should be noted that 2.6 % of the onaBoNT-A pre-treated patients had nAbs at screening.[28,29]

In conclusion, incoBoNT-A was well tolerated and effective over the study period in the treatment of blepharospasm and CD after a total of maximum six injections. Injections administered in shorter injection intervals were as well tolerated as those given in long-injection intervals. No cumulative AEs were reported with repeated doses and the majority of AEs were mild or moderate and temporary. The clinical study data support the relative safety of short-injection intervals for incoBoNT-A. ■

Is Botulinum Toxin Adequate for a Patient-centric Treatment Approach?

Alberto Albanese

Istituto Nazionale Neurologico Carlo Besta, Milan, Italy

Professor Albanese began by summarising the evidence-based reviews that have resulted in BoNT-A becoming the first-choice treatment for most types of focal dystonia.[34–36] BoNT-A has been given an American Academy of Neurology level A recommendation in this indication.[37] BoNT-A provides dose-related temporary denervation, targets specific muscles, maintains strength in non-treated muscles, corrects deformity without generating generalised weakness and reduces pain independently of muscle tone. Treating more severely dystonic muscles may also quell hyperactivity in other involved muscles.[38] In addition, results are long lasting.[39] However, when using a patient-centric approach, we need to guarantee reproducible results with guaranteed safety and tolerability.

Three formulations of BoNT-A are currently available: onaBoNT-A, aboBoNT-A and incoBoNT-A. All contain neurotoxin type A, derived from the Hall strain of Clostridium botulinum, but differ in their exact molecular composition and excipient. The formulations are supplied as powder that is reconstituted in saline for injection. In aboBoNT-A and onaBoNT-A the powder in the vial contains BoNT-A, however, the active 150 kDa neurotoxin is part of a larger complex with other proteins, for which no biological activity, influence on the diffusion profile or change of the stability of the neurotoxin have been demonstrated, although additional denatured/inactive neurotoxin is likely to be present.[40] By contrast, incoBoNT-A contains only active neurotoxin. In an analysis of neurotoxin content of the three formulations, the mean concentration of BoNT-A in onaBoNT-A was 0.73 ng per 100 unit vial (coefficient of variation [CV] = 3.5 %), in aboBoNT-A, 0.65 ng per 100 units (CV = 11.4 %) and 0.44 ng per 100 unit vial of incoBoNT-A (CV = 1.9 %).[41]

In placebo-controlled studies in CD, all three formulations have demonstrated efficacy and safety, showing improvements in postural head deviation, TWSTRS reduction and decrease in pain rating. Most AEs have been mild and transient; some dysphagia and injection pain, blurred vision and muscle weakness has been reported.[1,31,42–44]

Three comparative studies have also been reported in CD. In a study designed to establish whether a ratio of 1:3 aboBoNT-A: onaBoNT-A is equivalent, the mean time to retreatment was 3 days shorter in the aboBoNT-A group than in the onaBoNT-A group (not significant).[45] In another study, higher improvement of Tsui scores (primary outcome criteria) was seen with aboBoNT-A compared with onaBoNT-A (ratios of 1:3 or 1:4 were used). No significant difference was seen between the 1:3 and 1:4 groups, and more AEs were reported with aboBoNT-A, the most frequent being dysphagia (3 % with onaBoNT-A, 15.6 % with aboBoNT-A 1:3, and 17.3 % with aboBoNT-A 1:4), but the effect was minor.[46] In the first comparative study of onaBoNT-A and incoBoNT-A in CD, a 1:1 ratio was used. No difference was seen between the two groups in the mean change from baseline in TWSTRS severity score 1-month post injection.[47]

In terms of blepharospasm, the use of BoNT-A is based on four placebo-controlled trials.[30,32,44,48] Three comparative studies have also been reported, and all show no differences in efficacy and safety outcomes between onaBoNT-A and incoBoNT-A.[49–51] Using a 4:1 ratio for aboBoNT-A and onaBoNT-A, similar results were obtained for the two treatments, suggesting that this conversion factor is a good estimate of their comparative clinical potencies.[52] In addition, numerous placebo-controlled trials support the use of all three formulations of BoNT in spasticity.[53–67]

In terms of switching from one product to another, while several studies have shown that a 1:1 ratio of onaBoNT-A: incoBoNT-A is appropriate for clinical dose conversion,[41,68–74] the potency of aboBoNT-A relative to onaBoNT-A has been estimated to range from 1:2 to 1:11.[75,76] A randomised controlled trial suggested a ratio of 1:3 but the products are still not equivalent at this ratio.[77] Recent studies suggest that 1:4 may be more appropriate.[73,78] AE rates are comparable for all three products with conversion ratios of 1:1 for onaBoNT-A and incoBoNT-A; and 1:4 for incoBoNT-A/onaBoNT-A and aboBoNT-A.[68,79]

In summary, in terms of a patient-centric approach, all three BoNT-A formulations have been shown to be effective and well tolerated in a range of indications but the switch from aboBoNT-A to onaBoNT-A or incoBoNT-A is more difficult due to the variable relative potency. ■

Summary and Concluding Remarks

The symposium was closed with the conclusion that currently available BoNT-A formulations are appropriate first-line therapies in CD, blepharospasm and spasticity. However, shorter injection intervals may improve overall patient satisfaction since re-emergence of symptoms could be prevented. Recent data have shown that incoBoNT-A is suitable for use in a patient-centric approach with injection intervals starting from 6 weeks, with excellent efficacy and tolerability. This has not been investigated in the other formulations. Concerns over an increased risk of nAbs with short injection intervals were largely based on an early study with the original formulation of onaBoNT-A, which showed a much higher incidences of nAbs. In the recent studies involving incoBoNT-A nAbs were not detected in any patients, despite the fact that incoBoNT/a have been used in intervals as short as 6 weeks. Further research is warranted to determine parameters for optimising and individualising the treatment using the three available formulations of BoNT-A. Practicalities for incorporation of a flexible dosing regimen should be explored in clinical practice, and future design of studies should take into account patient needs. ■

1. Greene P, Kang U, Fahn S, et al., Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis, *Neurology*, 1990;40:1213-8.
2. IOM (Institute of medicine) Committee on Quality of Heath care in America, Crossing the Quality Chasm: A new health system for the 21st century. *Washington, DC: National Academy Press*, 2001
3. Bakheit AM, Zakine B, Maisonobe P, et al., The profile of patients and current practice of treatment of upper limb muscle spasticity with botulinum toxin type A: an international survey, *Int J Rehabil Res*, 2010;33:199-204.
4. Turner-Stokes L, Fheodoroff K, Jacinto J, et al., Results from the Upper Limb International Spasticity Study-II (ULISII):a large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management, *BMJ Open*, 2013;3:.
5. Bhatia KP, Charles, D., Paus, S. et al. , Toxincon 93S 2015 S10 Differences in the management of cervical dystonia in the United States (US) versus Europe (EU): the patients' perspective, *Toxicon*, 2015;93S:S10.
6. Misra VP, Ehler E, Zakine B, et al., Factors influencing response to Botulinum toxin type A in patients with idiopathic cervical dystonia: results from an international observational study, *BMJ Open*, 2012;2:.
7. Skogseid IM, Kerty E, The course of cervical dystonia and patient satisfaction with long-term botulinum toxin A treatment, *Eur J Neurol*, 2005;12:163-70.
8. Spasticity in adults: management using botulinum toxin National guidelines, London: Royal College of Physicians, 2009. ISBN 978-1-86016-350-0 Available at: https://http://www.rcplondon.ac.uk/sites/default/files/documents/spasticity-in-adults-management-botulinum-toxin.pdf Accessed 20 January 2015, .
9. Scottish Intercollegiate Guidelines Network, Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline. ISBN 978-1-905813-63-6 Available at: http://www.sign.ac.uk/pdf/sign118.pdf Accessed 20 January 2015, .
10. White book on Physical and Rehabilitation Medicine in Europe, *J Rehabil Med*, 2007;6-47.
11. Deutsche Gesellschaft fur Neurologie, Therapie des spastischen Syndroms AWMF-Registernummer 030/078 Availale at: http://www.awmf.org/uploads/tx_szleitlinien/030-078l_S1_Spastisches_Syndrom_Therapie_2012_1.pdf Accessed 20 January 2015, .
12. Simpson DM, Gracies JM, Graham K, et al., Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review), *Neurology*, 2009;73:736-7; author reply 7-8.
13. Yelnik AP, Simon O, Bensmail D, et al., Drug treatments for spasticity, *Ann Phys Rehabil Med*, 2009;52:746-56.
14. Wissel J, Ward AB, Erztgaard P, et al., European consensus table on the use of botulinum toxin type A in adult spasticity, *J Rehabil Med*, 2009;41:13-25.
15. Esquenazi A, Albanese A, Chancellor MB, et al., Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome, *Toxicon*, 2013;67:115-28.
16. Xeomin® UK Summary of Product Characteristics Available at: https://http://www.medicines.org.uk/emc/medicine/20666 Accessed 20 January 2015, .
17. Botox® UK Summary of Product Characteristics Available at: https://http://www.medicines.org.uk/emc/medicine/112 Accesed 20 January 2015, .
18. Dysport® UK Summary of Product Characteristics. Available at: https://http://www.medicines.org.uk/emc/medicine/870/SPC/Dysport+300+units,+Dysport+500+units/, .
19. Xeomin® US Prescribing Information. Available at: http://www.xeomin.com/consumers/pdf/xeomin-full-prescribing-information.pdf, .
20. Botox® US Prescribing Information. Available at: http://www.allergan.com/assets/pdf/botox_pi.pdf, .
21. Dysport® US Prescribing Information. Available at: http://www.dysport.com/hcp/PDFs/Dysport_Patiens_PI_Aug2012.pdf, .
22. Watkins CL, Leathley MJ, Gregson JM, et al., Prevalence of spasticity post stroke, *Clin Rehabil*, 2002;16:515-22.
23. Sommerfeld DK, Eek EU, Svensson AK, et al., Spasticity after stroke: its occurrence and association with motor impairments and activity limitations, *Stroke*, 2004;35:134-9.
24. Lundstrom E, Terent A, Borg J, Prevalence of disabling spasticity 1 year after first-ever stroke, *Eur J Neurol*, 2008;15:533-9.
25. Sethi KD, Rodriguez R, Olayinka B, Satisfaction with botulinum toxin treatment: a cross-sectional survey of patients with cervical dystonia, *J Med Econ*, 2012;15:419-23.
26. Bensmail D, Hanschmann A, Wissel J, Satisfaction with botulinum toxin treatment in post-stroke spasticity: results from two cross-sectional surveys (patients and physicians), *J Med Econ*, 2014;17:618-25.
27. Evidente VG, Fernandez HH, LeDoux MS, et al., A randomized, double-blind study of repeated incobotulinumtoxinA (Xeomin((R))) in cervical dystonia, *J Neural Transm*, 2013;120:1699-707.
28. Truong DD, Gollomp SM, Jankovic J, et al., Sustained efficacy and safety of repeated incobotulinumtoxinA (Xeomin((R))) injections in blepharospasm, *J Neural Transm*, 2013;120:1345-53.
29. Evidente VG, Truong D, Jankovic J, et al., IncobotulinumtoxinA (Xeomin(R)) injected for blepharospasm or cervical dystonia according to patient needs is well tolerated, *J Neurol Sci*, 2014;346:116-20.
30. Jankovic J, Comella C, Hanschmann A, et al., Efficacy and safety of incobotulinumtoxinA (NT 201, Xeomin) in the treatment of blepharospasm-a randomized trial, *Mov Disord*, 2011;26:1521-8.
31. Comella CL, Jankovic J, Truong DD, et al., Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN(R), botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia, *J Neurol Sci*, 2011;308:103-9.
32. Jankovic J, Orman J, Botulinum A toxin for cranial-cervical dystonia: a double-blind, placebo-controlled study, *Neurology*, 1987;37:616-23.
33. Consky E, S, and Lang, A,E. , Clinical assessments of patients with cervical dystonia. , In: Jankovic J, Hallett M, eds. Therapy with Botulinum Toxin. New York, NY: Marcel Dekker, Inc.:1994; 211-237., .
34. Albanese A, Barnes MP, Bhatia KP, et al., A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force, *Eur J Neurol*, 2006;13:433-44.
35. Albanese A, Asmus F, Bhatia KP, et al., EFNS guidelines on diagnosis and treatment of primary dystonias, *Eur J Neurol*, 2011;18:5-18.
36. Hallett M, Albanese A, Dressler D, et al., Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders, *Toxicon*, 2013;67:94-114.
37. Simpson DM, Blitzer A, Brashear A, et al., Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, *Neurology*, 2008;70:1699-706.
38. Reichel G, Cervical dystonia: a new phenomenological classification for botulinum toxin therapy. , *Basal Ganglia,* 2011;1:5-12.
39. Jankovic J, Treatment of dystonia, *Lancet Neurol*, 2006;5:864-72.
40. Eisele KH, Fink K, Vey M, et al., Studies on the dissociation of botulinum neurotoxin type A complexes, *Toxicon*, 2011;57:555-65.
41. Frevert J, Content of botulinum neurotoxin in Botox(R)/Vistabel(R), Dysport(R)/Azzalure(R), and Xeomin(R)/Bocouture(R), *Drugs* R D, 2010;10:67-73.
42. Poewe W, Deuschl G, Nebe A, et al., What is the optimal dose of botulinum toxin A in the treatment of cervical dystonia? Results of a double blind, placebo controlled, dose ranging study using Dysport. German Dystonia Study Group, *J Neurol Neurosurg Psychiatry*, 1998;64:13-7.
43. Truong D, Duane DD, Jankovic J, et al., Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study, *Mov Disord*, 2005;20:783-91.
44. Truong D, Brodsky M, Lew M, et al., Long-term efficacy and safety of botulinum toxin type A (Dysport) in cervical dystonia, *Parkinsonism Relat Disord*, 2010;16:316-23.
45. Odergren T, Hjaltason H, Kaakkola S, et al., A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia, *J Neurol Neurosurg Psychiatry*, 1998;64:6-12.
46. Ranoux D, Gury C, Fondarai J, et al., Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia, *J Neurol Neurosurg Psychiatry*, 2002;72:459-62.
47. Benecke R, Jost WH, Kanovsky P, et al., A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia, *Neurology*, 2005;64:1949-51.
48. Girlanda P, Quartarone A, Sinicropi S, et al., Unilateral injection of botulinum toxin in blepharospasm: single fiber electromyography and blink reflex study, *Mov Disord*, 1996;11:27-31.
49. Wabbels B, Reichel G, Fulford-Smith A, et al., Double-blind, randomised, parallel group pilot study comparing two botulinum toxin type A products for the treatment of blepharospasm, *J Neural Transm*, 2011;118:233-9.
50. Roggenkamper P, Jost WH, Bihari K, et al., Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm, *J Neural Transm*, 2006;113:303-12.
51. Jankovic J, Clinical efficacy and tolerability of Xeomin in the treatment of blepharospasm, *Eur J Neurol*, 2009;16 Suppl 2:14-8.
52. Sampaio C, Ferreira JJ, Simoes F, et al., DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A--Dysport and Botox--assuming a ratio of 4:1, *Mov Disord*, 1997;12:1013-8.
53. Simpson DM, Alexander DN, O'Brien CF, et al., Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial, *Neurology*, 1996;46:1306-10.
54. Bakheit AM, Thilmann AF, Ward AB, et al., A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke, *Stroke*, 2000;31:2402-6.
55. Bakheit AM, Pittock S, Moore AP, et al., A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke, *Eur J Neurol*, 2001;8:559-65.
56. Dunne JW, Gracies JM, Hayes M, et al., A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke, *Clin Rehabil*, 2012;26:787-97.
57. Brashear A, Gordon MF, Elovic E, et al., Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke, *N Engl J Med*, 2002;347:395-400.
58. Jahangir AW, Tan HJ, Norlinah MI, et al., Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after stroke, *Med J Malaysia*, 2007;62:319-22.
59. McCrory P, Turner-Stokes L, Baguley IJ, et al., Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centred outcomes, *J Rehabil Med*, 2009;41:536-44.
60. Kaji R, Osako Y, Suyama K, et al., Botulinum toxin type A in post-stroke upper limb spasticity, *Curr Med Res Opin*, 2010;26:1983-92.
61. Shaw L, Rodgers H, Price C, et al., BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A, *Health Technol Assess*, 2010;14:1-113, iii-iv.
62. Pittock SJ, Moore AP, Hardiman O, et al., A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke, *Cerebrovasc Dis*, 2003;15:289-300.

63. Cousins E, Ward A, Roffe C, et al., Does low-dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size, *Clin Rehabil*, 2010;24:501-13.
64. Bhakta BB, O'Connor RJ, Cozens JA, Associated reactions after stroke: a randomized controlled trial of the effect of botulinum toxin type A, *J Rehabil Med*, 2008;40:36-41.
65. Smith SJ, Ellis E, White S, et al., A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury, *Clin Rehabil*, 2000;14:5-13.
66. Rosales RL, Kong KH, Goh KJ, et al., Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial, *Neurorehabil Neural Repair*, 2012;26:812-21.
67. Kanovsky P, Slawek J, Denes Z, et al., Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity, *Clin Neuropharmacol*, 2009;32:259-65.
68. Jost WH, Kohl A, Brinkmann S, et al., Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT 201) compared with commercially available botulinum toxin type A (BOTOX) in healthy volunteers, *J Neural Transm*, 2005;112:905-13.
69. Jost WH, Blumel J, Grafe S, Botulinum neurotoxin type A free of complexing proteins (XEOMIN) in focal dystonia, *Drugs*, 2007;67:669-83.
70. Dressler D, Routine use of Xeomin in patients previously treated with Botox: long term results, *Eur J Neurol*, 2009;16 Suppl 2:2-5.
71. Benecke R, Xeomin in the treatment of cervical dystonia, *Eur J Neurol*, 2009;16 Suppl 2:6-10.
72. Benecke R, Hauschke, D. , IncobotulinumtoxinA demonstrated equivalent efficacy to onabotulinumtoxinA in the treatment of cervical dystonia, *The Botulinum J*, 2013;2:3-4.
73. Dressler D, Tacik P, Adib Saberi F, Botulinum toxin therapy of cervical dystonia: comparing onabotulinumtoxinA (Botox((R))) and incobotulinumtoxinA (Xeomin ((R))), *J Neural Transm*, 2014;121:29-31.
74. Saad J, Gourdeau A, A direct comparison of onabotulinumtoxina (Botox) and IncobotulinumtoxinA (Xeomin) in the treatment of benign essential blepharospasm: a split-face technique, *J Neuroophthalmol*, 2014;34:233-6.
75. Wohlfarth K, Schwandt I, Wegner F, et al., Biological activity of two botulinum toxin type A complexes (Dysport and Botox) in volunteers: a double-blind, randomized, dose-ranging study, *J Neurol*, 2008;255:1932-9.
76. Marchetti A, Magar R, Findley L, et al., Retrospective evaluation of the dose of Dysport and BOTOX in the management of cervical dystonia and blepharospasm: the REAL DOSE study, *Mov Disord*, 2005;20:937-44.
77. Wohlfarth K, Sycha T, Ranoux D, et al., Dose equivalence of two commercial preparations of botulinum neurotoxin type A: time for a reassessment?, *Curr Med Res Opin*, 2009;25:1573-84.
78. Grosset DG, Tyrrell EG, Grosset KA, Switch from abobotulinumtoxinA (Dysport(R)) to incobotulinumtoxinA (Xeomin(R)) botulinum toxin formulation: A review of 257 cases, *J Rehabil Med*, 2014;.
79. Chapman MA, Barron R, Tanis DC, et al., Comparison of botulinum neurotoxin preparations for the treatment of cervical dystonia, *Clin Ther*, 2007;29:1325-37.