

Botulinum neurotoxin and dystonia: a case for greater flexibility in treatment regimens?

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ABSTRACT

The causes of dystonia are not fully understood and although currently available treatments can provide effective symptomatic relief, they cannot provide curative disease modification. Botulinum neurotoxin type A injections are well established for the symptomatic treatment of focal dystonias and post-stroke spasticity. Three proprietary injectable formulations of botulinum neurotoxin type A are currently available: Botox® (onabotulinumtoxinA), Dysport® (abobotulinumtoxinA), and Xeomin® (incobotulinumtoxinA). Of these, only Xeomin® is purified to remove associated complexing proteins, and the resultant reduced protein load may confer reduced immunogenicity. Product labelling currently restricts conventional botulinum toxin type A treatments to a minimum injection interval of 12 weeks; however, feedback from published patient surveys shows a substantial proportion of patients experience re-emergence of symptoms in the weeks prior to reinjection. This review examines clinical studies conducted with Xeomin® (incobotulinumtoxinA) that have featured more flexible injection intervals based on individual patient needs. The available evidence suggests that for selected patients, a more flexible and tailored treatment approach with injection intervals of ≥ 6 and up to 20 weeks may help optimize symptom relief. In studies where flexibility in injection interval timing was permissible, interval preferences were varied. Although shorter injection intervals (< 12 weeks) with incobotulinumtoxinA were requested and administered to almost half of patients in a pooled analysis of two studies in patients with blepharospasm and cervical dystonia, approximately 25-30% of these patients requested considerably longer injection intervals of between 14-20 weeks. In these studies, effective symptomatic relief was demonstrated and no increases in side effect liability, or increased production of neutralizing antibodies that can lead to treatment failure were observed with < 12 -week injection intervals compared with ≥ 12 -week injection intervals.

Key words: incobotulinumtoxinA, Xeomin®, injection, dystonia

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INTRODUCTION AND HISTORICAL PERSPECTIVE

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. It is characterized by highly distressing, often painful, and disabling muscle spasms that can interfere significantly with motor performance and the ability to carry out everyday tasks, leading to loss of mobility and independence. Dystonic movements are typically patterned and twisting, and may be tremulous. It is often initiated or worsened by voluntary action and associated with overflow muscle activation (Albanese 2013). The causes and pathophysiology of dystonias are not fully understood, but are associated with over-activity in several areas of the brain (i.e. basal ganglia, thalamus, cerebellum and cerebral cortex). Pathophysiological deficits in primary dystonia are well characterized and include reduced inhibition at many levels of the motor system and increased plasticity, while emerging evidence suggests additional cerebellar deficits (Kojovic 2013).

Currently there is no definitive cure for dystonia. Available pharmacological treatments are limited and only provide symptomatic relief. Accordingly, there is a duty of care to use available treatments to best effect by maximising the potential benefits to patients, helping them manage their condition more effectively, reducing the burden of disease, and improving patients' quality of life.

Botulinum neurotoxin is produced by the anaerobic bacterium *Clostridium botulinum*. *C. botulinum* elaborates eight antigenically distinguishable exotoxins (A, B, C₁, C₂, D, E, F and G). All serotypes, with the exception of C₂, interfere with neural transmission by blocking the release of acetylcholine, the principal neurotransmitter at the neuromuscular junction, causing muscle paralysis. Of these, Type A is the most potent toxin (Nigam 2010). The active botulinum toxin occurs naturally as part of a high molecular weight complex (approximately 900 kDa); this contains the neurotoxin component (150 kDa) together with 6-7 complexing proteins of clostridial origin, also called neurotoxin-associated proteins (Sharma & Singh 2000).

Proprietary pharmaceutical preparations of botulinum toxin type A have been developed for treating disorders resulting from increased muscle tone, notably: cervical dystonia, hemifacial spasm and blepharospasm. Conventional botulinum toxin type A drugs, including Botox® (onabotulinumtoxinA; Allergan Inc, Irvine, CA), and Dysport® (abobotulinumtoxinA; Ipsen Ltd, Berkshire, UK), contain these complexing proteins in addition to the neurotoxin. Xeomin® (also known as incobotulinumtoxinA, NT 201, botulinum toxin type A [150 kDa], Bocouture®; Merz Pharmaceuticals GmbH, Frankfurt, Germany), however, is free from complexing proteins (Frevert & Dressler 2010).

The current standard of care for botulinum toxin is injection intervals of three months or longer (Swope 2008); this recommendation is largely based on a 1994 retrospective review of patients with cervical dystonia (Greene 1994). Eight of 76 patients (10.5%) in this study developed botulinum toxin resistance of whom three had developed neutralizing antibodies. Patients with resistance had a shorter injection interval, more booster injections, and a higher dose administered over a 3-month period. Notably, these patients were treated with the original botulinum toxin from Allergan (Lot 79-11, onabotulinumtoxinA), a formulation that contains complexing proteins and other bacterial proteins that may have contributed to antibody formation and observed resistance to treatment in some patients. Since then most clinical studies used a minimum injection interval of 12 weeks. In the following years, in order to reduce immunogenicity, the formulation of onabotulinumtoxinA was changed and the bacterial protein content was reduced. Concerns continue with the use of botulinum toxin type A treatments with respect to their potential to stimulate neutralizing antibodies, following repeated injections, leading to secondary treatment failure (Torres 2014). Currently, only incobotulinumtoxinA is highly purified to remove complexing proteins and reduce bacterial proteins further and potentially reduce immunogenicity.

Current US and European product labelling for botulinum toxin type A formulations, licensed for the treatment of focal dystonias, such as blepharospasm, and cervical dystonia, recommends injection intervals of at least three months or 12 weeks for ona- and abobotulinumtoxinA. IncobotulinumtoxinA has a minimum interval of 10 weeks in the prescribing information for cervical dystonia in Europe. More recently, some countries (e.g. Australia, Canada, Russia) have accepted greater flexibility with incobotulinumtoxinA injection intervals based on clinical studies with a six weeks' minimum interval for Xeomin® when clinically needed.

A substantial proportion of patients receiving ona- or abobotulinumtoxinA report the re-emergence of symptoms prior to the end of the standard 12-week injection interval. In one survey, approximately 45% of patients with cervical dystonia reported they would prefer a treatment cycle of ≤ 10 weeks (Sethi 2012). Patient feedback therefore suggests a less prescriptive treatment approach with botulinum toxin type A treatment allowing patients, after careful clinical assessment, to receive

multiple injection series with more flexible dosing and injection intervals may be a means of maximizing patients' symptom management. This would permit adjustments of treatment for individual patients based on their clinical need. This review examines the available evidence that supports more flexible treatment regimens with Xeomin® (incobotulinumtoxinA) in physician-selected patients with focal dystonias such as cervical dystonia, blepharospasm and in post-stroke spasticity.

INCOBOTULINUMTOXINA: SAFETY ASPECTS

The safety profile and treatment-emergent adverse events reported with incobotulinumtoxinA are comparable with abobotulinumtoxinA (Truong 2005, Truong 2008) and onabotulinumtoxinA (Allergan US Prescribing Information). No new or unexpected safety findings are therefore evident that might be attributable to the purification process and the removal of complexing proteins from the incobotulinumtoxinA formulation. The treatment-emergent adverse events reported in a randomized, placebo-controlled trial (Comella 2011), in patients with cervical dystonia ($n = 233$), following single placebo, incobotulinumtoxinA 120, and 240 U injections treatments, are summarised in Table 1. Most treatment-related adverse events in this study were reported to be mild or moderate in intensity. The most frequently reported adverse events in the active treatment arms were dysphagia, neck pain and muscular weakness; these adverse events are consistent with other reported studies of incobotulinumtoxinA (Benecke 2005).

In a randomized, double-blind, repeated-dose, flexible-interval (minimum injection interval of six weeks utilized at the discretion of the investigator) extension study, with a duration of up to 88 weeks, repeated injections of incobotulinumtoxinA, at total doses of 240 or 120 U, were reported to be well tolerated in patients with cervical dystonia (Evidente 2013). During the 68-week extension period (completed by 169 patients) the most frequently reported adverse drug reaction (ADR) during injection cycles was dysphagia (5.4-20.4% in the 240 U group; 10-28.8% in the 120 U group). Most of these ADRs were mild or moderate in intensity. It should be noted that patients in the Comella et al (2011) study were prompted with direct questions to elicit any adverse events and this may have affected the extent of AE reporting.

Of note, this study (Evidente 2013) did not show significant differences in the incidence of adverse events between those patients who received shorter injection intervals (median interval 6 to ≤ 10 weeks) and those with longer intervals. These findings suggest there are no additional safety concerns associated with shorter injection intervals when incobotulinumtoxinA is injected, according to each patient's needs, with a flexible dosing period of up to 88 weeks (up to six injections and during the 20-week main study period where patients could return for re-injection after eight weeks). A further reassuring observation was that no difference in the number of patients testing positive for neutralizing antibodies was

	Placebo n = 74 n (%)	IncobotulinumtoxinA 120 U n = 78 n (%)	IncobotulinumtoxinA 240 U
Related ^a AEs >5% of subjects in any treatment group			
Subjects with ≥ 1 related AE	11 (14.9)	28 (35.9)	29 (35.8)
Dysphagia	2 (2.7)	8 (10.3)	13 (16.0)
Neck pain	1 (1.4)	4 (5.1)	10 (12.3)
Muscular weakness	1 (1.4)	5 (6.4)	8 (8.9)
Musculoskeletal pain	0	5 (6.4)	3 (3.7)
Injection site pain	4 (5.4)	7 (9.0)	3 (3.7)

AE = adverse event

^a Relationship assessed by investigator

Ref: Comella CL, Jankovic J, Truong DD et al. Efficacy and safety of incobotulinumtoxinA (NT 201, Xeomin®, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia. *J. Neurol Sci* 2011; 308(1-2): 103-109.

Table 1. Treatment-emergent adverse events reported by Comella et al (2011)

evident at the beginning of the study compared with the end of the study. Of the six patients who tested positive for neutralizing antibodies at screening and at the end of the extension phase, all had received botulinum toxin prior to study entry.

In a similarly designed study (Truong 2013), patients with blepharospasm (n = 88) who had previously received at least two treatments with onabotulinumtoxinA, received flexible, repeated doses of incobotulinumtoxinA (≤ 50 U per eye), administered via flexible injection intervals (minimum six weeks). No patient developed neutralizing antibodies during this study after up to six injection sessions, and the most frequently reported adverse events were eyelid ptosis (31.4%) and dry eye symptoms (17.6%). In this study, patients were actively asked at each visit if they had experienced specific adverse events, and this may have affected the frequency of reported adverse events. Additionally, at baseline and prior to administration of incobotulinumtoxinA, 56 (54.9%) of patients reported pre-existing dry eye symptoms and 40 (39.2%) reported ptosis. In fact, the rate of dry eyes and ptosis dropped once patients had stopped their onabotulinumtoxinA treatment and received incobotulinumtoxinA instead.

Benecke (2012) notes that development of neutralizing antibodies against botulinum neurotoxin is often the reason for secondary treatment failure. The presence of complexing proteins within botulinum neurotoxin agents increases the protein load, and this may exacerbate an immune response. Animal data suggest the absence of complexing proteins in incobotulinumtoxinA is associated with reduced immunogenicity (Eisele 2008), and unlike onabotulinumtoxinA and abobotulinumtoxinA, did not induce the formation of neutralizing antibodies (Blümel 2006). However, definitive clinical studies to investigate the long-term immunological effects of repeated

administration of different botulinum toxin products would be required to verify these findings in the clinical setting.

Long-term clinical data with more flexible botulinum neurotoxin type A regimens are currently limited. Dressler and colleagues (2013) report that repeated injections of highly purified incobotulinumtoxinA, administered using flexible dosing regimens (10-24 weeks; ≤300 U) in a setting close to real-life practice, were well tolerated in the long-term treatment (49-114 weeks) of patients with cervical dystonia (n = 76 enrolled). The most common drug-related AEs were dysphagia (28.8%), neck pain (10.5%), and muscle weakness (6.6%) as reported in other trials. Importantly, no accumulation of AEs was observed over the treatment course and the incidence of AEs tended to decrease over time. No patients developed neutralizing antibodies during this study after receiving five injection sessions of incobotulinumtoxinA.

The international observational SPAsTicity in practiCE (SPACE) study recruited 701 adult patients, with 687 eligible for efficacy evaluation. These patients had spasticity of any aetiology (but predominantly post-stroke; 64.6%), and were followed up for up to two years (up to nine visits). Investigating physicians independently decided on specific treatment (incobotulinumtoxinA, onabotulinumtoxinA or abobotulinumtoxinA), dose (total and per muscle), injection sites, and treatment intervals according to their usual clinical practice. Key objectives of this study were to identify areas of overlap or disagreement between real-life clinical practice and treatment guidelines, and improve physicians' understanding of treating spasticity with botulinum neurotoxin type A treatments.

All treatments were well tolerated and the overall number of ADRs was low (2.7%). The proportion of patients with ADRs was similar across the treatment

groups: incobotulinumtoxinA, 3.0% (11/369); onabotulinumtoxinA, 2.1% (3/142); abobotulinumtoxinA, 2.7% (2/75). The observed ADRs were injection site pain, fatigue, muscular weakness, diplopia, dry mouth and dysphagia. Eight patients experienced serious ADRs, with a similar incidence across the three treatments: incobotulinumtoxinA, 1.4% (5/369); onabotulinumtoxinA, 1.4% (2/142); abobotulinumtoxinA, 1.3% (1/75). The majority of physicians (n=101, 59.1%) would have injected higher doses of all botulinum toxins if there had been no labelling restrictions, to enable them to treat more spasticity patterns in patients with complex multifocal spasticity. The mean (SD) doses that physicians wanted to inject were: 651.8 (191.6) units for incobotulinumtoxinA, 640.3 (170.4) units for onabotulinumtoxinA, and 1751.9 (844.2) units for abobotulinumtoxinA (Harriss 2013, Wissel 2016).

OPTIMIZING INCOBOTULINUMTOXINA OUTCOMES WITH TREATMENT FLEXIBILITY

A consistent finding to emerge from recent patient surveys that utilized open-ended question protocols (i.e. without prompting) to assess satisfaction with botulinum toxin

treatments is a clear and universal request for treatment individualization. Key insights from published patient surveys are summarized in Table 2 below.

Patient experience with botulinum toxin type A treatments from these surveys indicates that the current standard of no less than 12 weeks between injections can be sub-optimal and does not adequately control symptoms in a substantial proportion of patients, particularly in the lead-up period immediately prior to re-injection. These reported patient experiences indicate there are very real unmet medical needs for many patients with focal dystonias and post-stroke spasticity. Currently, symptomatic management with botulinum neurotoxin treatments is based on quite rigid treatment regimens. More flexible, individualized, treatment approaches may help to improve outcomes and treatment satisfaction for these patients.

IncobotulinumtoxinA is the only neurotoxin formulation studied in clinical trials that has permitted flexible dosing intervals (Dressler 2013, Evidente 2013, Truong 2013, Evidente 2014). Summary commentary on the reported outcomes from these studies are presented in the following sections.

Dressler (2013): This was a prospective, open-label, multicentre Phase IV study. Sixty-four patients with

Survey	Patient participant population	Key insights
Sethi 2012	Cervical dystonia (n = 136)	Approximately 45% of participants treated with onabotulinumA and abobotulinumtoxinA reported they would prefer a treatment cycle of ≤ 10 weeks. Patient satisfaction typically declines with re-emergence of symptoms prior to re-injection with a standard ≥12-week injection cycle.
Poliziani 2016	Cervical dystonia (n = 31)	When asked about “their ideal injection cycle” participants wanted longer-lasting and/or more stable symptom relief, with shorter and/or more flexible injection intervals in accordance with the individual needs of the patient.
Fezza 2016	Blepharospasm (n = 114)	36.6% of participants reported treatment effects usually declined within 8 weeks; 69.6% within 10 weeks. 52.3% of participants would prefer an injection interval of <12 weeks; 30.6% would prefer <10 weeks.
Bensmail 2016	Post-stroke spasticity (n = 79)	36.6% of patient participants expressed a preference for injection intervals of ≤10 weeks. Participating physicians estimated that 16.2% of their patients with post-stroke spasticity could benefit from shorter injection intervals, and 24.6% of patients could benefit from higher doses than those permitted by current country directives. Patients and physicians expressed a need for treatment individualization. Many physicians felt the restrictions on treatment intervals and dosing in their respective countries were impeding both treatment outcomes and patient satisfaction.

Table 2. Key insights from patient satisfaction surveys with botulin toxin treatment

cervical dystonia received five injection sessions of incobotulinumtoxinA using flexible injection intervals (10-24 weeks) and flexible, individualised dosing (≤ 300 U) based on patients' needs. The primary efficacy assessment was the mean improvement on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS; Consky 1990). Other outcomes were measured with The Dystonia Discomfort Scale (DDS; Dressler 2014), Investigator Global Assessment of Efficacy (IGAI) and Patient Evaluation of Global Response (PEGR). Significant improvements were maintained after subsequent injection sessions. The mean changes in TWSTRS-Total scores from baseline to the respective control visits, four weeks after injection sessions 2-5, ranged from -13.4 to -14.3. Mean changes in TWSTRS-Severity, TWSTRS-Disability, and TWSTRS-Pain sub-scores also indicated consistent significant improvements. Four weeks after each injection DDS scores were consistently and significantly improved compared with baseline. Mean improvements ranged from -20.2 to -23.0, and the AUC of the DDS scores for the four weeks after each injection session, was highly stable over the duration of the study. Up to 81.6% of investigators rated incobotulinumtoxinA efficacy as good or very good (IGAI), and up to 78.9% of patients rated their treatment response as improved (PEGR). The authors concluded that long-term administration of incobotulinumtoxinA, using more flexible dosing regimens than those permitted in previous controlled studies, is effective for the treatment of cervical dystonia, in a setting close to real-life clinical practice.

Evidente (2013): This study was conducted in patients with cervical dystonia as an initial ≤ 20 -week placebo-controlled, randomized, double-blind, placebo-controlled, single-dose main period (minimum duration 8 weeks). After this main period, patients could enter a ≤ 68 -week, prospective, randomized, double-blind, repeated-dose, flexible-interval (minimum 6 weeks) extension period (EP); this was completed by 169 patients who received fixed dose 240 U or 120 U incobotulinumtoxinA injections (≤ 5 injections). Both doses of incobotulinumtoxinA significantly improved mean TWSTRS-Total, TWSTRS-severity, TWSTRS-Disability and TWSTRS-Pain scores at follow-up visits four weeks after each injection session in the EP ($p < 0.001$). The authors concluded that repeated injections of incobotulinumtoxinA provide clinically relevant and sustained efficacy for up to five treatment cycles when administered to patients with cervical dystonia at total fixed doses of 240 or 120 U, using flexible dosing intervals according to patient needs.

Truong (2013): This study, in patients with blepharospasm previously treated with onabotulinumtoxinA, had similarities in design to the Evidente (2013) study described above but utilized flexible doses. Patients who completed a ≤ 20 -week (minimum 6 weeks) placebo-controlled, randomized, double-blind, placebo-controlled, single-dose main period ($n = 102$) entered a ≤ 69 -week open-label extension period and received ≤ 5 additional incobotulinumtoxinA injections, administered at flexible doses (≤ 50 u per eye), and flexible injection intervals (minimum six weeks, maximum 20 weeks). Dose, dilution, number of injections, and injection sites were flexible

and tailored to each individual patient by the investigator based on the severity and frequency of spasms, individual response, and history of adverse events. Of the 82 patients who completed the study, 56 received the maximum five additional injections. Efficacy was assessed with the Jankovic Rating Scale (JRS; Jankovic & Oman 1987) and the patient-rated Blepharospasm Disability Index (BSDI; Roggenkämper 2006; Jankovic 2009). At each control visit, six weeks after each injection, both JRS and BDI scores showed significant improvement ($p \leq 0.001$ for all comparisons between injection and control visits). For JRS, the mean (SD) differences between each control and respective injection visit ranged from -1.6 (1.8) to -2.4 (2.2). For BSDI, the mean (SD) difference in BSDI mean score, between each control and the respective injection visit, ranged from -0.27 (0.59) to -0.50 (0.67). This study showed that repeated incobotulinumtoxinA injections, administered at flexible doses and injection intervals from six to 20 weeks, according to patients' needs, provide sustained efficacy in the treatment of blepharospasm.

Evidente (2014): In this publication, post-hoc analyses based on the Evidente (2013) study in cervical dystonia, and the Truong (2013) study in blepharospasm, showed that repeated injections of incobotulinumtoxinA provided sustained efficacy in both patient populations, when administered via flexible injection intervals of between six and 20 weeks. This pooled assessment reported that although almost half the patients in the two studies requested and were administered treatment with injection intervals of < 12 weeks, approximately 25-30% of these patients requested considerably longer intervals of between 14 and 20 weeks. Furthermore, the absence of neutralizing antibody development in patients during these studies supports accumulating evidence that incobotulinumtoxinA is associated with low immunogenicity, at least during the first six injection cycles studied.

CONCLUSIONS

Further long-term clinical studies to investigate the safety and efficacy of more flexible botulin toxin type A treatment regimens may provide more comprehensive insights and guidance in optimizing botulin toxin A treatment regimens. The available clinical data based on more flexible dosing and injection intervals with incobotulinumtoxinA are, so far, highly encouraging. There is a promising and growing body of evidence indicating that patients specifically selected by physicians, based on defined clinical needs, may benefit from more flexible incobotulinumtoxinA treatment algorithms, with shorter (and in some cases longer) injection intervals and greater dosing flexibility. The use of multiple (≤ 6) injections of incobotulinumtoxinA with shorter (≤ 12 weeks) treatment intervals does not appear to increase immunogenicity, or the potential for adverse events, compared with injection intervals of ≥ 12 weeks. Accordingly, more flexible individualised treatment with incobotulinumtoxinA (Xeomin®) may help to optimize

treatment benefits and improve outcomes and quality of life for patients with dystonia and post-stroke spasticity.

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