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IncobotulinumtoxinA (Xeomin®) injected for blepharospasm or cervical dystonia according to patient needs is well tolerated

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ABSTRACT

Typically, botulinum toxin injections for blepharospasm or cervical dystonia (CD) are administered at approximately 3-month intervals, reflecting concerns that shorter intervals might increase the risk of adverse events (AEs) and development of neutralizing antibodies. These post-hoc analyses investigated flexible incobotulinumtoxinA (Xeomin®) injection intervals (6–20 weeks) in patients with blepharospasm or CD. Patients received up to 6 injections at intervals ≥6 weeks, as determined by physician assessment upon patient request. The blepharospasm study permitted flexible doses (≤50 U/eye). The CD study employed fixed dosing using incobotulinumtoxinA 120 U, 240 U, or placebo for the first treatment followed by subsequent randomization to 120 U or 240 U for the extension period. Standard safety assessments were performed. Intervals <12 weeks were employed in 207 of 461 (44.9%) treatment cycles for blepharospasm and in 369 of 821 (44.9%) treatment cycles for CD. The most frequent AEs were eyelid ptosis and dry eyes in patients treated for blepharospasm, and dysphagia and neck pain in patients with CD. AE frequency and severity were similar for intervals <12 weeks and ≥12 weeks in both studies. In conclusion, repeated incobotulinumtoxinA injections employing flexible intervals (6–20 weeks) per patients' needs were well tolerated. No additional safety concerns were observed with <12-week intervals compared with ≥12-week intervals.

1. Introduction

Repeated intramuscular injections of botulinum toxin are the recommended first-line treatment for focal dystonias, including blepharospasm and cervical dystonia (CD) [1–3].

IncobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany; also known as NT 201), a purified botulinum toxin type A formulation free from complexing (or accessory) proteins [4], has been shown to be effective and well tolerated in pivotal Phase III clinical studies in blepharospasm [5,6] and CD [7,8]. In the CD study, subgroup analyses confirmed that incobotulinumtoxinA efficacy and tolerability were similar for patients who were naïve to botulinum toxin treatment and those who had previously received treatment with onabotulinumtoxinA (Botox®, Allergan Inc., Irvine, CA, USA) [9]. The effectiveness of incobotulinumtoxinA in treating CD has been further confirmed in a prospective, long-term, open-label Phase IV study [10]. Further pivotal, randomized, parallel-group head-to-head studies have demonstrated that, at a clinical conversion 1 U:1 U dose ratio, incobotulinumtoxinA and onabotulinumtoxinA showed comparable efficacy and adverse-event (AE) profiles when used to treat blepharospasm [11,12] or CD [13].

Current product labeling of botulinum toxin type A formulations licensed for the treatment of blepharospasm and CD in the USA and Europe recommends injection intervals of at least 3 months or 12 weeks [14–18], with the exception of European labeling for incobotulinumtoxinA, which recommends a minimum treatment interval of 12 weeks for blepharospasm and 10 weeks for CD [19].

The recommended minimum interval of 12 weeks is largely based on a retrospective chart review of patients with CD who received treatment with the early botulinum toxin formulation of onabotulinumtoxinA [20]. However, for many patients with CD, the duration of botulinum toxin treatment effect is less than 12 weeks [21]. Moreover, a recent patient survey revealed that many patients who receive botulinum toxin type A for the treatment of CD would prefer more frequent injections than the currently recommended 12-week inter-dose interval permits [22].

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A survey of patients with spasticity resulted in similar findings [23]. However, the tolerability of flexible botulinum toxin dosing regimens with shorter or longer treatment intervals than the 12-week standard of care has not been evaluated in prospective clinical studies. Here, we report findings from exploratory post-hoc analyses evaluating the safety of flexible incobotulinumtoxinA injection intervals of 6–20 weeks in the treatment of blepharospasm and CD from the only two prospective, randomized, double-blind, multicenter studies and their extension phases.

2. Materials and methods

2.1. Study design

The designs of the studies in blepharospasm and CD have been described in detail [5–8]. Briefly, the main periods of both studies comprised a randomized, placebo-controlled, double-blind period of up to 20 weeks' duration followed by a long-term extension period.

In the blepharospasm study, patients received injections of incobotulinumtoxinA (≤50 U per eye) at flexible intervals ≥6 weeks according to clinical need indicated by a Jankovic Rating Scale (JRS) Severity subscore >2. Over the entire study, i.e. the main and extension periods, patients could receive up to six incobotulinumtoxinA injections [5,6].

The CD study was designed with flexible injection intervals using fixed doses. In the main period, patients were randomized to receive placebo, incobotulinumtoxinA 120 U or 240 U. In the double-blind extension period, all patients were re-randomized to either incobotulinumtoxinA 120 U or 240 U, independently of their treatment allocation in the main period. Injection intervals were flexible, with minimum intervals of ≥8 weeks after the main period injection and ≥6-week intervals for the extension period. Clinical need for re-injection was defined as a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total score ≥20. In total, patients could receive up to six incobotulinumtoxinA injections [7,8].

2.2. Patients

Detailed inclusion and exclusion criteria for each study have been described previously. Briefly, the blepharospasm study enrolled patients who had previously been treated with onabotulinumtoxinA (≥2 treatments) and who had a stable therapeutic response directly prior to study entry [5]. The CD study included both botulinum toxin type A treatment-experienced and -naïve patients [7].

2.3. Safety outcome measures

Standard safety assessments were performed throughout the main and extension periods of both the blepharospasm and CD studies, including recording of AEs, with active questioning for the occurrence of AEs of special interest.

In the blepharospasm study, patients were specifically asked about any occurrence of AEs that could indicate local or distant toxin spread, in particular eyelid drooping, vision problems, dry mouth, swallowing difficulties, speech problems, shortness of breath, respiratory infection, local weakness, facial weakness, general body weakness, and stomach or bowel disturbances [5,6].

In the CD study, AEs that could indicate the possible spread of the toxin, including muscular weakness, dysphagia, and dry mouth, were recorded. In addition, patients were specifically assessed for swallowing difficulties at each clinic visit and during telephone contacts between visits using a 5-point dysphagia rating scale [7,8].

2.4. Exploratory post-hoc analyses

The exploratory analyses of both studies included all incobotulinumtoxinA injections that were administered with injection intervals of 6–20 weeks during the main and extension periods (an injection interval that was not a whole number, when counted in weeks, was allocated to the next higher week). Injections given at intervals <6 weeks or >20 weeks were excluded. Injection cycle 1 denoted the interval between a patient's first and second incobotulinumtoxinA injection. The last injection cycle was defined as the interval between the last incobotulinumtoxinA injection and the study termination visit (up to 20 weeks after the last injection).

For both studies, the frequency of injection interval length (in weeks) was analyzed by injection cycle. The occurrence of AEs was summarized for intervals of different lengths and analyzed for all injection cycles combined.

3. Results

3.1. Patients

In the blepharospasm study, 102/109 patients (93.6%) completed the main period and entered the extension period; 82/102 patients (80.4%) completed the extension period. Baseline demographics have been described [5,6]. In the CD study, 214/233 patients (91.8%) completed the main period and entered the extension period; 169/214 patients (79.0%) completed the extension period. Baseline demographics have been published [7,8].

3.2. Frequency of injection intervals

In the blepharospasm study, 461 incobotulinumtoxinA injection sessions were administered at intervals of 6–20 weeks during the main and extension periods and were included in this analysis (Table 1). Of these, 44.9% of treatments were administered with injection intervals <12 weeks and 55.1% were administered with intervals ≥12 weeks (Fig. 1a). For injection cycle 1, the injection interval was <12 weeks for 59.8% of treatments and <10 weeks for 48.5% (Table 1). Overall, 26.5% of injections were administered with intervals <10 weeks.

In the CD study, 821 incobotulinumtoxinA injection sessions were administered at intervals of 6–20 weeks during the main and extension period and included in the exploratory analysis (Table 1). As in the blepharospasm study, 44.9% of treatments overall were administered with intervals <12 weeks and 55.1% with intervals ≥12 weeks (Fig. 1b). For injection cycle 1, the injection interval was <12 weeks for 59.9% of treatments and <10 weeks for 47.8% (Table 1). Throughout the study, 29.5% of treatments were administered at intervals <10 weeks.

3.3. Frequency of adverse events by injection interval

In the blepharospasm study, the overall frequency of AEs was similar for all incobotulinumtoxinA injection interval groups (Table 2). There were no differences in the frequency of AEs between injection intervals <12 weeks and ≥12 weeks for each injection cycle, even for intervals as short as 6–7 weeks. Regardless of the length of the injection interval, the most frequently reported AEs were dry eyes, ptosis, and dry mouth (Table 2).

Similarly, in the CD study, the overall frequency of AEs for each injection cycle was comparable between treatments at incobotulinumtoxinA injection intervals <12 weeks and ≥12 weeks, even for the shortest treatment intervals (Table 2). Dysphagia, muscular weakness, neck pain, and injection-site pain were the most frequently reported AEs, irrespective of the length of the injection interval (Table 2).

Table 1
Frequency of injection interval length for each injection cycle among patients in the blepharospasm and cervical dystonia studies.

Injection interval (weeks)	Frequency of injection interval length for each injection cycle (% of treatments)						
	Injection cycle 1	Injection cycle 2	Injection cycle 3	Injection cycle 4	Injection cycle 5	Injection cycle 6	Cycles 1–6 combined
Blepharospasm study							
Number of treatments	n = 97	n = 90	n = 85	n = 83	n = 71	n = 35	n = 461
6–7	30.9	16.7	8.2	8.4	5.6	8.6	14.3
8–9	17.5	6.7	15.3	8.4	12.7	11.4	12.1
10–11	11.3	22.2	14.1	20.5	19.7	31.4	18.4
12–13	23.7	26.7	36.5	34.9	35.2	17.1	29.9
14–15	8.2	16.7	14.1	18.1	11.3	17.1	13.9
16–17	3.1	7.8	7.1	3.6	7.0	5.7	5.6
18–20	5.2	3.3	4.7	6.0	8.5	8.6	5.6
Cervical dystonia study							
Number of treatments	n = 207	n = 170	n = 145	n = 140	n = 106	n = 53	n = 821
6–7	5.3	12.4	6.2	9.3	8.5	3.8	7.9
8–9	42.5	16.5	15.9	14.3	13.2	7.5	21.6
10–11	12.1	16.5	13.1	15.7	25.5	11.3	15.5
12–13	19.3	20.6	25.5	22.9	33.0	32.1	23.9
14–15	10.1	15.3	17.2	17.1	5.7	26.4	14.1
16–17	4.3	10.0	11.0	12.9	7.5	5.7	8.6
18–20	6.3	8.8	11.0	7.9	6.6	13.2	8.4

All incobotulinumtoxinA injections (main period and extension period) with treatment intervals of 6–20 weeks were included in the analyses. Any injection interval that was not a whole number, when counted in weeks, was allocated to the next higher week.

4. Discussion

The current standard of care for patients who receive botulinum toxin injections for blepharospasm or CD is treatment intervals of no less than 3 months [14–19,24]. However, in clinical practice many patients with CD experience a duration of botulinum toxin treatment effect of <12 weeks [21]. A strict 3-monthly injection interval regimen may mean that many patients experience a re-emergence of symptoms before a new injection is administered, resulting in a decrease in treatment satisfaction toward the end of the injection cycle among patients treated with onabotulinumtoxinA or abobotulinumtoxinA [22]. A recent survey among patients who received botulinum toxin injections for the treatment of CD showed that more flexible dosing regimens were considered a desirable aspect of treatment; 45% of patients indicated a preference for treatment intervals ≤10 weeks [22]. According to the survey, the main rationale for setting patients' treatment intervals was a perceived increased risk of side effects and immunoresistance with shorter intervals [22]. However, clinical data evaluating a potential effect of botulinum toxin injection intervals on tolerability are lacking.

We have performed exploratory analyses assessing AEs at different injection interval lengths in two clinical studies of incobotulinumtoxinA in patients with blepharospasm or CD. In both studies, 12–13 weeks was the most frequent injection interval length. However, many injections were administered with shorter or longer intervals, and nearly half of treatments were administered with intervals <12 weeks. Patients had to approach their clinic when they felt they required a new injection and a clinical need for re-injection then had to be confirmed by the treating physician using a clinical rating scale (JRS in the blepharospasm study; TWSTRS in the CD study). Hence, the injection intervals in these studies reflect both patient preferences and clinical need. Importantly, in both studies there was no apparent trend for an increased frequency of AEs with shorter injection intervals and no difference between AE rates for incobotulinumtoxinA injections given at <12-week intervals versus ≥12-week intervals, even for incobotulinumtoxinA injections given at intervals as short as 6–7 weeks.

The recommendation of a 3-month injection cycle is largely based on a retrospective patient chart review by Greene et al. [20]. The authors compared the treatment regimens of eight patients with CD who had become unresponsive to botulinum toxin type A with a cohort of 32 patients who remained responsive and found that patients who lost responsiveness had received treatment with significantly shorter intervals and higher dosing, and had had more booster injections than patients who remained responsive [20]. However, the patients included in the review had started botulinum toxin therapy in 1988 and were injected with an old formulation of onabotulinumtoxinA. This formulation has subsequently been shown to be much more immunogenic than the current onabotulinumtoxinA formulation, probably owing to a higher protein load and greater inactive neurotoxin content [25]. Hence, it is unclear if the findings of Greene et al. can be applied to the

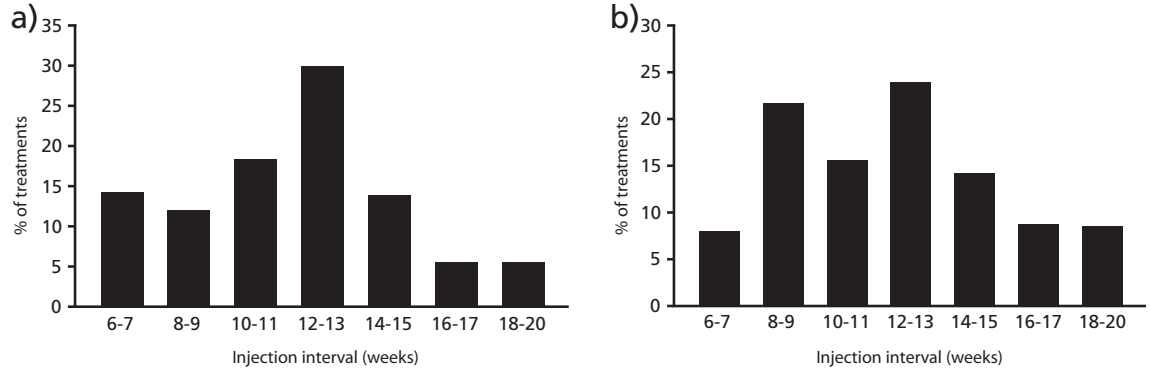

Fig. 1. Frequency of injection interval length for all injection cycles among patients in a) the blepharospasm study and b) the cervical dystonia study. All incobotulinumtoxinA injections (main period and extension period) with treatment intervals of 6–20 weeks were included in the analyses. Any injection interval that was not a whole number, when counted in weeks, was allocated to the next higher week.

Table 2
Frequency of adverse events by injection interval class summarized for all incobotulinumtoxinA treatments in the blepharospasm and cervical dystonia studies.

Frequency of adverse event (%)	Injection interval (weeks)						
	6–7	8–9	10–11	12–13	14–15	16–17	18–20
Blepharospasm study							
Number of injections	n = 66	n = 56	n = 85	n = 138	n = 64	n = 26	n = 26
Dry eye	4.5	7.1	8.2	5.8	7.8	7.7	7.7
Eyelid ptosis	16.7	3.6	10.6	8.0	17.2	7.7	15.4
Dry mouth	6.1	1.8	3.5	2.9	3.1	3.8	3.8
Cervical dystonia study							
Number of injections	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

All incobotulinumtoxinA injections (main period and extension period) with treatment intervals of 6–20 weeks were included in the analyses. Any injection interval that was not a whole number, when counted in weeks, was allocated to the next higher week.

current formulations of botulinum toxin type A, particularly incobotulinumtoxinA, which is free from complexing (accessory) proteins. In the studies included in these analyses, no patients newly developed neutralizing antibodies (as measured using the mouse hemidiaphragm assay), even in patients with the shortest injection intervals [5–8]. This is consistent with other recent studies of repeated incobotulinumtoxinA treatments in CD [10] and spasticity [26,27] and supports accumulating evidence that incobotulinumtoxinA is associated with low immunogenicity, at least during the first six injection cycles. More long-term studies with a greater number of injection cycles are necessary to determine if injection intervals <12 weeks have any influence on the development of possible immunoresistance.

Accumulating evidence in recent literature suggests that, after peripheral injection, botulinum toxin acts not only on neuromuscular junctions but may have additional effects on the central nervous system [28,29]. It is currently unclear if these central actions are clinically relevant for patients who receive botulinum toxin treatment for CD or blepharospasm and if they are affected by treatment intervals.

In conclusion, exploratory analysis of clinical study data in blepharospasm and CD showed that repeated injections of incobotulinumtoxinA were well tolerated when administered with flexible injection intervals of between 6 and 20 weeks according to patients' request and clinical need. No additional safety concerns and no cumulative effects were observed when incobotulinumtoxinA was given at short intervals of 6 to <12 weeks compared with longer intervals of ≥12 to 20 weeks.

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This study was sponsored by Merz Pharmaceuticals GmbH Frankfurt am Main, Germany. The sponsor was involved in study design and in the collection and analysis of data since the studies were part of the study program requested by the FDA for the approval of incobotulinumtoxinA. Medical writing support was provided by Simone Boldt from Complete Medical Communications Ltd, funded by Merz Pharmaceuticals GmbH.

Conflict of interest

Virgilio Gerald H. Evidente: speaker for Merz, Ipsen, USWorldMeds, Solstice, UCB, Medtronic, GE Healthcare, and Teva; consultancy or advisory board activities for Merz, Ipsen, Acadia, and USWorldMeds; receives research support from Ipsen and Acadia.

Daniel Truong: has been a speaker for US WorldMeds; has been involved in consultancy or advisory board activities for Merz, and Ipsen; received research grants from AbbVie, Acadia, NINDS, Ipsen, Merz, Adamas, Merck Schering Plough, Neurocrine Biosciences, and Kyowa Hakko Kirin Inc.

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Susanne Grafe: employee of Merz Pharmaceuticals, LLC.

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Virgilio Gerald H. Evidente: Data acquisition, data analysis and interpretation.

Daniel Truong: Data acquisition, data analysis and interpretation.

Joseph Jankovic: Data acquisition, data analysis and interpretation.

Cynthia L. Comella: Data acquisition, data analysis and interpretation.

Susanne Grafe: Conception or design of the study, data acquisition, data analysis and interpretation.

Angelika Hanschmann: Conception or design of the study, data acquisition, data analysis and interpretation.

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