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Review

A guide to dosing in the treatment of cervical dystonia and blepharospasm with Xeomin®: A new botulinum neurotoxin A

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ABSTRACT

Xeomin® (incobotulinumtoxinA; Merz Pharmaceuticals, Frankfurt am Main, Germany) was first introduced in Germany for movement disorders in 2005. In 2010, it was approved for use in the United States by the FDA for the treatment of cervical dystonia (CD) and blepharospasm. It is a unique botulinum type A formulation free of any complexing proteins and contains only the pure 150 kD neurotoxin. Thus, the formation of neutralizing antibodies is not induced even after long-term treatment. The purpose of this report is to review the safety profile and dosing schedule for Xeomin for the treatment of CD and blepharospasm.

The recommended dose for patients with CD is 120 U/treatment, with administration intervals normally between 3 and 6 months. However, clinical studies have found Xeomin to be safe and effective at doses up to 400 U in both previously treated and treatment-naïve patients. The recommended starting dose in patients with blepharospasm is 2.5–5.0 U/injection site. Patients can be switched using a 1:1 conversion ratio from Botox® (onabotulinumtoxinA, Allergen Inc., Irvine, CA, USA) to Xeomin without any loss of efficacy or safety concerns. Xeomin does not differ from Botox in terms of its potency, onset, diffusion profile, or duration and waning of effect. It is the only botulinum treatment that is stable for up to 3 years at room temperature. Xeomin offers a new and important treatment option for movement disorders.

Contents

1. Part I

1.1. Xeomin overview

In the United States, incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Frankfurt am Main, Germany) is indicated for the treatment of adults with cervical dystonia (CD) to decrease the severity of abnormal head position and neck pain in both botulinum toxin (BoNT)-naïve and previously treated patients and blepharospasm in adults previously treated with onabotulinumtoxinA (Botox®, Allergen Inc., Irvine, CA, USA) [1].

The clinical effect of Xeomin begins to appear within 4 days of injection, peaks at approximately 4–6 weeks, and is sustained for about 3–4 months. When injected directly into muscles, Xeomin inhibits local neuromuscular cholinergic transmission, causing

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focal weakness. It binds to motor nerve terminal presynaptic receptors, is internalized via receptor-mediated endocytosis, and then selectively cleaves a protein called SNAP-25, one of several 'SNARE' proteins involved in exocytosis. Cleavage of SNAP-25 inhibits the secretion of acetylcholine causing a localized weakness of the muscle [2].

Xeomin is a highly purified formulation containing pure neurotoxin *Clostridium botulinum* type A, free of any accessorial complexing proteins (hemagglutinins and non-hemagglutinins), often implicated in formation of antibodies. In contrast to the other BoNT products, Xeomin only contains the 150 kD neurotoxin and no inactive neurotoxins that might act as antigens [2]. However, it should be noted that in 1997 the formula for onabotulinumtoxinA (Botox) was changed to eliminate complexing proteins associated with neutralizing antibody formation. Based on a large meta-analysis ($n = 2240$), the frequency of antibody conversion after onabotulinumtoxinA treatment is very low and infrequently leads to loss of efficacy [3].

A preclinical study in NZW rabbits demonstrated that repeated treatment with Xeomin did not induce the formation of BoNT-A neutralizing antibodies [4]. In an ongoing study evaluating the antigenicity of Xeomin in 50 treatment-naïve and 50 previously treated (i.e., Botox [onabotulinumtoxinA], [Dysport®, Ipsen Ltd., Slough, UK [abobotulinumtoxinA], or NeuroBloc®/Myobloc®, Solstice Neurosciences Inc., Malvern, PA, USA [rimabotulinumtoxinB]), focal dystonia patients were switched to Xeomin. After 2 years, no patient developed secondary non-responsiveness or anti-BoNT-A antibodies [5]. Recently reported data from a study in 147 patients with upper-limb poststroke spasticity showed that even after a mean duration of exposure to Xeomin of approximately 63 weeks (median dose 374 U; mean cumulative dose 1333 U), no patient developed neutralizing antibodies [6].

Animal studies have established the safety profile of Xeomin. In repeated-dose rodent and non-rodent toxicity studies, no unexpected findings were seen that would impact the clinical safety profile [1,7]. Xeomin did not interact negatively with *human ether-á-go-go*–related gene (*hERG*) channels at concentrations exceeding the maximum achievable in human blood by a factor of at least 10,000. Xeomin is devoid of deleterious effects on the atrio- and intraventricular conduction velocity or ventricular depolarization up to dose levels at least 3 times the recommended therapeutic human dose in monkeys [7]. In rats, intramuscular (IM) injections of Xeomin at least 6 times higher than the maximum recommended clinical dose had no effect on gastrointestinal motility [8]. Finally, in an acute intravenous toxicity study in mice, the lowest dose (20% mortality) was 9-fold above the recommended therapeutic maximum dose of 300 lethal-dose U (kills 50% of mice by intraperitoneal injection) for patients with CD [7].

Xeomin is the only BoNT that is stable for 3 years at room temperature [9]. In a comprehensive real-time and accelerated stability study based on International Conference of Harmonisation guidelines, no detrimental effects on the quality of Xeomin were detected after storage at temperatures between 40° and 60 °C for up to 1 month [9].

Xeomin is available in 50-U and 100-U vials [1]. One hundred units of Xeomin contains approximately 0.6 ng (600 pg) of clostridial protein, compared with 55 ng for Myobloc, 5 ng for Botox, and 12.5 ng for Dysport [10]. The recommended dose for patients with CD is 120 U per treatment session [1], with administration intervals normally between 3 and 6 months [7].

In patients with blepharospasm, the dose, number, and location of injections should be based on the previous dosing of Botox. If that dose is not known, the recommended starting dose is 2.5–5.0 U per injection site [1]. In a placebo-controlled trial in which patients were dosed with the same number of units as they had received previously with Botox, the mean dose per eye was about 33 U (range 10–50 U), and the mean number of injections per eye was 6. The maximum dose per eye in the controlled trials was 50 U, with a range of 10–50 U. In the controlled trial, few patients received a total dose of greater than 75 U [1,11].

There is some evidence of a dose response. After single injections of Xeomin (2, 4, 16, or 32 U) into the extensor digitorum brevis (EDB) muscle of healthy volunteers, a dose–response relationship for efficacy and duration of effect was apparent when comparing the highest dose (32 U) with the lowest dose (2 U) but not the intermediate doses [12]. In a phase 2 dose-ranging study the greatest patient benefits for Xeomin were observed with the highest dose (i.e., 30 U in the sternocleidomastoid muscle and 60 U in the splenius capitis muscle) [7].

Prior to injection, Xeomin should be reconstituted with sterile, preservative-free 0.9% Sodium chloride Injection USP using the diluent volumes specified in the product prescribing information [1]. Once reconstituted Xeomin solution should be administered within 24 h during which time the diluted solution should be refrigerated at 2°–8 °C (36°–46 °F) [1].

As Xeomin is a relatively new product in the United States market and neurologists may be unfamiliar with dosing, this review will discuss the 1:1 dose ratio between Xeomin and Botox and the advantages of using Xeomin for treating movement disorders.

2. Part II

2.1. Xeomin clinical trial dosing experience

Xeomin has been used safely in doses of up to 840 mouse units (MU; 400 U) without risk of secondary treatment failure [13]. In patients previously treated with Botox switched to Xeomin, there were no differences in onset latencies, maximum and duration of their therapeutic effects, adverse event profile, or long-term use profile. The potencies of the Xeomin (103.0 ± 5.7) and Botox batches (101.7 ± 6.2) were not statistically different ($p = 0.734$) [14]. The potencies were determined using the LD_{50} bioassay (i.e., the dose that is lethal to 50% of mice tested) for batch release of Xeomin in a blinded fashion. Potency quantification was performed using the Xeomin reference standard qualified against the NIBSC standard. The biological potencies for the 2 agents were within the range specified in the European Pharmacopeia. A sensitive sandwich ELISA procedure using rabbit and guinea pig antibodies raised against the 150 kD BoNT-A neurotoxin purified from *C. botulinum* type A, showed that 100 units of Botox, Dysport, and Xeomin contained 0.73 ng, 0.65 ng, and 0.44 ng of BoNT-A, respectively, with the highest specific neurotoxin activity found in Xeomin [15].

Although LD_{50} is usually the assay procedure used to test for biological activity of botulinum neurotoxins, assay procedures can vary between companies. For this reason the most informative comparisons between BoNT drugs has been made in clinical studies. In clinical trials in patients with CD (total doses ranged from 70 to 300 U) [16], blepharospasm (≤35 U/eye) [17], and glabellar frown lines (24 U) [18], Xeomin was as effective and safe as Botox when used at a clinical conversion ratio of 1 U:1 U. Thus, similar doses of Xeomin and Botox can be used allowing exchange of both BoNT drugs in a therapeutic setting [19].

In a prospective, randomized, double-blind, placebo-controlled, phase 3 study of 120 and 240 U of Xeomin in 233 patients with CD, the change in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores at 4 weeks was significantly greater for both doses of Xeomin compared with placebo ($p < 0.001$). The lack of an efficacy difference between the 2 doses reported in this study was explained by the fact that the study was not powered to detect

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a difference between the 120 U and 240 U doses. However, the authors did state that there was a slightly larger mean change in the TWSTRS-Total score in the 240 U group than in the 120 U group and the higher dosage group showed a significantly greater improvement in the TWSTRS-Severity subscale. Adverse events (AEs), which occurred more often in treated groups, were dysphagia, neck pain, and muscle weakness [20]. Results of subanalyses of these data reported similar efficacy for both doses of Xeomin in both treatment-naïve patients [21] and patients previously treated with Botox [22]. Results from a long-term (≥48 weeks) double-blind extension of this study showed that repeated injections of both doses of Xeomin were well tolerated with no apparent cumulative effect [23].

Another prospective, double-blind, placebo-controlled, randomized, phase 3 study investigated individual doses of Xeomin (maximum 50 U/eye) compared with placebo for the treatment of blepharospasm in 109 patients previously treated with Botox. Patients were followed for up to 20 weeks. Treatment with Xeomin was associated with a significant ($p < 0.001$) improvement in the primary study endpoint (Jankovic Rating Scale [JRS] score at 6 weeks). Significant benefits in favor of Xeomin were also found for all secondary endpoints. AEs were reported in 70.3% of subjects in the Xeomin group and 58.8% of subjects in the placebo group. The most commonly reported AEs were eyelid ptosis (18.9% vs 5.9%), dry eye (18.9% vs 11.8%), and dry mouth (14.9% vs 2.9%), respectively [11].

Xeomin is effective even at low doses as shown in 2 experimental studies. In a phase 1 study, 14 healthy volunteers received a single IM injection into the EDB muscle of either 4 U of Xeomin or Botox randomized by foot. Both drugs produced a maximum decline of compound muscle action potential (CMAP) between day 7 and day 14. At day 90, administration of both drugs resulted in approximately a 40% CMAP decline as compared with baseline. The effects of both agents were comparable in terms of efficacy, time to onset of action, duration of action, and tolerability [19]. Similar results were shown in a phase 1b study using the same study design but different doses of Xeomin or Botox (2, 4, 16, or 32 U). Significant (Xeomin $p = 0.019$; Botox $p = 0.002$) paretic effects were observed in all dose groups of both products at week 4; results were sustained for 52 weeks in the highest (32 U) dose group for both products [12].

Results of an open-label, phase 2 study showed that equivalent doses of Xeomin and Botox were equally effective in treating rotational CD in 53 patients who were naïve to BoNT treatment [7]. A number of studies have demonstrated the comparable effectiveness of Xeomin and Botox administered in a dosing ratio of 1:1 [5,12,13,16,17,24,25]. In a double-blind randomized trial, 463 CD patients received IM injections of 70–300 U of Xeomin or Botox. On average, 39.3 ± 24.1 U were injected per muscle in the patients randomized to Xeomin and 39.3 ± 24.5 U in the patients receiving Botox. By week 16, Xeomin reduced the TWSTRS severity score by 39% and Botox by 37%. There were no significant differences between the treatment arms with respect to duration of effect (Xeomin: median, 110 days; Botox: median, 109.5 days) [16].

Xeomin was shown equivalent to Botox and superior to placebo for the treatment of blepharospasm in 2 multicenter, randomized, double-blind, phase 3 studies [11,17]. In the first study, patients were randomized to receive either Xeomin (≤50 U/eye) or placebo. Primary efficacy parameter was change in JRS Severity Subscore at 6 weeks. Significant improvement was seen in the Xeomin group compared with placebo ($p < 0.001$) [10]. In the second study, patients were randomized to receive an injection of either Xeomin or Botox (≤35 U/eye). The mean total doses of study medication injected were similar in the 2 groups (Xeomin 39.6 ± 13.3 U; Botox 40.8 ± 14.2 U). Both treatments resulted in a significant ($p < 0.0001$) decrease in the primary efficacy variable (JRS sum score at week 3). No significant differences were found between Xeomin and Botox for any efficacy variables. Maximum effect occurred at 21 days. Median onset of action (4 days), duration of action (110 days), and waning of effect (11 weeks) was the same for both preparations. Both products showed a comparable safety profile [17].

Xeomin is a formulation of pure BoNT-A free of complexing proteins and, therefore, may have a reduced immunogenic potential compared with other BoNT-A preparations. To evaluate the propensity for neutralizing antibody production during long-term Xeomin therapy, a real-world open-label study was begun in 2006. Over a period of approximately 2 years, 100 patients with focal dystonia (50 de novo and 50 patients previously treated with Botox, Dysport, or NeuroBloc/Myobloc) were switched to Xeomin. For the previously treated patients, a 1:1 dose relationship was used for the Botox to Xeomin switch, and a 1:4 dose relationship was used for the Dysport to Xeomin switch. Patients previously treated with NeuroBloc/Myobloc had been previously treated with Botox or Dysport. These patients were switched to NeuroBloc/Myobloc because they developed antibody-induced non-responsiveness to BoNT-A. The ratio used for these patients was based on their current therapy. Switching to Xeomin provided similar efficacy and duration of therapeutic effect [5]. Although patients previously treated with Botox or Dysport had negative results to antibody treatment at the beginning of Xeomin treatment, to date, no patient has developed secondary non-responsiveness or anti-BoNT-A antibodies after continuous Xeomin treatment.

In a study [24] designed to assess the diffusion/AE profile of Xeomin, 37 patients previously treated with Botox for 3.2 ± 1.9 years for CD (arm or leg spasticity or generalized spasticity) were switched to Xeomin (300–840 MU) using a 1:1 conversion ratio. All patients were blinded to treatment. No differences between Xeomin and Botox were reported with respect to intensity and duration of the therapeutic effect or safety.

Xeomin was originally developed to reduce drug antigenicity by extraction of the complexing proteins, which reduces the size of the BoNT-A component to 150 kD compared with 900 kD for Botox. It was originally hypothesized that this reduction in molecular size would result in more rapid and easy diffusion away from the target tissue into adjacent tissues, producing a different adverse event profile compared with Botox. However, studies have shown similar adverse event as well as diffusion profiles for these 2 agents [13]. This finding can be explained by a dissociation of the complex consisting of botulinum neurotoxin, non-toxic proteins, and excipients immediately after injection at a physiologic pH [2,26]. As size differences between Xeomin and Botox do not affect their therapeutic efficacy, tissue diffusion, and adverse effect profile, identical potency labeling allows easy exchange between both products.

Long-term use of Xeomin revealed no additional safety aspects. Two hundred and sixty-three patients with dystonia, spasticity, hemifacial spasm and re-innervation synkinesias, hyperhidrosis, or hypersalivation, who were previously treated with Botox for at least 1 year under stable conditions, were converted in a blinded fashion to Xeomin using a 1:1 conversion ratio and identical treatment parameters. Patients were treated for up to 3 years within a dose range of 45–840 MU. There were no subjective or objective differences between Botox and Xeomin treatments with respect to latency onset, maximum and duration of their therapeutic effects, and AE profiles. None of the patients lost therapeutic efficacy during the observation period. There were no diffusion differences between Botox and Xeomin. Even when applied in high doses, Xeomin did not produce secondary therapy failure [13].

In another long-term (89 weeks) study, repeated treatments with Xeomin (median dose 400 U) in 145 patients with poststroke

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upper-limb spasticity improved muscle tone and functionality without any evidence of neutralizing antibody formation [6]. However, it should be noted that since the change in the production formula for onabotulinumtoxinA in 1997 to eliminate complexing proteins associated with neutralizing antibody formation, the rate of antibody-induced therapy failure is reportedly less than 1% [27].

2.1.1. Correlation of dose with other factors

The treatment effects of Xeomin can be affected by other factors. In the blepharospasm studies, gender and age influenced treatment effect for all parameters tested. Response rates were generally higher in females (Xeomin/placebo: 59.2%/18.2%, respectively) than in males (46.2%/8.3%, respectively) and in younger subjects compared with older. Baseline mean JRS Subscore influenced the treatment effect significantly ($p < 0.0001$), with higher response rates corresponding to higher baseline scores (data on file). Pooled country and dose also had a significant ($p = 0.007$ and $p = 0.01$, respectively) effect on the final model for the control visit (data on file).

Baseline TWSTRS score, country, gender, and age are also correlated with outcome when treating CD. The separate analysis of the TWSTRS score regarding the subgroup's age (<50 years vs ≥50 years) and gender (male/female) resulted in an overall greater improvement of the score in the younger patients, which was slightly more pronounced in male than in female patients (data on file). In the full model, an influence of gender ($p = 0.043$) and baseline TWSTRS-Total score ($p = 0.017$) was identified. The mean reduction in the TWSTRS-Total score was higher in females than in males and tended to increase with increasing baseline score (the most marked change was generally found in subjects with a baseline score >50). Slightly higher reductions were observed in age groups 50–64 years and ≥65 years than in age group <50 years (data on file).

3. Conclusions

Xeomin, first introduced in Germany in 2005 for the treatment of cervical dystonia and blepharospasm, is a novel, highly purified BoNT type A free of all clostridial contaminants, especially complexing proteins, which can lead to partial or complete failure of therapy. This issue becomes more relevant with the high and repeated dosing often needed in chronic conditions, such as dystonia and spasticity. Antibody production is negligible during long-term Xeomin treatment, suggesting that complexing proteins are not needed for clinical efficacy.

Xeomin offers a new and important treatment option for movement disorders as noted in a number of studies that have shown that Xeomin is safe and effective for the treatment of blepharospasm and CD. It is a safe and effective treatment for CD in both previously treated and treatment-naïve patients. Higher doses (up to 840 MU) have been used in the treatment of generalized spasticity without revealing any safety concerns [13]. Although patients can be switched using a 1:1 conversion ratio from Botox to Xeomin with a number of studies showing comparable efficacy and safety, it is recommended that physicians gain experience with 1 or more formulations and avoid changing formulations wherever possible unless this is the only option for successful treatment. It is important to keep in mind that formulations of BoNT are distinct and that even the same serotype formulations have different molecular structures and sizes, as well as possible safety and efficacy profiles [28].

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