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Xeomin® in the treatment of cervical dystonia

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Background and purpose: Botulinum toxin type A (BoNT/A) is a highly effective and well-tolerated treatment for focal dystonias. The BoNT/A in Botox® and Dysport® is part of a high-molecular-weight complex that contains hemagglutinins and other non-toxic proteins, whilst Xeomin® is a highly purified BoNT/A free of such complexing proteins. In the largest controlled study of BoNT/A published to date (Neurology 2005; 64: 1949), it was demonstrated that Xeomin® is non-inferior to Botox® and has 1:1 efficacy in the treatment of cervical dystonia. A possible limitation of continued BoNT/A treatment is antibody development. Based on its physiochemical properties and toxicological evidence, Xeomin® is expected to have a reduced incidence of non-responders after long-term treatment compared with other marketed BoNT/A products.

Methods and results: In our ongoing open-label study, 100 patients suffering from cervical dystonia are continuously treated with Xeomin®; 50 patients were treated *de novo*, the remaining patients had been previously treated with Botox®, Dysport® or NeuroBloc®/Myobloc®. All patients showed negative results in antibody testing at the beginning of Xeomin® treatment. During continuous treatment with Xeomin® up to 2 years, patients continued to respond well to Xeomin® treatment.

Conclusion: The treatment was well tolerated and no patient has developed neutralizing antibodies as measured using the sensitive mouse hemidiaphragma assay within these first 2 years.

Introduction

Cervical dystonia, sometimes known as spasmodic torticollis, is a focal dystonia of the neck believed to be the result of abnormal functioning of the basal ganglia, and the age of onset is typically around 40 years and above [1]. The disorder is characterized by involuntary, inappropriate muscular hyperactivity of neck and shoulder muscles, leading to abnormal head movements and postures. Symptoms may vary from mild to severe, and the muscular spasms may also result in pain and discomfort. Some patients experience progression followed by stabilization of their condition whilst others experience no progression at all.

Botulinum toxin injections are the most effective treatment for this condition [1]. Several preparations are currently available including Botox® (Allergen Inc, Irvine, CA, USA), Dysport® (Ipsen Ltd, Berkshire, UK) and NeuroBloc®/MyoBloc® (Solstice Neurosciences Inc, South San Francisco, CA, USA), each being pharmacologically distinct, associated with differences in individual adverse event rates, and all are associated with the development of immunoresistance because of antibody formation [3]. Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a new botulinum toxin type A (BoNT/A) preparation that is free from complexing proteins. These complexing proteins that are thought to facilitate the development of anti-botulinum toxin antibodies during treatment with alternative preparations [4,5].

This paper will review the design and results of the largest phase III clinical study performed to date to evaluate the efficacy and tolerability of Xeomin® and Botox® in cervical dystonia. Data from an ongoing, real-world experience study of Xeomin® in *de novo* patients and patients previously treated with Botox® or Dysport® will also be reviewed.

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Xeomin® – a newly formulated BoNT/A preparation

The BoNT/A is obtained from specific strains of the bacterium *Clostridium botulinum* and is produced as a

part of a high-molecular-weight complex that also contains several hemagglutinins and other non-toxic proteins. A high-molecular-weight complex preparation is currently marketed as Botox® and Dysport®. In contrast, Xeomin® which is also obtained from *C. botulinum* is a highly purified BoNT/A which is free of such complexing proteins.

A possible limitation of continued intramuscular BoNT/A treatment, especially at higher doses, is the development of neutralizing antibodies. Based on its pharmacological properties, Xeomin® is expected to have a reduced incidence of non-responders after long-term treatment compared with other marketed BoNT/A products. However, this latter aspect has yet to be assessed in long-term safety studies in the clinic using antibody testing.

Xeomin® in the treatment of cervical dystonia: a randomized controlled study

In the largest controlled study of BoNT/A performed to date, it was demonstrated that Xeomin® is non-inferior to Botox® in the treatment of cervical dystonia and that on average the efficacy of 1 unit of Xeomin® is comparable to 1 unit of Botox® [2].

In this randomized, double-blind, active-controlled, parallel-group study, 463 patients received intramuscular injections of 70–300 U of Xeomin® or Botox® and were followed for 16 weeks. Patients with cervical dystonia of the predominantly rotational form (i.e., spasmodic torticollis) requiring a BoNT/A injection and with a documented stable therapeutic response to Botox® as a result of the last two consecutive injection sessions directly prior to trial entry (70–300 U) were included. Patients' last injection session with Botox® was required to be at least 10 weeks prior to randomization. A control visit took place 4 weeks after baseline (day 28 ± 3) and a final visit between days 109 and 112. Optional intermediate visits were carried out only at the request of the patient. The doses administered were based on the doses of Botox® received by patients in the two previous consecutive sessions directly prior to trial entry. The primary efficacy end-point was changed from baseline in the Toronto Western Spasmodic Torticollis Scale (TWSTRS) severity score at the control visit. Secondary end-points included change in the TWSTRS severity score at the final visit, the TWSTRS pain subscale score, the TWSTRS factorial scores, patient evaluation of global response, a visual analog scale pain score, duration, onset and waning of treatment effect, responder analysis and a global assessment of efficacy.

A total of 466 patients with cervical dystonia were enrolled, and 463 were randomized to treatment. Of these, 231 received treatment with Xeomin® and 232 with Botox®. The medical history of cervical dystonia was comparable between the two treatment groups (Table 1). Xeomin® proved non-inferior to Botox® in terms of the primary study end-point of change in the TWSTRS severity score at the control visit (Fig. 1). There were no significant differences between the treatment arms with respect to duration of effect (Xeomin®: median 110 days; Botox®: median 109.5 days). The improvement from baseline was less pronounced but still persisted at the final study visit (Fig. 1). A similar proportion of patients reported an improvement in their global response to treatment in the Xeomin® and Botox® arms at both the control and final study visits (Fig. 2).

On average, the efficacy of 1 unit of Xeomin® was equivalent to 1 unit of Botox®. The safety and tolerability profiles for both treatments were comparable (Table 2).

Table 1 Medical history of cervical dystonia in the study population (data from [2])

Characteristic	Xeomin® (N = 231)	Botox® (N = 232)
Mean duration of cervical dystonia, years ± SD	9.4 ± 7.7	9.2 ± 7.6
Hypertrophy of muscles, N (%)	92 (39.8)	93 (40.1)
Rotational form, N (%)		
Right	123 (53.2)	102 (44.0)
Left	107 (46.3)	130 (56.0)
Underlying type of cervical dystonia, N (%)[a]		
Retrocollis	71 (30.7)	42 (18.1)
Anterocollis	41 (17.7)	42 (18.1)
Laterocollis	138 (59.7)	151 (65.1)
Right	74 (32.0)	77 (33.2)
Left	64 (27.7)	74 (31.9)
Previous surgical intervention for cervical dystonia, N (%)	2 (0.9)	3 (1.3)
Mean number of injections since diagnosis (±SD)	8.5 ± 5.6	8.1 ± 4.7
Mean time from last injection, weeks (±SD)	14.8 ± 4.2	15.0 ± 4.2

[a]Sum of percentages may not total 100 as patients could be in more than one category and data are missing for some patients.

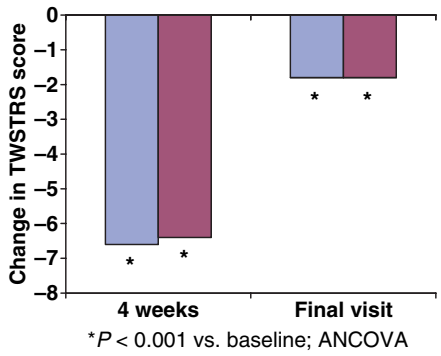

Figure 1 Change in Toronto Western Spasmodic Torticollis Scale Severity Score following treatment with either Xeomin® or Botox® amongst adults with cervical dystonia (data from [2]). *$P < 0.001$ vs baseline; ANCOVA.

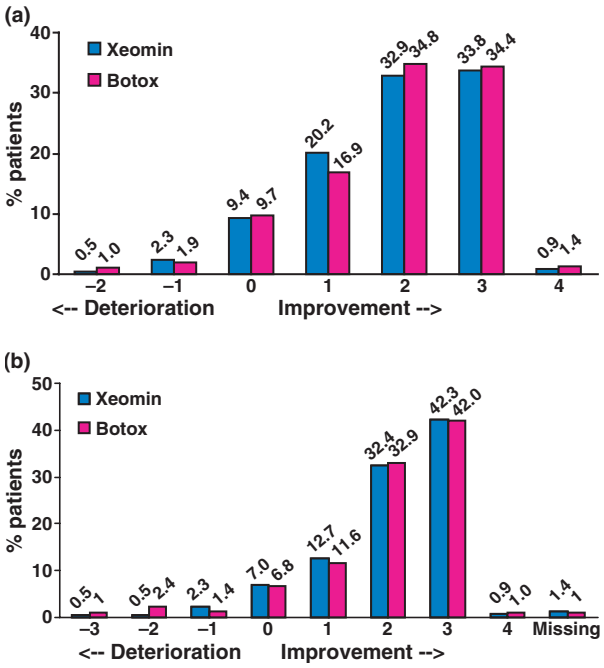

Figure 2 Patient evaluation of global response amongst adults with cervical dystonia treatment with either Xeomin® or Botox® at (a): the control visit (week 4); and (b) at the final study visit (data from [2]).

In summary, Xeomin® proved equipotent to Botox® in the treatment of cervical dystonia with a comparable safety profile.

Xeomin® in the treatment of cervical dystonia: an ongoing, open-label study

To begin to evaluate the propensity for neutralizing antibody production during long-term Xeomin® therapy, an open-label study in 100 patients suffering from cervical dystonia has been initiated. In the following, preliminary data of an ongoing long-term evaluation of the antigenicity of Xeomin are presented.

Table 2 Adverse events after a single injection with either Xeomin® or Botox® amongst 463 adults with cervical dystonia (data from [2])

Adverse event, *N* (%)	Xeomin® (*N* = 231)	Botox® (*N* = 232)
All	65 (28.1)	56 (24.1)
Dysphagia	25 (10.8)	19 (8.2)
Skeletal pain	8 (3.5)	5 (2.2)
Back pain	5 (2.2)	2 (0.9)
Muscle weakness	4 (1.7)	1 (0.4)
Headache	2 (0.9)	3 (1.3)
Vomiting	2 (0.9)	2 (0.9)
Erythematous rash	2 (0.9)	2 (0.9)
Diarrhoea	1 (0.4)	3 (1.3)
Fatigue	0	3 (1.3)
Arthralgia	3 (1.3)	0
Myalgia	2 (0.9)	1 (0.4)
Mouth dry	1 (0.4)	2 (0.9)
Dizziness	1 (0.4)	2 (0.9)

Over a period of approximately 2 years, 50 consecutive *de novo* patients and a further 50 patients suffering from focal dystonia who have been previously treated with Botox®, Dysport® or NeuroBloc®/Myobloc® have been switched to Xeomin® (mean age: 52 years) in our clinic. 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® were treated with Botox® or Dysport® prior to this and had been switched to NeuroBloc®/Myobloc® because of the development of non-responsiveness because of neutralizing antibodies against BoNT/A.

All *de novo* patients and all patients having been pre-treated with Botox® or Dysport® showed negative results in antibody testing using the sensitive mouse hemidiaphragm assay at the beginning of Xeomin® treatment [6]. Antibody testing was repeated after continuous treatment with Xeomin® for 1 and 2 years. To date, no patient has developed secondary non-responsiveness or anti-BoNT/A antibodies including 100 patients who have been treated continuously for more than 1 year and 34 patients treated continuously for more than 2 years.

Efficacy in *de novo* patients was excellent as expected. Patients reported a significant reduction in symptom severity following treatment, and the majority of patients evaluated their improvement as 'good' or 'very good' following Xeomin® injection 4 weeks after injection. Amongst patients pre-treated with Botox® or Dysport®, equivalent efficacy was observed with Xeomin® both in terms of change in symptom severity and in terms of a subjective evaluation for which patients

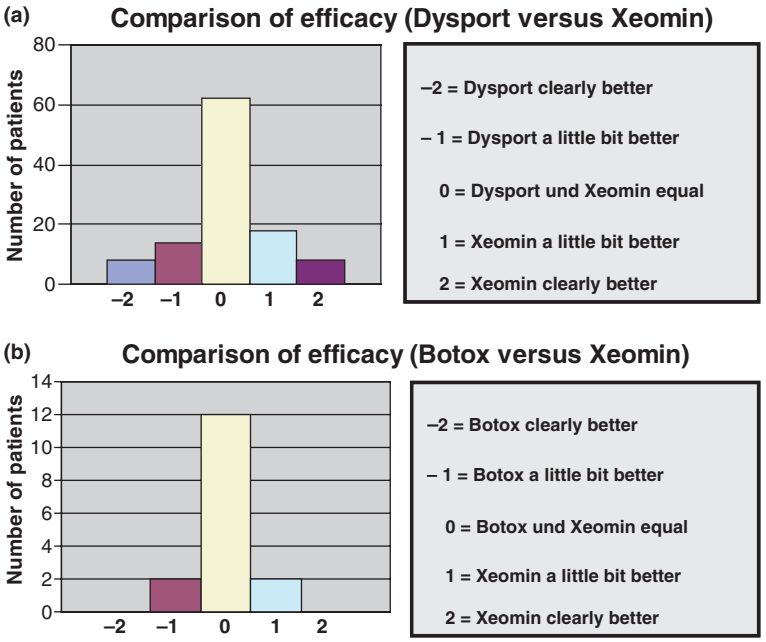

Figure 3 Patient evaluation of efficacy of Xeomin® compared with previous treatments: (a) Dysport®; and (b) Botox®.

were asked to compare the efficacy of their previous treatment with that of Xeomin® on a five-point scale (Fig. 3). Six patients exhibiting secondary non-responsiveness during treatment with Botox® or Dysport® as a result of antibody formation also failed to gain any clinical benefit with Xeomin® treatment, highlighting the importance of minimizing the risk for anti-botulinum toxin antibody formation.

Conclusions

A previous, large-scale, randomized, controlled study has demonstrated the comparable efficacy and tolerability of the new BoNT/A preparation Xeomin® with the currently available preparation Botox® in the treatment of cervical dystonia [2]. However, the potential for neutralizing BoNT/A antibody production remains a clinical concern given the resulting loss of therapeutic effect. It has been shown that complexing proteins could enhance the immunogenicity of the botulinum neurotoxin complex as well as the neurotoxin [4,5]. Xeomin® is free of the complexing proteins found with BoNT/A and retained in currently available preparations including Botox® and Dysport®. As such, Xeomin® may be less prone to stimulate the production of anti-BoNT/A antibodies during routine clinical use.

To determine whether Xeomin® is associated with anti-BoNT/A antibody production during long-term use in the real-world clinical setting, a clinical trial has been initiated in which patients presenting *de novo* or with previously treated cervical dystonia are switched to Xeomin® therapy and followed. To date, 100 patients have been recruited, 50 of whom have received previous BoNT/A treatment; none have so far evidenced the production of anti-botulinum toxin antibodies. The observation that amongst the six patients with secondary non-responsiveness during previous BoNT/A therapy because of antibody formation also failed to gain clinical benefit from Xeomin® therapy highlights the need to minimize the risk for antibody formation from first diagnosis and suggests that Xeomin®, with its potentially reduced propensity for antibody formation, may be a more appropriate first-line treatment choice for the treatment of focal dystonia.

Encouragingly, following successful treatment with the currently available BoNT/A preparations Botox® or Dysport®, switching to Xeomin® provided similar efficacy and duration of therapeutic effect in this open-label study. *De novo* patients treated with Xeomin® also gained considerable clinical benefit from therapy, reporting a significant improvement in symptom severity.

The clinical data reviewed here support the use of Xeomin® in the treatment of cervical dystonia and suggest that anti-BoNT/A antibody production is negligible during long-term Xeomin® treatment.

Conflicts of interest

The author acted as a consultant to Allergen, Ipsen and Merz.

References

1. Benecke R, Dressler D. Botulinum toxin treatment of axial and cervical dystonia. *Disabil Rehabil* 2007; **29:** 1769–1777.
2. Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. *Neurology* 2005; **64:** 1949–1951.
3. Chapman MA, Barron R, Tanis DC, *et al*. Comparison of botulinum neurotoxin preparations for the treatment of cervical dystonia. *Clin Ther* 2007; **29:** 1325–1337.
4. Kukreja R, Chang TW, Cai S, *et al*. Immunological characterization of the subunits of type A botulinum neurotoxin and different components of its associated proteins. *Toxicon* 2009; **53:** 616–624.
5. Lee JC, Yokota K, Arimitsu H, *et al*. Production of anti-neurotoxin antibody is enhanced by two subcomponents, HA1 and HA3b, of *Clostridium botulinum* type B 16S toxin-haemagglutinin. *Microbiology* 2005; **151:** 3739–3747.
6. Sesardic D, Jones RG, Leung T, *et al*. Detection of antibodies against botulinum toxins. *Mov Disord* 2004; **19**(Suppl. 8)**:** S85–S91.

