*European Journal of Neurology* 2009, **16** (Suppl. 2): 2–5

# Routine use of Xeomin® in patients previously treated with Botox®: long term results

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**Keywords:**
botulinum toxin type A, complexing proteins, conversion ratio, dystonia, efficacy, hemifacial spasm, hyperhidrosis, hypersalivation, re-innervation synkinesias, safety, spasticity

**Background and purpose:** Based upon large and carefully performed studies Xeomin® was first registered in 2005. However, its real potential can only be assessed, when it is used outside of study design restrictions, in an independent setting, in off-label indications and during continued use.

**Methods and results:** Two hundred and sixty-three patients (91 with dystonia, 84 with spasticity, 17 with hemifacial spasm and re-innervation synkinesias, 64 with hyperhidrosis, 7 with 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. Therapeutic outcome and adverse effects were monitored by neurological examination and structuralised interviews. In 223 patients (all except those with axillary hyperhidrosis) Xeomin® was used continuously throughout a 3 year period. Altogether 1050 injection series were performed. Patients with dystonia received 261.5 ± 141.0 MU Botox®/Xeomin®, patients with spasticity 450.5 ± 177.1 MU, patients with hemifacial spasm and reinnervation synkinesias 44.7 ± 19.5 MU and patients with hyperhidrosis 286.9 ± 141.6 MU. The maximum botulinum toxin dose applied was 840 MU. There were no subjective or objective differences between Botox® and Xeomin® treatments with respect to onset latency, maximum and duration of their therapeutic effects and their adverse effect profiles. Long-term use did not reveal additional safety relevant aspects. None of the patients lost therapeutic efficacy during the observation period.

**Conclusions:** Xeomin® can be used safely in doses of up to 840 MU. Even when applied in high doses it did not produce secondary therapy failure. There were no diffusion differences between Botox® and Xeomin®. Using a conversion ratio of 1:1 Xeomin® and Botox® can easily be exchanged in a continued treatment.

## Introduction

Botulinum toxin (BoNT) is now widely accepted as a treatment for a variety of disorders caused by muscle or exocrine gland hyperactivity. Xeomin®, first introduced in Germany in July 2005 for the treatment of cervical dystonia and blepharospasm [1,2], is a novel BoNT/A drug free of complexing proteins otherwise contained in all conventional BoNT/A drugs. Registration studies based on large cohorts of patients with cervical dystonia [1] and blepharospasm [2] showed Xeomin®'s safety and efficacy. They also showed identical potency labelling for Botox® and for Xeomin®. However, the real potential of a new BoNT/A drug can only be assessed when it is used without the restrictions of registration studies, in an independent setting, in off-label indications and during continued use. We are reporting this experience in a large group of patients previously treated with Botox®.

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## Methods

### Patients

Two hundred and sixty-three consecutive patients who returned for re-injections to the Movement Disorders Clinic, Department of Neurology, Rostock University, between June 2005 and May 2008 were included in the study. Their diagnoses and demographic data are presented in Table 1. Conditions were diagnosed based upon their predominant features, but could also include additional manifestations.

**Table 1** Diagnoses and demographic data of the patients examined

| Indication | Number of patients (*n*) | Females/ males (*n*) | Age (mean ± SD) (years) | Disease duration (mean ± SD) (years) |
|---|---|---|---|---|
| Cervical dystonia | 75 | 49/26 | 56.3 ± 12.3 | 13.1 ± 10.9 |
| Bleparospasm | 12 | 6/6 | 66.7 ± 8.3 | 5.8 ± 3.8 |
| Axial dystonia | 2 | 2/0 | 72.5 ± 13.4 | 10.0 ± 1.4 |
| Hemispasticity | 36 | 17/19 | 57.7 ± 15.7 | 8.1 ± 6.7 |
| Arm spasticity | 22 | 8/14 | 59.0 ± 13.4 | 5.8 ± 5.4 |
| Generalised spasticity | 16 | 4/12 | 40.3 ± 21.3 | 16.5 ± 13.3 |
| Paraspasticity | 7 | 5/2 | 36.6 ± 19.4 | 14.9 ± 8.8 |
| Leg spasticity | 3 | 2/1 | 54.0 ± 9.5 | 11.0 ± 10.8 |
| Hemifacial spasm | 11 | 9/2 | 61.1 ± 11.6 | 6.8 ± 3.9 |
| Re-innervation synkinesias | 3 | 3/0 | 51.7 ± 11.0 | 5.8 ± 5.3 |
| Axillary hyperhidrosis | 41 | 34/7 | 29.0 ± 9.8 | 11.6 ± 9.7 |
| Cranial hyperhidrosis | 15 | 11/4 | 54.4 ± 14.1 | 13.2 ± 11.4 |
| Palmar hyperhidrosis | 5 | 3/2 | 31.6 ± 15.2 | 17.2 ± 11.7 |
| Axillary plus hyperhidrosis | 3 | 1/2; | 42.3 ± 16.1 | 30.0 ± 18.0 |
| Hypersalivation | 7 | 2/5 | 73.4 ± 7.8 | 2.4 ± 2.5 |

### Study design

The study followed a cross-over design, i.e. all patients were previously treated with Botox® for at least 1 year under stable conditions before they entered the study and were converted in a blinded fashion to Xeomin®. Patients receiving more than 300 MU of Botox® were included in the study following a dose-escalation scheme. In 223 patients (all except those with axillary hyperhidrosis) Xeomin® was used continuously throughout the 3 year observation period.

### BoNT/A therapy

BoNT/A therapy was performed with Xeomin® (Merz Pharmaceuticals, Frankfurt/M, Germany, 100 MU in 2.5 ml 0.9%NaCl/$H_2O$) and with Botox® (Allergan, Irvine, CA, USA, 100 MU in 2.5 ml 0.9%NaCl/$H_2O$) using identical injection schemes, i.e. identical BoNT/A doses, target muscles and injection sites, for the Xeomin® and the Botox® treatments.

### Outcome measurements

Therapeutic efficacy and adverse effects were monitored by neurological examination and structuralised interviews of the patients and – where available – their care givers and physiotherapists. The structuralised interview used is shown in Fig. 1.

**Efficacy**
The therapeutic effect of botulinum toxin therapy can be described by the time it takes to kick in, its extent after 3 weeks and its duration.
Was any of this different after the last and the previous treatment?

**Adverse Effects**
Adverse effects of botulinum toxin therapy can include the following:
- weakness of the injected body part
- generalised weakness
- shortness of breath
- malaise
- difficulties reading texts at your usual reading distance
- dry mouth
- dry eyes
- altered sweating pattern
- swallowing difficulties
- double vision
- increased sensitivity to light
- urination difficulties
- altered bowel movements

Did you experience any of these adverse effects after your last botulinum toxin therapy? If so, were they any different from the previous treatment?

**Figure 1** Structuralised interview to monitor efficacy and adverse effects of botulinum toxin therapy.

## Results

Altogether 1050 injection series were given in the 263 patients throughout the 3 year observation period. 433 injection series were given in patients with dystonias, 398 in patients with spasticity, 63 in patients with hemifacial spasm, 23 in patients with re-innervation synkinesias, 119 in patients with hyperhidrosis and 14 in patients with hypersalivation. In 223 patients (all patients except those with axillary hyperhidrosis), Xeomin® was used continuously throughout the observation period. In those a total of 1050 injection series was administered as shown in Table 2. Each patient received an average of 4.52 injection series. The maximum number of injection series given to a single patient was 11. Figure 2 presents the distribution of the number of injection series applied. The average Xeomin® doses given per patient in each indication are also shown in Table 2. The indication receiving the lowest Xeomin® doses was hemifacial spasm with an average dose of 43.3 ± 15.0 MU. The indication receiving the highest Xeomin® doses was generalised spasticity with an average dose of 552.2 ± 217.1 MU. The maximal Xeomin® dose applied to a single patient was 840 MU.

**Table 2** Number of injection series and total doses of Xeomin® applied

| Indication | Number of injection series (*n*) | Total dose of Xeomin® (mean ± SD) (years) |
|---|---|---|
| Cervical dystonia | 376 | 284.7 ± 133.2 |
| Blepharospasm | 43 | 85.1 ± 32.6 |
| Axial dystonia | 14 | 350.0 ± 99.0 |
| Arm spasticity | 81 | 368.7 ± 100.5 |
| Leg spasticity | 22 | 206.7 ± 90.2 |
| Hemispasticity | 195 | 476.5 ± 168.3 |
| Paraspasticity | 39 | 435.7 ± 160.0 |
| Generalised spasticity | 61 | 552.2 ± 217.1 |
| Hemifacial spasm | 63 | 43.3 ± 15.0 |
| Re-innervation synkinesias | 23 | 50.0 ± 37.0 |
| Axillary hyperhidrosis | 41 | 108.3 ± 36.8 |
| Cranial hyperhidrosis | 51 | 333.0 ± 136.3 |
| Axillary plus hyperhidrosis | 18 | 500.0 ± 100.0 |
| Palmar hyperhidrosis | 9 | 200.0 ± 0.0 |
| Hypersalivation | 14 | 171.4 ± 48.8 |

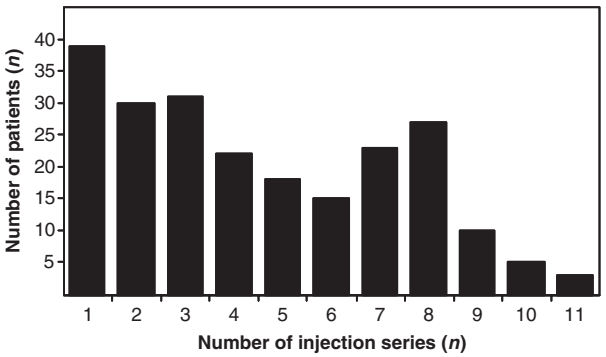


**Figure 2** Number of injection series applied during the continuation phase of the observation period.

When the therapeutic outcomes of the Botox® and Xeomin® treatments were compared with respect to their onset latencies, maximal extents and durations there were no subjective or objective differences detectable. Evaluation of the long-term treatment did not reveal additional safety relevant aspects. None of the patients lost therapeutic efficacy during the observation period.

Adverse effects observed after the Botox® and the Xeomin® treatments were not different. None of the patients experienced systemic adverse effects, neither motor nor autonomic ones.

## Discussion

### Systemic toxicity

BoNT/A can produce obligatory, local and systemic adverse effects. Whereas obligatory and local adverse effects are therapeutically of minor concern, systemic adverse effects indicate imminent systemic toxicity which might eventually produce the clinical picture of botulism with its motor and autonomic impairment. Experience with high dose use of BoNT/A, therefore, is needed. Results obtained from this study show that Xeomin® as well as Botox® can be used in doses of up to 840 MU without producing clinically detectable systemic adverse effects. These doses substantially exceed therapeutic doses so far reported for Xeomin® as well as for Botox®. With sufficient experience of the injector and following general safety recommendations both products may, therefore, be used in doses substantially exceeding those so far believed to be safe. This allows expanding the use of BoNT/A therapy into more widespread and more severe muscle hyperactivity disorders.

### Diffusion

Xeomin® was originally developed to reduce drug antigenicity by extraction of the complexing proteins. This substantially reduces the size of the BoNT/A component [3]. With a size-reduced BoNT/A component, however, it could be hypothesized that Xeomin® might more rapidly and more easily diffuse away from the target tissue into adjacent tissues. These diffusion differences should, if they exist, produce an adverse effect profile different from that of conventional BT drugs such as Botox®. Comparing the adverse effect profiles of Botox® and Xeomin®, however, did not reveal any of those differences. Thus, diffusion from the target tissue into adjacent tissues does not seem to be different. This unexpected finding can be explained by a dissociation of the complex consisting of botulinum neurotoxin and complexing proteins immediately after injection [4]).

### Potency labelling

Standardisation of the biological activity of BoNT/A drugs has shown to be difficult in the past [3]. Whenever a new BoNT/A drug becomes available, therefore, its potency labelling has to be evaluated. When Xeomin® became available the manufacturer assumed, based upon preclinical studies, identical potency labelling as for Botox®. Subsequently, the registration studies using a cross-over design were based on identical potency labelling. Results from both registration studies [1,2] together with recent head-to-head potency testing using a mouse lethality assay [5] confirmed identical potency labelling. Data from our present study further confirm identical potency labelling and show that it is valid even when BoNT/A doses are pushed to their current limits.

 

With identical potency labelling comparisons between Xeomin® and Botox® become possible. Clinically Xeomin® and Botox® can be exchanged easily using a straight-forward 1:1 conversion ratio.

### Off-label indications

The use of Xeomin® has so far been published for cervical dystonia and blepharospasm only. Our present study expands its use for the first time into off-label indications. Apart from additional indications requiring striate muscle injections including axial dystonia and spasticity we publish for the first time the use of Xeomin® for the treatment of disorders caused by overactivity of the cholinergic autonomic nervous system including hyperhidrosis and hypersalivation. These findings further confirm that Xeomin®, based upon the same botulinum neurotoxin and the same serotype, behaves therapeutically very similar to Botox®.

## Conflicts of interest

D.D. is or was consultant to Allergan, Ipsen, Merz and Eisai/Elan. D.D. has been employed by the Hannover Medical School.

## References

1. 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:** 19490–19510.
2. Roggenkämper P, Jost WH, Bihari K, Comes G, Grafe S. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. *J Neural Transm* 2006; **113:** 303–312.
3. Dressler D, Bigalke H. Pharmacology of botulinum toxin drugs. In: Truong D, Dressler D, Hallett M, eds. *Manual of Botulinum Toxin Therapy*. Cambridge, UK: Cambridge University Press, 2009: 13–22.
4. Friday D, Bigalke H, Frevert J. In vitro stability of botulinum toxin complex at physiological pH and temperature. *Naunyn Schmideberg's Arch Pharmacol* 2002; **365**(Suppl. 2)**:** 46.
5. Dressler D, Mander G, Fink K. Equivalent Potency of Xeomin® and Botox®. *Mov Disord* 2008; **23**(Suppl. 1)**:** S20–S21.

 