European Journal of Neurology 2009, **16** (Suppl. 2): 14–18

Clinical efficacy and tolerability of Xeomin® in the treatment of blepharospasm

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Keywords:
blepharospasm,
botulinum toxin type A,
efficacy, safety, Xeomin®

Background and purpose: Blepharospasm is classified as a focal dystonia, and botulinum toxin type A (BoNT/A) has been shown to be a highly effective and well-tolerated symptomatic treatment. Xeomin®, the latest addition to BoNT/A preparations, is a purified, freeze-dried BoNT/A that is free from complexing proteins.

Methods and results: In a double-blind, parallel-group, multicentre study, 300 patients with blepharospasm received either Xeomin® or Botox® 15–80 U (J Neural Transm 2006; 113: 303). Both treatments produced statistically significant improvements from baseline in the Jankovic Rating Scale at week 3 (primary efficacy variable; Xeomin®: −2.90; Botox®: −2.67; $P < 0.0001$ from baseline for both), with the difference between treatments (−0.23) indicating that Xeomin® was clinically non-inferior to Botox®. No significant differences were found between Xeomin® and Botox® for all secondary variables. There were no clinically relevant differences between Xeomin® and Botox® in safety parameters, with 40 of 148 patients (27.0%) treated with Xeomin® reporting adverse events versus 45 of 155 patients (29.0%) treated with Botox®. The most common adverse event was ptosis (6.1% Xeomin® and 4.5% Botox®).

Conclusion: Clinical evidence to date suggests that Xeomin® is an effective treatment for blepharospasm that does not differ from Botox® in terms of its potency, duration of effect or adverse reaction profile.

Introduction

Blepharospasm is a progressive neurological disorder characterized by spontaneous, spasmodic, bilateral, intermittent or persistent involuntary contractions of the orbicularis oculi muscles [6,8]. In patients with the so-called benign essential blepharospasm, the most common form of blepharospasm, these contractions are thought to be caused by abnormal functioning of the basal ganglia [1,7]. Blepharospasm is classified as a focal dystonia, and botulinum toxin (BoNT) has been shown to be a highly effective and well-tolerated symptomatic treatment of focal dystonias, including blepharospasm [13,15].

Recently, the Therapeutics and Technology Assessment Committee of the American Academy of Neurology concluded that there is level B (probably effective) evidence for the efficacy of botulinum toxin type A (BoNT/A) therapy for the treatment of blepharospasm [19]. This recommendation was based on the results of two Class II studies (with regard to design) that evaluated the efficacy and tolerability of an established BoNT/A preparation – Botox® [5,9] and one Class I study that compared Botox® with Xeomin®, an alternative BoNT/A preparation [18].

This article provides an overview of blepharospasm treatment with Xeomin®, as this is the most novel of BoNT/A preparations tested in the treatment of focal dystonia.

Xeomin®

Xeomin® is a purified, freeze-dried BoNT/A, which is free from complexing proteins as they are removed during the biological manufacturing process. These proteins are normally required to protect the native toxin from destruction in the gastrointestinal tract when the toxin is ingested orally (its natural route of entry) but have no therapeutic activity [22]. The presence of complexing proteins in commercially available preparations may facilitate an immunogenic reaction and the development of anti-BoNT/A antibodies resulting in

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the loss of therapeutic activity [10]. Removing the complexing proteins in the manufacture of Xeomin® may reduce this risk [13].

The efficacy and safety of Xeomin® compared with a currently marketed preparation (Botox®) in the treatment of blepharospasm has been demonstrated in a phase III study [18]. The aim of the study was to demonstrate the non-inferiority of Xeomin® compared with Botox® in this setting.

Study design

The study utilized a randomized, double-blind, parallel-group design to demonstrate the non-inferiority of Xeomin® compared with Botox® in the treatment of blepharospasm. Patients were randomized to receive an injection of either Xeomin® or Botox® in the range with a maximum dose of 35 U per eye (maximum total dose 70 U). The investigators were allowed to decide the most appropriate number of sites and the distribution of the dose between these sites, but most used 8–10 injection sites. The doses administered were equivalent to the Botox® doses received in the previous successful two injection sessions before trial entry. The evaluation of previous, stable therapeutic response was judged by both the investigator and patient and included: no change in injection scheme with respect to injected dose and volume, in time interval between injections (difference ≤3 weeks) or in injection points. Patients were monitored for up to 16 weeks following the injection. A control visit took place 3 weeks after baseline (day 21 ± 1) and a final visit between days 109 and 112. The date of the final visit was based on the patient's need for a new injection. Optional intermediate visits were carried out only at the request of the patient.

The primary efficacy variable was the difference in the total score between baseline and the control visit on the Jankovic Rating Scale (JRS) [9,11,12]. Secondary endpoints included the change from baseline in the JRS total score at the final visit and in the Blepharospasm Disability Index (BSDI), patient evaluation of global response, assessment of efficacy by the investigator, duration of treatment effect, time to onset of treatment effect and time to waning of treatment effect. Safety evaluations included the recording of adverse events, assessment of the tolerability by the investigator, standard clinical laboratory tests, general physical and neurological examination, assessment of vital signs, an electrocardiogram and antibody testing.

Patient flow and demographics

A total of 304 patients with blepharospasm were enrolled, and 303 were randomized to treatment in this multicentre study. Of these, 300 received treatment with either Xeomin® (N = 148) or Botox® (N = 152). Table 1 provides an overview of the baseline demographics of the 300 patients who received treatment.

Table 1 Baseline demographics of the study population

Parameter	Characteristic	Treatment	
		Xeomin® (N = 148)	Botox® (N = 152)
Sex, N (%)	Male	32 (21.6)	50 (32.9)
	Female	116 (78.4)	102 (67.1)
Age, years	Mean (SD)	63.9 (9.31)	61.5 (11.14)
	Median	66.0	65.0
	Range	37–87	25–81
Weight, kg	Mean (SD)	71.5 (12.28)	73.7 (13.45)
	Median	72.0	72.0
	Range	41.0–103.4	49–110
Height, cm	Mean (SD)	163.7 (7.47)	166 (7.88)
	Median	164.0	166.0
	Range	148.0–184.0	148–185
BMI, kg/m^2	Mean (SD)	26.7 (4.03)	26.7 (4.14)
	Median	26.2	26.3
	Range	17.0–39.0	18–40

Efficacy

Improvement in blepharospasm symptoms

Both treatments produced statistically significant improvements from baseline in the JRS at week 3 (primary efficacy variable; Xeomin®: −2.90; Botox®: −2.67; $P < 0.0001$ versus baseline for both). The non-significant difference between treatments (−0.23) indicated that Xeomin® was clinically non-inferior to Botox® (Fig. 1). The mean change in JRS total score at the final visit was slightly greater in the Xeomin® group

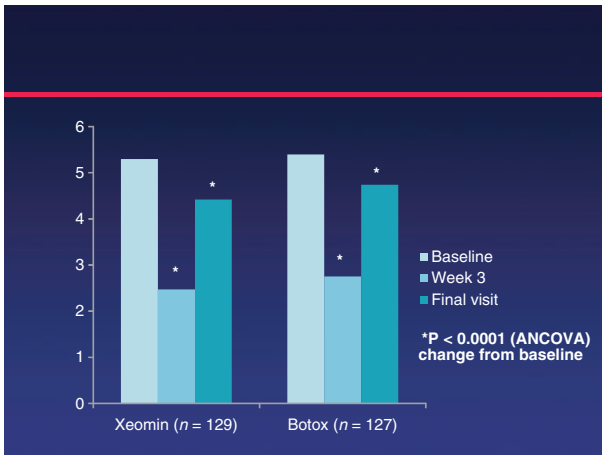

Figure 1 Mean change from baseline in total Jankovic Rating Scale total score at week 3 and up to 16 weeks after a single injection with either Xeomin® or Botox® amongst 300 adults with blepharospasm (data [18]).

(−0.84) than in the Botox® group (−0.66), but this was not statistically significant. The mean change in JRS total score at the final visit was highly significant for both treatments ($P < 0.0001$) indicating that both treatments resulted in a significant improvement of blepharospasm.

Amongst the secondary end-points, BSDI was developed for self-assessment by the patient, as published functional scales are not adequate to reliably capture the specific functional deficits associated with blepharospasm [11,12]. This new scale consists of six 5-points scaled items on driving a vehicle, reading, watching TV, shopping, getting about on foot and doing everyday activities. The retest reliability of the single items ($0.453 \leq r \leq 0.595$, Spearman's Rank coefficient), and validity of the BSDI was evaluated during the course of the trial. The change from baseline in the BSDI was −0.83 for Xeomin® and −0.82 for Botox®.

No significant differences were found between Xeomin® and Botox® for any of the other secondary variables.

Onset and duration of effect

Onset of effect was defined as the time from the initial injection until onset of perceptible effect as subjectively estimated by the patient. An onset of treatment effect was reported in 125 patients (96.9%) in the Xeomin® group and in 121 patients (95.3%) in the Botox® group. The median time to onset of treatment effect was the same (4 days) in both treatment groups.

The duration of effect was defined as the time from the initial injection until the need for a new injection (study end). The mean duration of treatment effect, evaluated in a time-to-event analysis using a Cox proportional hazards regression analysis, was slightly more than 96 days for both treatment groups (Table 2). From the final model, the relative risk for the duration of treatment effect was 1.03 [95% confidence interval (CI): 0.78–1.34; $P = 0.86$], suggesting no significant difference between treatments with respect to duration of effect. This is further highlighted by the Kaplan–Meier survival curves plotting duration of treatment effect in both treatment groups and the log-rank test of equality over strata ($P = 0.73$) (Fig. 2).

Waning of effect, defined as the time from the initial injection until perceptible waning of effect as subjectively estimated by the patient, was reported in 108 patients (83.7%) in the Xeomin® group and in 110 patients (86.6%) in the Botox® group. There were no significant differences between treatment groups with respect to time to waning of effect, nearly 10 weeks, confirmed by the Cox proportional hazards regression model (relative risk = 1.08, 95% CI: 0.83–1.40; $P = 0.58$) and visualized with the Kaplan–Meier plots (log-rank test $P = 0.39$) (Table 2).

Table 2 Duration of treatment effect after a single injection with either Xeomin® or Botox® amongst 300 adults with blepharospasm (data from[18])

	Xeomin®		Botox®	
Parameter	*N*	Mean ± SD	*N*	Mean ± SD
Onset of effect, days	122	5.5 ± 5.5	118	5.0 ± 4.3
Waning of effect, weeks	111	9.9 ± 3.6	115	9.8 ± 3.9
Duration of effect, days	112	96.2 ± 25.9	116	96.8 ± 29.0

Safety

There were no clinically relevant differences between Xeomin® and Botox® in safety parameters. In all, 40 of 148 patients (27.0%) treated with Xeomin® reporting adverse events versus 45 of 155 patients (29.0%) treated with Botox®. The most common adverse event was ptosis (6.1% Xeomin® and 4.5% Botox®) (Table 3). Eight patients in the Xeomin® group and seven patients in the Botox® group experienced other vision disorders including abnormal vision and xerophthalmia.

A higher percentage of investigators assessed the tolerability of Xeomin® as 'very good' compared with that for Botox® (70.3% vs. 61.9%), but this difference did not reach statistical significance. The overall assessment of tolerability was not significantly different between treatment groups as tested using a two-sample Wilcoxon Rank-Sum test ($P = 0.17$).

Discussion

Up to two-thirds of patients with blepharospasm are rendered functionally blind [8]. Several studies have demonstrated that injections of botulinum toxin into the

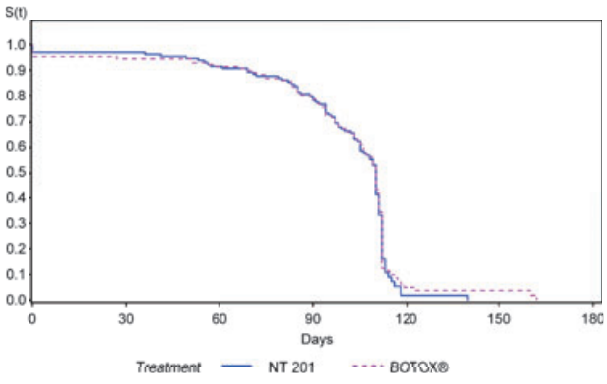

Figure 2 Duration of treatment effect after a single injection with either Xeomin® or Botox® amongst 300 adults with blepharospasm (data [18]).

Table 3 Adverse events after a single injection with either Xeomin® or Botox® amongst 300 adults with blepharospasm (data from[18])

Adverse event, *N* (%)	Xeomin® (*N* = 148)	Botox® (*N* = 155)
Ptosis	9 (6.1)	7 (4.5)
Vision abnormal	2 (1.4)	5 (3.2)
Back pain	2 (1.4)	4 (2.6)
Rash	1 (0.7)	2 (1.3)
Upper RTI	1 (0.7)	2 (1.3)
Face oedema	1 (0.7)	2 (1.3)
Xerophthalmia	3 (2.0)	0
Arthralgia	1 (0.7)	1 (0.6)
Dizziness	2 (1.4)	0
Headache	1 (0.7)	1 (0.6)
Paraesthesia	1 (0.7)	1 (0.6)
Depression	0	2 (1.3)
Palpitation	0	2 (1.3)
Photophobia	2 (1.4)	0
Dyspnoea	2 (1.4)	0
Urinary tract infection	2 (1.4)	0

RTI, respiratory tract infection.

orbicularis oculi and other muscles involved in eye closure provide the most effective symptomatic relief of this focal dystonia [19]. Whilst Botox® has been most extensively studied, other preparations have been also found to be effective in blepharospasm and other focal dystonias. However, there are only a very few head-to-head comparisons of the different products in patients with cervical dystonia [2,3,4,17,20], and none in patients with blepharospasm. Based on the results of a phase III, randomized, parallel-group, multicentre study, Xeomin® is as effective and safe in the treatment of patients suffering from blepharospasm as Botox® [18]. Both preparations have similar efficacy and safety profiles at a 1:1 dose ratio in blepharospasm, and both treatment groups showed a decrease in the JRS total score at the control visit signifying an improvement in the symptoms of blepharospasm during this time period.

In addition to Xeomin® and Botox®, another form of BoNT/A studied in the treatment of blepharospasm is Dysport®. In a multicentre, clinical, fixed-dose, trial Dysport® (40, 80 and 120 units/eye) or placebo (in a 3:1 randomization ratio) were administered to 119 patients with blepharospasm, 85 of whom completed the 16 week follow-up, several parameters showed robust improvement in Dysport® arms compared to placebo, particularly at 80 units [21]. Although Dysport® was not systematically compared to the other BoNT/A preparations, there is no reason to believe that one preparation is more effective or safer. In contrast to the Blepharospasm Disability Scale [16] at 4 weeks after injection, used as the primary efficacy measure in the Dysport® blepharospasm study, the Xeomin® versus Botox® study utilized the JRS and BSDI in assessing the response. The metric properties of the two latter scales were analysed and compared to the Patient Evaluation of Global Response (PEGR) and Global Assessment Scale (GAS) [11,12]. Both JRS and BSDI were found to have high internal consistency and reliability. Furthermore, when correlated with PEGR and GAS, a reduction of two points on the JRS and 0.7 points on the BSDI were thought to be 'clinically meaningful'. Thus, the reduction of 2.90 and 2.67 in the JRS score and of 0.83 and 0.82 in the BSDI score with Xeomin® and Botox®, respectively, provides confirmation of clinical efficacy of both products.

The efficacy and safety of Xeomin® in the treatment of blepharospasm has been also confirmed by a prospective, double-blind, placebo-controlled, randomized, multicentre study [11,12]. In this study involving 109 patients (mean total dose of Xeomin® per treatment visit was 64.8 U), the JRS severity subscore was significantly reduced compared to placebo ($P < 0.001$). The most commonly reported adverse effects related to Xeomin® versus placebo were eyelid ptosis (18.9 vs. 8.8%), dry eye (16.2 vs. 11.8%), and dry mouth (16.2 vs. 2.9%).

In conclusion, the clinical evidence to date suggests that Xeomin® is an effective treatment for blepharospasm, which does not differ from Botox® in terms of its potency, duration of effect, or adverse reaction profile. The data summarized here support the clinical utility of BoNT as the treatment of choice for blepharospasm [14].

Acknowledgements

Some of the data reported in this manuscript was previously published by Roggenkämper *et al*. in 2006. The author thanks Ian K Wright, PhD for his assistance in preparation of the manuscript.

Conflicts of interest

J.J. has acted as a consultant to Allergen, Ipsen, Merz.

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