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Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm

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Summary. NT 201 is a new development of Botulinum Toxin Type A free of complexing proteins. In this double-blind Phase III trial, we compared the efficacy and safety of NT 201 and BOTOX® in patients suffering from blepharospasm. Of 304 enrolled patients, 300 patients received study medication (intent-to-treat population), and 256 patients completed the study as planned (per-protocol population). At baseline, patients received a single injection of NT 201 or BOTOX® (≤35 units per eye). No significant differences were found between NT 201 and BOTOX® for all efficacy and safety variables three weeks after injection. Both the NT 201 and the BOTOX® group showed a decrease in the Jankovic Rating Scale (JRS) sum score signifying an improvement in the symptoms of blepharospasm during this time period. These data show that NT 201* is an effective and safe treatment for patients suffering from blepharospasm.

Keywords: Botulinum toxin type A, blepharospasm.

* The trade name of NT 201 is Xeomin®

Abbreviations

AE adverse event; *ANCOVA* analysis of covariance; *BSDI* Blepharospasm Disability Index; *CI* confidence interval; *ECG* electrocardiogram; *IEC* independent ethics committee; *ITT* intent-to treat; *JRS* Jankovic Rating Scale; *PP* per-protocol; *SAE* serious adverse event.

Introduction

Benign idiopathic blepharospasm is a progressive disease characterized by spontaneous, spasmodic, bilateral, intermittent, or persistent involuntary contractions of the orbicular oculi muscles (Grandas et al., 1988; Jankovic and Orman, 1984; Mauriello et al., 1996). The contractions are thought to be caused by abnormal functioning of the basal ganglia (Aramideh et al., 1994; Galardi et al., 1996; Vitek, 2002).

Blepharospasm is classified as a focal dystonia. The spasmodic and repetitive eye contractions can lead to functional blindness in up to 15% of patients. Blepharospasm primarily affects women in their fifties and

sixties (female to male ratio 2–3 to 1) (Anderson et al., 1998). Prevalence data are limited, but the estimated figure is 1.4 to 13.3 per 100,000 persons (Nakashima et al., 1995; Epidemiologic Study of Dystonia in Europe, 1999; Defazio et al., 2001). In addition, specific ocular abnormalities may predispose a patient to blepharospasm (Jankovic and Orman, 1984).

The introduction of botulinum neurotoxin in the 1980s was a milestone for patients suffering from focal dystonias (Brin et al., 1987, 1990) including blepharospasm (Aramideh et al., 1995). Botulinum neurotoxin injections are now considered the treatment of choice for these patients (Costa et al., 2004; Subcommittee of the American Academy of Neurology, 1994).

NT 201 is a highly purified botulinum neurotoxin type A (BoNT/A) preparation obtained from a well-characterized strain of *Clostridium botulinum*. Haemagglutinins of clostridial origin are removed by a biological manufacturing process. Each vial of NT 201 contains an amount of sterile lyophilized solid material which has the biological activity of 100 mouse LD_{50} units of *Clostridium botulinum* Neurotoxin Type A. This corresponds to approximately 600 pg of clostridial protein. In this paper, we present the results from a non-inferiority trial comparing NT 201 with BOTOX® in the treatment of blepharospasm.

Patients and methods

Patients

A total of 304 patients (mean age: 63 years ± 10.3; range: 25 to 87 years) were enrolled in 42 centres in Europe and Israel between March 2001 and January 2002. For inclusion in the study, patients had to have a confirmed clinical diagnosis of blepharospasm requiring treatment by injection. In addition, patients had to have been exposed to at least two previous BOTOX® injections resulting in a stable therapeutic response. If other dystonia medications (e.g., anticholinergics or benzodiazepines) were taken, the doses had to be kept stable. Patients were excluded if they had an atypical variant of blepharospasm caused by inhibition of the levator palpebrae muscle, myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, or any other significant neuromuscular disease. In addition, patients with known alcoholism or other drug abuse or those suffering from severe or uncontrolled systemic diseases were not allowed to participate.

Overall, 300 patients received study medication (NT 201: n = 148; BOTOX®: n = 152; ITT population). The two groups were comparable with respect to baseline and demographic data. In keeping with the characteristics of blepharospasm, the majority of patients were female (72.7%).

Overall, 44 patients (NT 201: n = 19; BOTOX®: n = 25) had major protocol deviations for which they were excluded from the per-protocol (PP) analysis (n = 256; NT 201: n = 129; BOTOX®: n = 127). There were 11 major violations in the NT 201 group and 16 in the BOTOX® group of the inclusion criterion dealing with a stable response to previous BOTOX® injections. Other major violations included irregularities in the JRS Rating (rater not trained 7 in the NT 201 group and 5 in the BOTOX® group). Other major protocol violations were time window violation, administration of non-authorised medication, injections of study drug of more than 45 units per eye, non-performance of safety assessments and control visits in single cases.

Study design

This was a randomised, multicentre, double-blind Phase III study lasting for 16 weeks. The study was conducted in compliance with Good Clinical Practice (GCP) and the ethical standards laid down in the Declaration of Helsinki. The local independent ethics committees (IECs) of the centres approved the trial protocol before study initiation.

Study medication

NT 201 (Merz Pharmaceuticals GmbH, Germany) was provided as sterile lyophilised powder in glass vials. Each vial contained approx. 600 pg of highly purified BoNT/A (biological activity approx. 100 units), human serum albumin, and sucrose. One unit of BoNT/A corresponds to the calculated median lethal intraperitoneal dose (LD_{50}) in mice. NT 201 was produced in accordance with Good Manufacturing Practice (GMP) and fulfilled the GMP safety and quality standards.

BOTOX® (Allergan, Inc., USA) consisted of BoNT/A complex (4.8 ng; biological activity approx. 100 units/vial) with human serum albumin (0.5 mg/vial), and NaCl (0.9 mg/vial) as excipients. Previous studies had demonstrated that identical units of NT 201 and BOTOX® were equally effective (Jost et al., 2004; Wohlfarth and Mueller, 2005). Therefore the dose and dilution of BoNT/A preparations and

injection sites were determined individually for each patient, based on two pre-study BOTOX® injections the patient had received.

The mean total doses of study medication injected were similar in the two groups (NT 201: 39.6 units, SD: 13.3 units); BOTOX®: 40.8 units, SD: 14.2 units). NT 201 and BOTOX® were diluted on average in 3.0 ml 0.9% sodium chloride solution (SD = 1.2 ml, range: 1.0 to 5.0 ml) per vial.

All investigators and the study personnel were blinded. One unblinded person per centre was exclusively responsible for blinding and preparing the study medication. This person was not involved in any other trial procedures to ensure proper blinding.

Study procedures

Eligible patients were randomly allocated to either NT 201 or BOTOX®. At the baseline visit, patients received an injection of the assigned BoNT/A preparation. In compliance with clinical practice, the maximum dose per eye was 35 units ($\leq$70 units in total). Each patient's individual dose was matched with the dose of the two pre-study BOTOX® injections that were required for study entry. Subsequently, patients were monitored for up to 16 weeks. A control visit took place three weeks after their baseline visit (Day 21 $\pm$ 1 day) and a final visit between days 109 and 112, or before, at the patient's request. Optional intermediate visits were carried out only at the request of the patient.

The primary efficacy variable was the change from baseline in the sum score of the Jankovic Rating Scale (JRS) at the control visit. The JRS ranges from 0–8 points and includes two categories: Severity and Frequency, each with five rating classes of 0–4 points (Jankovic and Orman, 1987; Iwashige et al., 1995). Secondary efficacy variables included the change from baseline in the sum score of the JRS at the final visit and the changes from baseline in the mean total score of the Blepharospasm Disability Index (BSDI) at the control visit and the final visit. The BSDI, a disease-specific functional scale developed for the self-assessment by the patient, consisted of six 5-point items assessing vehicle driving, reading, watching TV, shopping, getting about on foot, and doing everyday activities (see Fig. 1). The retest reliability of the single items ($0.453 \leq r \leq 0.595$, Spearman's Rank coefficient) and validity of the BSDI were evaluated during the course of the trial (Goertelmeyer et al., 2002). All investigators underwent a special training for the scales used in this study.

As an additional secondary efficacy variable, patients evaluated the global response to study treatment at both visits, using a 9-point scale ranging form 'very marked worsening' (−4 points) to 'complete abolishment of signs and symptoms' (+4 points). The scale was adapted from Wissel et al. (2000) and was translated into all languages relevant to the study and subsequently back-translated to ensure linguistic accuracy and comparability. At the end of the study, efficacy was also assessed by the investigators, using a 4-point scale ranging from 'very good' to 'poor'. The time to onset of effect was estimated by the patient at the control visit (i.e., the period from the injection until start of treatment effect), and time to waning of effect (i.e., the period from the injection until decline of effect) was assessed by the patient at the final visit. The patient had the opportunity to come to optional visits whenever a need for injection was felt. Whenever a new injection was necessary the final visit was performed. Duration

Items	Reading		
	Driving a vehicle		
	Watching television		
	Shopping		
	Doing everyday activities		
	Getting about on foot (walking)		
	Categories	no impairment	0
		mild impairment	1
		moderate impairment	2
		severe impairment	3
		not possible due to disease	4
		not applicable	

Fig. 1. Blepharospasm disability index

of effect was calculated as the interval between the initial injection and final visit. Safety assessments included adverse event (AE) monitoring, standard clinical and haematological laboratory tests, assessment of vital signs (pulse, blood pressure, respiratory rate), electrocardiograms (ECGs), and assessments of tolerability by the investigators on a 4-point scale ranging from 'very good' to 'poor'.

Statistical analyses

The sample size calculation was based on the assumption that a clinically irrelevant difference (Δ) of the JRS sum score between the two treatments was 0.8 points with a common standard deviation of 2.0 points. With a one-sided significance level set at 0.025 and a power of 85%, 114 patients per treatment group had to be included in the per-protocol (PP) population.

The hypothesis of non-inferiority of NT 201 to BOTOX®, based on the primary efficacy variable, was tested using 95% confidence intervals (CI) derived from an analysis of covariance (ANCOVA), with the change in the JRS sum score as the dependent variable and with at least the JRS sum score at baseline and treatment group as independent variables. This procedure was one-sided with the alpha-level set to 0.025. Other covariates included 'total dose', 'sex', 'age', 'number of injection sessions since diagnosis of blepharospasm' (grouped as 0–2 sessions, 3–5 sessions, and >5 sessions), 'pooled country', and the 'treatment*pooled country' interaction. The final model used for statistical inference included all variables influencing the primary efficacy variable ($p<0.2$).

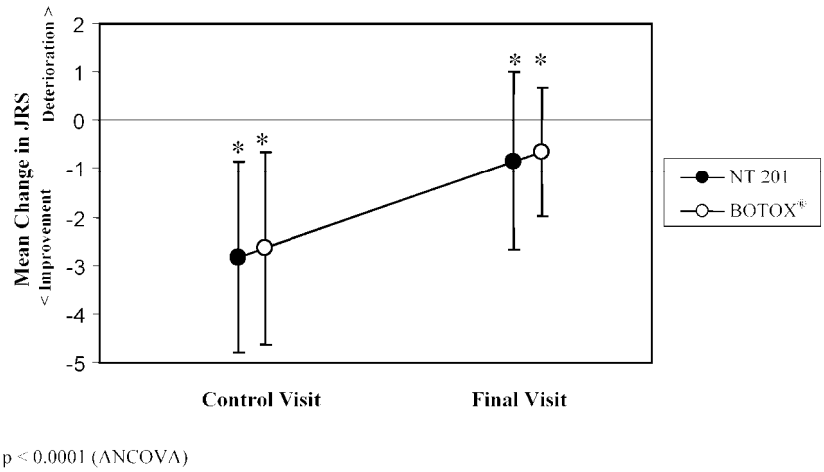
Statistical procedures for secondary efficacy variables were two-sided with the level of type I error set to 0.05. No adjustments were made for multiple tests. Safety variables were analyzed using exploratory statistical methods.

Results

Efficacy

Figure 2 shows the changes in JRS sum scores from baseline to the control visit (21 ± 1 days after the injection) for the PP population. Both treatments resulted in reduced mean sum scores. The adjusted mean change in the JRS sum score at the control visit was −2.90 for the NT 201 group and −2.67 for the BOTOX® group. These changes were significant ($p<0.0001$, ANCOVA), demonstrating that both treatments were effective in improving the symptoms of blepharospasm (Table 1). The covariates that had a significant effect on the results were 'baseline JRS sum score', 'pooled country', and 'dose'. The difference between the two adjusted group means was −0.23 with the upper limit of the 95% CI amounting to 0.22. Since this was below the predefined limit for non-inferiority (0.8), NT 201 was non-inferior to BOTOX® with respect to the primary efficacy variable.

Non-inferiority of NT 201 vs. BOTOX® was supported by all secondary efficacy variables (Table 1). In both treatment groups,



* $p < 0.0001$ (ANCOVA)

Fig. 2. Mean change in baseline JRS sum scores at control visit and final visit (per-protocol population)

Table 1. Summary of efficacy variables – PP population

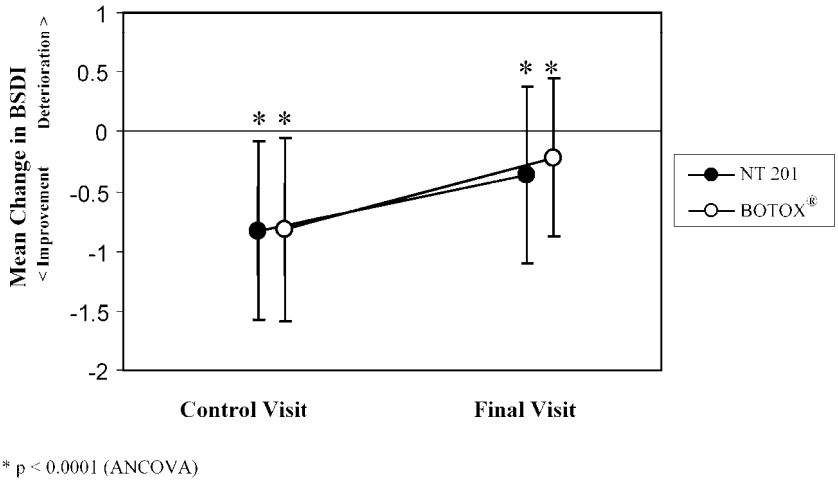
Variable	N	NT 201	N	BOTOX®	Treatment comparisons
JRS sum score					
Baseline visit (injection)	129	5.3	127	5.4	
Control visit (week 3)	129	2.5	127	2.8	
Change Control-baseline	129	−2.83	127	−2.65	
p value (ANCOVA)		<0.0001		<0.0001	0.31
Final visit (109–112 days)	129	4.5	127	4.8	
Change Final-baseline	129	−0.84	127	−0.66	
p value (ANCOVA)		<0.0001		<0.0001	0.27
Mean total BSDI score					
Baseline visit (injection)	129	1.60	125	1.67	
Control visit (21 ± 1 days)	129	0.77	127	0.83	
Final visit (109–112 days)	128	1.24	127	1.45	
Change Control-baseline	129	−0.83	125	−0.82	
p value (ANCOVA)		<0.0001		<0.0001	0.91
Change Final-baseline	128	−0.36	125	−0.22	
p value (ANCOVA)		<0.0001		<0.0001	0.06
Patient evaluation of global response					
Control visit (21 ± 1 days)	128	2.2	127	1.9	
p value (ANCOVA)		<0.0001		<0.0001	0.21
Final visit (109–112 days)	128	2.2	126	2.0	
p value (ANCOVA)		<0.0001		<0.0001	0.21
Global assessment of efficacy by investigator	NT %	201 N	BOTOX® N	%	
Very good	45	34.9	36	28.4	
Good	51	39.5	50	39.4	
Moderate	25	19.4	27	21.3	
Bad	8	6.2	14	11.0	
p-value (Wilcoxon)					0.14

the JRS sum scores at the final visit (109 to 112 days after the injection) were significantly lower than at baseline ($p<0.0001$; Fig. 2). Similarly, both NT 201 and BOTOX® significantly reduced the mean BSDI scores at both the control visit ($p<0.0001$) and the final visit ($p<0.0001$), but there was no statistically significant difference between the two treatments at either assessment (Fig. 3).

In both treatment groups, the mean scores for the patients' evaluation of global response were significantly different from zero at the control visit as well as the final visit (both $p<0.0001$), indicating that the patients in either group reported marked improvement of their symptoms. At both assessment points, slightly higher least-square means were obtained for NT 201 (2.18 and 2.23, respectively) than for BOTOX® (1.95 and 2.01, respectively), but the difference between the two treatments was not statistically significant (Table 1).

The percentage of patients for whom the investigators rated the efficacy of study medication as 'very good' was slightly higher for NT 201 than for BOTOX® (34.9% versus 28.4%), but this difference was not statistically significant.

Duration of effect as well as time to onset and waning of treatment effect were identical



* p < 0.0001 (ANCOVA)

Fig. 3. Changes in mean total BSDI score at control visit and final visit (per-protocol population)

in the two groups. Median duration of treatment effect was 110 days in both groups, while the median time to onset of treatment effect amounted to 4 days and median time to waning of treatment effect to 11 weeks.

In summary, there were no statistically significant differences between treatments for any of the secondary efficacy variables.

Safety

Both study medications were well tolerated, and none of the patients terminated the study prematurely because of an AE. Overall, more than 90% of AEs were of mild or moderate intensity. Slightly fewer AEs were reported in the NT 201 group than the BOTOX® group

Table 2. Patients reporting adverse events, by nature and treatment group

Adverse events	NT 201	BOTOX®
	No of patients with at least one AE (100% = 148)	No of patients with at least one AE (100% = 155)
Ptosis	9 (6.08%)	7 (4.52%)
Abnormal vision	2 (1.35%)	5 (3.23%)
Back pain	2 (1.35%)	4 (2.58%)
Rash	1 (0.68%)	2 (1.29%)
Upper respiratory tract infection	1 (0.68%)	2 (1.29%)
Face oedema	1 (0.68%)	2 (1.29%)
Xerophthalmia	3 (2.03%)	
Arthralgia	1 (0.68%)	1 (0.65%)
Diziness	2 (1.35%)	
Headache	1 (0.68%)	1 (0.65%)
Paraesthesia	1 (0.68%)	1 (0.65%)
Depression		2 (1.29%)
Palpitation		2 (1.29%)
Photophobia	2 (1.35%)	
Dyspnoea	2 (1.35%)	
Urinary tract infection	2 (1.35%)	

(56 vs. 62 events, see Table 2). Ptosis was the most frequent AE (NT 201: 6.1%; BOTOX®: 4.5%). Only one patient suffered from severe ptosis. All cases of ptosis were judged to be treatment-related (i.e. at least unlikely related).

Treatment-related xerophthalmia was reported in 3 (2.0%) patients receiving NT 201. Abnormal vision was reported in 2 (1.4%) patients treated with NT 201 and 5 (3.2%) patients treated with BOTOX®. However, a relationship to treatment was assumed in 3 of 5 patients in the BOTOX® group only. Back pain unrelated to the study medication occurred in 2 (1.4%) patients receiving NT 201 and 4 (2.6%) patients receiving BOTOX®. No statistically significant differences were observed between treatment groups.

Overall, 9 serious adverse events (SAEs) were reported (NT 201, $n=3$; BOTOX, $n=6$). Of these, 8 were considered unrelated and one unlikely related to the study medication. No major differences between treatments were found with respect to laboratory variables, physical and neurological examinations, and ECG results. The percentage of patients for whom the investigators rated the study medication as very well tolerated was higher for NT 201 than for BOTOX® (70.3% versus 61.9%), but this difference between treatments was not significant.

Discussion

In this double-blind Phase III study, NT 201 and BOTOX® exhibited consistent and comparable efficacy in the treatment of blepharospasm. Both treatments resulted in significantly lower adjusted mean JRS sum scores relative to the baseline scores at the control visit ($p<0.0001$). Because the two BoNT/A preparations exhibited similar efficacy, non-inferiority of NT 201 to BOTOX® was clearly established. This finding was supported by all other efficacy variables, both for the ITT and PP analysis populations.

In the ANCOVA model, covariates that had a significant effect on the results were 'baseline JRS sum score', 'pooled country', and 'dose'. Because the primary efficacy variable was defined as the change in JRS score from baseline, baseline values would be expected to affect the final results. The observed effect of 'pooled country' was thought to be caused by the variable assessment of blepharospasm symptoms in different countries. While the intra-country JRS sum scores were in close agreement, the inter-country scores differed substantially. With respect to 'dose', the results indicated that the patients requiring lower doses ($\leq$40 units) of study medication exhibited a greater change in baseline JRS sum scores at the control visit than did those requiring higher doses (>40 units). In line with literature data (Rollnik et al., 2000; Kristan and Stasior, 1987), this finding suggests that the spasmolytic effect of BoNT/A is saturated at a certain level, with higher doses not resulting in any stronger effect in the treatment of blepharospasm. The finding that the treatment effect still proved to be statistically significant at the final visit could be explained by the fact that the study had to be terminated at Day 112 even if the treatment effect was still present to some degree. In the setting of a clinical trial, patients can come in for an optional visit when they feel the need for a new injection which may occur more readily than when being cared for in an usual outpatient situation.

A clear and measurable treatment effect of the study medications is an important prerequisite for a non-inferiority study. In patients suffering from blepharospasm, objective assessment of the frequency and severity of symptoms at any particular assessment point is hindered by the transient nature of the typical complaints. A number of authors have suggested scales to grade the frequency and severity of symptoms in patients with blepharospasm. In our study, we opted for the JRS because of its relative simplicity and broad application. However, published scales, if used on their own, are of limited

usefulness because they fail to cover the specific functional deficits typically occurring in patients with blepharospasm. For example, a patient may exhibit increased blinking of the eye, prolonged lid closure, or difficulties in lid opening at examination, but no information on the duration of this complaint and its influence on daily activities can be obtained. To support the JRS data, we used a new disease-specific disability scale, the BSDI, that allowed the patients' self-assessment of daily functioning. The results obtained from the two scales were in good agreement, indicating that the symptoms in terms of severity and frequency translate into a corresponding functional impairment.

NT 201 and BOTOX® exhibited comparable safety profiles, with similar AE patterns in terms of type and frequency reported in the two groups. Approximately 31% of AEs were considered possibly related to the study medication. In congruence with the known side effects of BoNT/A preparations, ptosis was the most frequent AE (NT 201: 6.1%; BOTOX®: 4.5% of patients). In our study, ptosis was markedly less frequent than in earlier studies quoting frequencies up to 21% (Allergan Pharmaceuticals (Ireland) Ltd., 2004; Burns et al., 1986; Scott et al., 1985). The lower incidence of ptosis in our study was thought to be the result of a refined injection technique applied (Jankovic, 2002).

One limitation of BoNT/A treatments is the development of antibodies potentially leading to partial or even complete therapy failure (Dressler, 2004; Göschel et al., 1997). In chronic conditions, such as blepharospasm, that often require life-long therapy, a potentially immunogenic agent may become a problem. The proportion of secondary non-responders to BoNT/A preparations can be as high as 10% (Greene et al., 1994), with a further 40% of treated patients developing titres of non-neutralising antibodies against the haemagglutinins (Göschel et al., 1997).

Several authors have suggested that a lower protein load translates into reduced immunogenicity (Borodic et al., 1996; Jankovic et al., 2003). There is good nonclinical evidence that NT 201 will be less immunogenic than BOTOX®, owing to the highly purified preparation and absence of immunogenic proteins. Thus, NT 201 may specifically be of therapeutic value in the long-term treatment of blepharospasm. Firm proof, however, warrants long-term clinical studies in conjunction with antibody tests.

Conclusions

In our study, both NT 201 and BOTOX® provided effective and long-lasting relief of the symptoms of blepharospasm. Based on the primary efficacy variable, non-inferiority of NT 201 over BOTOX® was clearly established.

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